PHYSIOLOGICAL REVIEWS
Vol. 77, No. 1, January 1997
*Printed in U.S.A.*

# Cellular and Molecular Neuroscience of Alcoholism

IVAN DIAMOND AND ADRIENNE S. GORDON

*Ernest Gallo Clinic and Research Center, Department of Neurology and The Neuroscience Program and Department of Cellular and Molecular Pharmacology, University of California, San Francisco General Hospital, San Francisco, California*



**Diamond, Ivan, and Adrienne S. Gordon.** Cellular and Molecular Neuroscience of Alcoholism. *Physiol. Rev.* 77: 1–20, 1997.—Recent advances in neuroscience have made it possible to investigate the pathophysiology of alcoholism at a cellular and molecular level. Evidence indicates that ethanol affects hormone- and neurotransmitter-activated signal transduction, leading to short-term changes in regulation of cellular functions and long-term changes in gene expression. Such changes in the brain probably underlie many of the acute and chronic neurological events in alcoholism. In addition, genetic vulnerability also plays a role in alcoholism and, perhaps, in alcoholic medical disorders.

## I. INTRODUCTION

Alcoholism, alcohol abuse, and the medical complications of excessive drinking are major world-wide health problems. In the United States, ~7% of adults are alcoholics, and >20% of hospitalized patients have a medical disorder related to heavy drinking (72). Recent advances in neuroscience have made it possible to investigate the pathophysiology of alcoholism at a cellular and molecular level. Evidence indicates ethanol affects hormone- and neurotransmitter-activated signal transduction, leading to short-term changes in regulation of cellular functions and long-term changes in gene expression. Such changes in the brain probably underlie many of the acute and chronic neurological events in alcoholism (202). In addition, genetic vulnerability also plays a role in alcoholism and, perhaps, in alcoholic medical disorders.

## II. ACUTE AND CHRONIC RESPONSES TO ETHANOL

There are two major central nervous system (CNS) responses to alcohol abuse: severe intoxication and adaptive changes that develop in alcoholics because of prolonged drinking. Ethanol is both water soluble and lipid soluble and is readily distributed into the cytoplasm and lipid membranes of all cells in the body. There is no blood-

brain barrier for ethanol; nuclear magnetic resonance studies in animals (265) and human volunteers (198) show that alcohol can be detected in the brain within a few minutes after drinking. Acute ethanol intercalates into cell membranes (297) and increases membrane fluidity (105), while chronic ethanol alters the lipid composition of cell membranes (323, 329). However, it is has never been clear how ethanol-induced disturbances in membrane order (104, 120, 298, 350) produce the characteristic short-term and long-term CNS effects of heavy drinking (201). These include such reversible clinical events as intoxication, memory loss during binge drinking (blackouts), tolerance to the intoxicating effects of ethanol in alcoholics, addiction (continued drinking despite adverse medical and socioeconomic complications), and a characteristic hyperexcitable alcohol withdrawal syndrome when alcohol abuse is discontinued (evidence of physical dependence).

Almost all of the important pathophysiological targets for ethanol in neural cells appear to be specific membrane proteins that mediate signal transduction (92, 201, 358). Ethanol does not appear to alter the activity of most soluble proteins. Not all membrane proteins are affected, but some signal transduction cascades are highly sensitive. Targets include certain ion channels, transporters, neurotransmitter receptors, G proteins, and enzymes that produce second messengers; interaction of ethanol with these target proteins leads to changes in activity of many enzymes, chaperones, and regulators of gene expression. In this review we consider first several membrane proteins that are specifically sensitive to ethanol, particularly because they have relevance for important clinical events in alcoholism and alcohol abuse. Then we discuss other regulatory signaling pathways that are also altered by ethanol and that may play a role in these events. It is also possible that over prolonged periods of time these ethanol-induced molecular changes contribute to the development of several alcoholic neurological disorders. Apart from the role of thiamine deficiency in Wernicke's disease, however, the pathogenesis of the neurologic disorders in alcoholism is not well understood (41, 71), but today, alcohol toxicity appears to be more important than nutritional deficiency.

## III. ETHANOL AND MEMBRANE PROTEINS

Alcohols with increasing carbon chain length have increasing solubility in cell membranes. Nevertheless, there is a "cut-off" in the biologic effect when alcohols of increasing chain length are studied in the same system (90, 164). Peoples and Weight (262) have recently shown that shorter chain length alcohols were increasingly potent inhibitors of neuronal *N*-methyl-D-aspartate (NMDA) receptor activated ion currents, but longer chain alcohols had no effect, despite greater solubility in membranes. These results suggest that there is a hydrophobic pocket in ethanol-sensitive membrane proteins. Because the cut-off response varies with different neurotransmitter receptor systems (164, 262), these hydrophobic sites are probably of different size in different membrane proteins. This is consistent with pioneering work by Franks and Lieb (92), who called attention to the molecular cut-off effects (90) and later documented highly specific hydrophobic binding sites on proteins that discriminate between optical isomers of anesthetic agents with identical lipid solubility (91). Taken together, these findings suggest the possibility of designing new drugs to compete with ethanol at selected hydrophobic sites to block or reverse specific adverse effects without affecting the function of other membrane proteins.

## IV. *N*-METHYL-D-ASPARTATE RECEPTORS

The NMDA receptor is one of several major receptors for glutamate (155), the principal excitatory neurotransmitter in the brain. *N*-methyl-D-aspartate receptors in the hippocampus are involved in learning and memory (300) and are critical for long-term potentiation (LTP) and long-term depression (LTD) in models of synaptic plasticity (183). Specific NMDA receptor subunits mediate these NMDA receptor responses (89, 156, 300). *N*-methyl-D-aspartate receptor activation by glutamate promotes calcium influx through an ion channel that is part of the receptor (27). Calcium, in turn, regulates synaptic signaling (47) via activation of protein kinases, phosphatases, and proteases. Ethanol inhibits LTP (222), perhaps by suppressing its induction (103). Lovinger et al. (174) were the first among several investigators (78, 126, 165) to discover that ethanol inhibits NMDA receptor activation at intoxicating blood alcohol levels. In *Xenopus* oocyte expression systems, ethanol inhibition is modulated by glycine (26) and may (26, 45, 188) or may not (218) vary with NMDA receptor subunit composition. Ethanol also inhibits kainate (79, 187) and DL-$\alpha$-amino-3-hydroxy-5-methylisoxazole-propionic acid (172, 187) responses, suggesting that non-NMDA receptors are also sensitive to ethanol (172). Indeed, ethanol modulates metabotropic glutamate receptors coupled to second messengers in cerebellar Purkinje cells (242). There is differential sensitivity to ethanol among NMDA receptor isoforms in the brain (211) or when expressed in *Xenopus* oocytes (218), and ethanol inhibition of NMDA receptor activation (188, 243, 262) appears to play a role in ethanol intoxication. For example, it is likely that ethanol inhibition of NMDA receptors accounts for alcoholic "blackouts" that occur during heavy drinking. These startling episodes are characterized by hours of amnesia for events that occurred while intoxicated; they are best explained by transient ethanol inhibition of NMDA receptors in the hippocampus. Several

agents prevent ethanol inhibition of LTP (43, 290, 322, 355, 375) and raise the possibility of new treatments for ethanol-induced memory loss in humans. Also, an agent like acamprosate, which appears to enhance NMDA receptor function (182), might also be useful. Perhaps this is related to the clinical impression that acamprosate helps to sustain abstinence in human alcoholics (253).

One of the adaptive CNS responses to chronic exposure to ethanol is an upregulation of NMDA receptors in human alcoholics (210) and in rats, particularly the hippocampus, measured by ligand binding (112, 304, 319) and NMDA receptor subunit immunoreactivity (334). Ethanol-induced upregulation could have serious neuropathological consequences (171) because overactivity of NMDA receptors appears to cause "excitotoxic" neuronal cell damage in several neurological disorders including ischemic strokes, hypoglycemia, and prolonged seizures (296). This was confirmed recently by demonstrating that antisense oligonucleotides to an NMDA receptor subunit protect specific neurons from excitotoxic cell death and reduce ischemic infarcts in the brain (344). Consistent with these findings, chronic exposure to ethanol causes increased NMDA receptor-mediated calcium flux (2, 134) and greater NMDA excitotoxicity in cultured neurons (2, 35, 125). These results suggest the possibility that memory deficits and neuronal cell loss in chronic alcoholics (118) might be due, in part, to chronic ethanol-induced upregulation of NMDA receptors. Unrestrained NMDA receptor activation is also implicated in alcohol withdrawal seizures because these receptors play a role in the pathogenesis of convulsions (150, 229). Therefore, new therapies directed against excessive glutamate release (294) and activation of NMDA receptors (289, 290) might prevent or reverse some complications of chronic alcohol abuse and withdrawal.

Paradoxically, ethanol inhibition of NMDA receptors might be of protective value for ischemic stroke in nonalcoholics where excitotoxic amino acids cause brain damage. Recent experiments show that ethanol can attenuate excitotoxic neuronal damage (36, 177, 356), presumably by blocking NMDA receptor activation and calcium influx (178, 356), leading to attenuation of stress-induced *c-fos* expression in vulnerable neurons as in the hippocampus (161, 299). However, unacceptably high concentrations of ethanol might be required for a protective effect in patients. Further research on agents, like ifenprodil (169), that mimic the acute interaction of ethanol with NMDA receptors might generate more effective anti-ischemic agents than available today.

## V. γ-AMINOBUTYRIC ACID RECEPTORS

γ-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the brain, activating $GABA_A$ and $GABA_B$ receptors. The $GABA_A$ receptor is an oligomeric protein complex containing a receptor-operated chloride channel and specific allosteric binding sites for benzodiazepines, barbiturates, and other agents (248, 318). The function of $GABA_A$ receptors is potentiated at intoxicating concentrations of ethanol in heterogeneous neural preparations and cells stably transfected with GABA receptor subunits (122). Also, there is cross-tolerance between ethanol, benzodiazepines, and barbiturates (196, 325). Thus benzodiazepines are very helpful in treating the alcohol withdrawal syndrome (72) by substituting for alcohol. On the other hand, benzodiazepine inverse agonists such as the imidazobenzodiazepine Ro 15-4513 prevent the intoxicating effects of ethanol in rodents apparently by antagonizing ethanol potentiation of $GABA_A$ receptors (25, 196, 254, 324). Although Ro 15-4153 is not suitable for patients because it causes seizures, it is likely that new and safe drugs will be developed to block or reverse the acute intoxicating effects of ethanol by modulating $GABA_A$ receptor function. In addition, promising results with γ-hydroxybutyrate suggest that novel agents affecting GABA function may be useful in treating alcohol dependence (95).

The response of GABA receptors to ethanol varies in different regions of the brain (56, 272, 274, 286), but the molecular basis of this regional sensitivity is not well understood. In hippocampus, ethanol enhances $GABA_A$ receptor function only when $GABA_B$ receptors are blocked (347). In addition, molecular cloning has determined that the $GABA_A$ receptor complex is a multigene family (159, 248). Genes for a variety of α-, β-, γ-, and δ-subunits have been cloned, and $GABA_A$ receptors in brain appear to be assembled in multiple combinations of these subunits (159, 194). Moreover, the subunit composition of $GABA_A$ receptors changes under different biological conditions, introducing an additional element of $GABA_A$ receptor variability. Differences in subunit composition may account for developmental changes in receptor properties with maturation (159), receptor localization in cells (263), and differences in receptor pharmacology in neurons (6, 85, 122, 193). The role of specific subunits in determining ethanol sensitivity may best be studied in transfected cell lines (119, 336). It may be anticipated, therefore, that chronic ethanol-induced changes in $GABA_A$ receptor subunits (56, 69, 124, 207-209, 223, 370) will have significant functional consequences in the brain.

Ethanol potentiation of GABA-induced responses in cerebellar neurons (162) appears to be regulated by β-adrenergic receptor activation (166), suggesting a role for adenosine 3′,5′-cyclic monophosphate (cAMP)-dependent protein kinase (PKA) phosphorylation in modulating sensitivity to ethanol. Other studies with mouse $GABA_A$ receptor subunits expressed in *Xenopus* oocytes by Wafford et al. (342) suggest that a specific γ-subunit confers sensitivity to ethanol potentiation of receptor activation, al-

though this was not observed with γ-subunits expressed in *Xenopus* oocytes (312) or human embryonic cells (186). Recent results with mouse and bovine subunits in a clonal cell line suggest that the γ-subunit may be necessary but not sufficient for ethanol sensitivity (122). The $\gamma_2$-subunit exists as alternatively spliced short ($\gamma_{2s}$) and long ($\gamma_{2l}$) forms; the long form contains 24 additional nucleotides that encode a phosphorylation site for protein kinase C (PKC) on an intracellular loop (342). Ethanol sensitivity appears to require PKC phosphorylation of the $\gamma_{2l}$-subunit expressed in *Xenopus* oocytes (343), and perhaps, in hippocampal CA1 neurons (359). However, there is suggestive evidence that ethanol sensitivity of hippocampus $GABA_A$ receptors may also involve PKA (347). The $GABA_A$ receptors in mutant mice lacking the γ-isoform of PKC show reduced sensitivity to ethanol (121), but this may be related to impaired cerebellar function in PKC-γ mutants (42, 139). These results are all consistent with studies suggesting a critical role for phosphorylation in regulating the response of other membrane proteins to ethanol (see sect. IX, *C–F*). Further studies are needed to determine the stoichiometry of $GABA_A$ receptor subunit expression and the substrates for phosphorylation that confer ethanol sensitivity in the brain. Progress in this area will need to identify highly specific pharmacological targets for the therapy of alcoholism.

## VI. SEROTONIN RECEPTORS

The serotonin ($5\text{-}HT_3$) receptor (138) has increased mRNA expression in certain brain regions, particularly the hippocampus (330), and is structurally similar to the nicotinic acetylcholine and $GABA_A$ receptors. These three receptors are ligand-activated ion channels and are sensitive to ethanol (122, 175, 367). The $5\text{-}HT_3$ receptor ionophore conducts monovalent cations, and low concentrations of ethanol potentiate $5\text{-}HT_3$ receptor-stimulated currents in several neural preparations (170, 173). Serotonin receptor antagonists block the ability to discriminate between drinking water or ethanol in pigeons (111) and specifically reduce ethanol drinking in conditioned and alcohol-preferring rodents (135, 148, 333). Serotonin receptors have also been implicated in the control of appetite, and $5\text{-}HT_{2c}$ receptor-deficient animals become overweight because of abnormal feeding behavior (331). Moreover, selected regions of the brain in alcohol-preferring rats have fewer serotonin $5\text{-}HT_2$ receptors (190) and increased $5\text{-}HT_{1A}$ receptors (191). Furthermore, serotonergic neurons and their axons appear to degenerate in alcohol-preferring rats (116) and in chronic alcoholics (117). Although $5\text{-}HT_2$ receptors have been implicated in alcohol preference in rodents (46), the effect of $5\text{-}HT_2$ antagonists on animal drinking behavior has been inconsistent (195, 256). Nevertheless, preliminary studies suggest that ondansetron, a serotonin receptor antagonist, reduces alcohol intake in normal men (137) and alcoholics with less severe drinking (311). These findings suggest that serotonin may play a role in alcohol intoxication and alcohol-seeking behavior. Because serotonin potentiates ethanol-induced excitation in the ventral tegmental area (21), pharmacological agents like ifenprodil (192), which react with specific sites on serotonin receptors, may be of value in treating craving in alcoholics.

## VII. VOLTAGE-DEPENDENT CHANNELS

### A. Calcium Channels

In addition to receptor-activated calcium influx, intracellular concentrations of calcium are increased in neurons following depolarization through voltage-dependent calcium channels (284). At low concentrations, calcium ions are critical second messengers, but high concentrations lead to excitotoxicity and cell death (47). Recent evidence suggests that ethanol-induced upregulation of calcium channels may account for many features of the alcohol withdrawal syndrome, including intense neuronal hyperactivity and life-threatening seizures (201).

Studies with isolated neural cells have identified molecular mechanisms that may be responsible for these events. Voltage-dependent calcium channels consist of multi-subunit complexes characterized by pharmacological and neurophysiological criteria (12, 34). Acute ethanol inhibits voltage-dependent L-type calcium channels (19, 44, 80, 114, 123, 199, 224, 225, 292, 315, 335, 353), N channels (351, 352), and T channels (335) but has no effect on P-type calcium channels (115). Ethanol may act specifically on the channel protein (353). Undifferentiated cells are most sensitive to ethanol inhibition (11, 225); this may involve the inhibitory G protein, $G_i$ (224). Chronic exposure of neural cells to ethanol, however, leads to increased depolarization-stimulated calcium influx (110, 199, 315) associated with an apparent increase in calcium channels measured by binding studies with labeled antagonists (82). Similar increases in brain calcium channel binding sites have also been found in alcohol-dependent animals (167) and Kupffer cells from the liver (109). This increase in voltage-dependent calcium channels requires PKC activity (205) and may be related to ethanol-induced increases in two PKC isoenzymes and PKC-mediated phosphorylation (204). Ethanol-induced upregulation of calcium channels persists for ~16 h after ethanol is removed (199), coinciding with the time of greatest risk for alcohol withdrawal seizures after alcoholics stop drinking (339). Increased voltage-dependent calcium channel activity could induce withdrawal symptoms by promoting neurotransmitter release (179), and enhancing NMDA receptor activation (363). Consistent with this hypothesis, treat-

ment with calcium channel blockers reduces alcohol withdrawal tremors, seizures, and mortality in animals (17, 168) and human alcoholics (147). Moreover, treatment with some calcium channel blockers like nimodipine also reduces alcohol consumption in alcohol-preferring rats (65).

Ethanol regulation of calcium channels also appears to be under genetic control, producing selective upregulation in long-sleep mice (131). Ethanol-induced upregulation of calcium channels (18, 113) and voltage-activated calcium currents (264) is much greater in mice selectively bred for severe alcohol withdrawal seizures than in mice bred for mild signs of alcohol withdrawal. It remains to be determined whether genetic variation in ethanol regulation of calcium channels contributes to human alcohol withdrawal seizures and chronic alcoholic brain damage.

### B. Potassium Channels

Ethanol appears to inhibit different kinds of potassium currents in a variety of neural preparations, but not all investigators agree (358). The expression of potassium channel subunits in the hippocampus has a spatial heterogeneity that varies with development (184), suggesting the possibility that specific potassium channels may be targets for ethanol. In recent years, investigators have turned to expression systems to study the ethanol inhibition of potassium channels (5). These results suggest that many voltage-gated potassium channels are insensitive to high concentrations of ethanol. Recently, four structurally homologous potassium channels cloned from *Drosophila* were investigated for sensitivity to ethanol, using a *Xenopus* oocyte expression system (52, 53). Only the Shaw 2 channel was blocked by clinically relevant concentrations of ethanol. Inhibition occurs at a discrete saturable site (53), thus making it possible to now determine the molecular basis of ethanol inhibition of a specific target membrane protein.

## VIII. ADENOSINE TRANSPORTERS

Adenosine is transported into mammalian cells by two different classes of transporters: one class characterized by sodium-dependent uptake of adenosine and the other characterized by facilitative diffusion down a concentration gradient (270). There are at least three different subtypes in each class. Recent work from our laboratory indicates that uptake by only one transporter, a subtype of facilitative transporter, is inhibited by ethanol; the others are unaffected (152). In naive cells, ethanol inhibition of the transporter results in the accumulation of extracellular adenosine (236). After prolonged exposure to ethanol, however, the transporter becomes tolerant or insensitive to the acute inhibitory effects of ethanol; adenosine uptake is no longer inhibited by ethanol, and consequently, there is no increase in extracellular adenosine (231, 236, 305). Tolerance of adenosine uptake to ethanol inhibition has also been produced in hepatocytes after chronic ethanol feeding (354). Our studies suggest that the ethanol sensitivity of the adenosine transporter appears to be regulated by PKA-mediated phosphorylation of the transporter or an associated regulatory component (50, 231). Therefore, the nucleoside transporter may become insensitive (tolerant) to ethanol inhibition after chronic exposure to ethanol because of decreased cAMP levels (see sect. IX*A*) and reduced PKA phosphorylation (50).

The same kinds of ethanol-induced changes in ethanol sensitivity of adenosine transport also occur in cells from actively drinking alcoholics. We find that adenosine uptake in lymphocytes (107) and in sealed erythrocyte membranes from alcoholics is insensitive to ethanol, whereas uptake is inhibited by ethanol in erythrocyte membranes from nonalcoholic controls (unpublished observations). These studies suggest that mechanisms identified in cultured cell lines are relevant to cellular pathophysiology in human alcoholism. Such simple systems may make it possible to develop a sensitive bioassay for heavy drinking and to determine the relationship between phosphorylation and transporter insensitivity to ethanol in cells from alcoholics.

## IX. ETHANOL AND OTHER REGULATORY SIGNALING PATHWAYS

The previous sections reviewed current information on the interaction of ethanol with specific identified membrane proteins. In addition, ethanol alters the activity of multiple signal transduction systems where the specific target is unknown. Here we review these ethanol-sensitive systems, since changes in the activity of second messengers and protein kinases in these pathways would be expected to have profound short-term and long-term effects on many neuronal functions.

### A. cAMP Signal Transduction

Ethanol affects receptor-mediated cAMP signal transduction in many biological preparations (108), which may vary with the expression of certain types of adenylyl cyclases (374). Because cAMP regulates the activity of PKA, which in turn regulates various cellular functions, ethanol-induced changes in cAMP could account for many of the pleiotropic effects of ethanol. Most investigators find that brief exposure to ethanol potentiates receptor-activated cAMP production. In contrast, chronic exposure to ethanol causes a decrease in receptor-stimulated cAMP production (108). This is well documented in cell culture where chronic treatment with ethanol decreases $\beta$-adren-

ergic receptor (16, 279, 280)-, adenosine receptor (40, 106, 220, 237, 278, 279, 281-283)-, and prostaglandin receptor-dependent cAMP production (288). Decreased cAMP production appears to be a cellular model for ethanol dependence, since stimulated cAMP levels are abnormally low after alcohol withdrawal but return to normal levels when ethanol is added back to NG108-15 neural cell cultures (106). We (106, 220) and others (40, 281, 288) have also found that chronic exposure to ethanol reduces cAMP signal transduction for several receptors within the same cell. In many cell types, this appears to be due to an ethanol-induced heterologous desensitization of receptors coupled to the stimulatory guanine nucleotide regulatory protein $G_s$. In homogeneous NG108-15 cultures of neural cells, we find that this desensitization is correlated with a decrease in mRNA for the $\alpha$-subunit of $G_s$ and a consequent reduction in $G_s\alpha$ protein and functional activity (220). Similar changes in $G_s\alpha$ mRNA or protein have been reported by others (40, 239, 281, 349), including an ethanol-induced decrease in $G_s\alpha$ mRNA in developing rat hippocampus (64). However, an increase in $G_i\alpha$ protein has also been described in some neural cells (40) and brain (348). This is consistent with neurophysiological evidence that different neurons have differential responses to ethanol. Some investigators (260, 327) have not found significant ethanol-induced changes in G proteins in brain. However, negative studies or variable results with crude brain preparations must be interpreted with caution because brain regions contain G proteins and adenylyl cyclases from diverse populations of neurons and glial cells, thereby masking specific ethanol-induced changes in certain neurons.

## B. G Protein-Coupled Receptors

### *1. Dopamine $D_2$ receptors*

Dopamine has been implicated in brain mechanisms of reward, reinforcement, and addiction (276, 310), and drinking alcohol is associated with increased release of dopamine in the nucleus accumbens (144, 360, 373). Also, ethanol added to brain slices in vitro increases the firing rate of dopaminergic neurons in the ventral tegmental area (20). In contrast, during ethanol withdrawal in rats, there is a decrease in dopamine release (295) and a reduction in dopaminergic firing in the nucleus accumbens (321), which persists beyond the clinical manifestations of alcohol withdrawal (77). However, ethanol self-administration restores withdrawal dopamine levels to normal in the nucleus accumbens, suggesting that decreased levels of dopamine may motivate ethanol-seeking behavior in dependent animals (361). However, others find that dopamine antagonists can reduce alcohol consumption in rats (255, 302). Nevertheless, in alcohol-preferring mice, low dopaminergic activity is associated with high alcohol consumption that can be reversed by increasing dopamine levels (102). Rats bred to prefer drinking alcohol will self-administer ethanol by intracranial infusion into the ventral tegmental area (97), suggesting genetic hypersensitivity to ethanol reinforcement of drinking in these animals, perhaps related to selectively reduced dopamine $D_2$ receptors in their brain (189). In these alcohol-preferring rats, a dopamine $D_2$ agonist reduces alcohol intake, whereas a $D_2$ antagonist tends to increase drinking (84). The $D_1$ ligands also affected drinking (84), suggesting a role for both $D_1$ and $D_2$ receptors in reinforcing drinking in this line of rats (84). Consistent with these findings, ibogaine, presumably acting as a dopamine agonist, also attenuates drinking in alcohol-preferring rats (287). Serotonin (373) and opioid (364) receptors also appear to be involved in ethanol reinforcement in this brain circuit by affecting dopamine release, since activation of serotonin receptors stimulates dopamine release (14) and potentiates ethanol-induced release (29). Dopamine reuptake sites vary in violent and nonviolent alcoholics (332) so that ethanol-induced dopamine release may affect other complex behaviors as well. Dopamine release induced by ethanol is blocked by serotonin (369) and opioid antagonists (1, 10), suggesting potential avenues for therapy in human alcoholism.

### *2. Opioid receptors*

Acute ethanol inhibits opiate binding to the $\delta$-opioid receptor (38, 39), but prolonged exposure to ethanol causes an increase in $\delta$-opioid receptor mRNA (37, 136), upregulation of the receptor (38, 39), and an increased response to opioid receptor ligands (39). Opioid receptors modulate ethanol-induced dopamine release in brain regions involved in craving (1), suggesting that alcohol craving may involve opioid receptors. Opioid receptor antagonists reduce alcohol consumption in experimental animals (3, 94, 96, 185, 228, 301), perhaps reversing ethanol-induced decreases in glutamatergic synaptic transmission (243) in the nucleus accumbens by interfering with dopamine release in this nucleus (10). This may involve $\delta_2$-opioid receptors specifically (153, 154). Indeed, recent studies in alcoholics suggest that naltrexone, an opioid receptor antagonist, helps alcoholics to stop drinking. In two independent short-term studies, naltrexone in combination with counseling significantly reduced craving for alcohol in abstinent alcoholics, with a 50% reduction in the relapse rate (250, 341). Naltrexone is not a cure for alcoholism but may be needed for long-term therapy with professional counseling to help some alcoholics remain abstinent (249).

### *3. Muscarinic receptors*

Extensive information about the role of muscarinic receptors in mediating ethanol responses has been dis-

cussed recently (181). Ethanol inhibits muscarinic receptor activation of phosphoinositide metabolism in primary cortical cultures (149) and neural cell lines (158), as well as in several brain preparations (8, 30, 328). In contrast, long-term exposure to ethanol increases muscarinic receptor gene expression in NG108-15 cells (130) and potentiates receptor inhibition of cAMP accumulation in PC12 cells (145). Nevertheless, recent evidence suggests that clinically intoxicating concentrations of ethanol actually enhance muscarinic synaptic transmission in slices from hippocampus (181), an area that subserves learning and memory. This finding is consistent with intriguing clinical studies showing that acute alcohol consumption in naive subjects actually improved memory for events experienced before drinking (258).

*4. Adenosine receptors*

Adenosine plays a role in many of the acute and long-term effects of ethanol in the nervous system (73). Adenosine appears to mediate acute ethanol-induced ataxia; adenosine receptor agonists increase ethanol-induced incoordination and antagonists diminish this response (59-63). Sensitivity to adenosine agonists and antagonists correlates with acute alcohol sensitivity in mice bred selectively for differential responses to ethanol (273), and the intoxicating effects of ethanol are exacerbated by drugs that interfere with adenosine reuptake via the adenosine transporter (59). Also, there is cross-tolerance between adenosine agonists and ethanol after chronic exposure to either agent (62).

We have found that adenosine mediates many acute and chronic effects of ethanol on cAMP signal transduction in several cultured cell lines (73, 74, 108). Adding ethanol to cells leads to an immediate increase in extracellular adenosine levels (see sect. VIII) (237). This is due to ethanol inhibition of adenosine uptake (236). Extracellular adenosine then reacts with adenosine $A_2$ receptors to stimulate the production of cAMP (237). Acute increases in cAMP levels are followed by a heterologous desensitization of receptors coupled via $G_s$ to stimulation of adenylyl cyclase activity (40, 106, 220, 237). This adenosine receptor-mediated desensitization is characterized by a decrease in mRNA, protein, and function for $G_s\alpha$ (220). Moreover, PKA appears to be necessary for ethanol-induced heterologous desensitization in S49 cells (231) and PC12 cells (281, 282). The implication of these findings is that a selective effect of ethanol on cAMP signal transduction mediated by adenosine receptors may lead to diverse adaptive changes affecting many components of cellular function in different tissues and organs.

Any metabolic event that increases extracellular adenosine levels should potentiate the acute effects of ethanol. Conversely, decreasing extracellular adenosine concentrations should attenuate the effects of ethanol. We have shown that coincubation of cells with ethanol and adenosine deaminase prevents both the acute and chronic effects of ethanol on cAMP signal transduction (237). We also found that the potent adenosine receptor antagonist BW-1434U blocks all of the acute and chronic effects of ethanol on cAMP signal transduction in NG108-15 cells, including initial increases in cAMP, decreases in $G_s\alpha$ protein, ethanol-induced heterologous desensitization of cAMP production, and loss of ethanol sensitivity of adenosine transport (305). However, other factors can also regulate cAMP responses to ethanol. For example, Rabin et al. (283) find in PC12 cells that adenosine may not be required for ethanol-induced desensitization of cAMP production. Also, if NG108-15 cells are studied while actively dividing, there are some complex effects of ethanol on G proteins and mRNA that appear to be independent of adenosine (366), probably because under proliferating conditions, ethanol inhibits cell division and promotes differentiation (142). Thus ethanol-induced changes in signal transduction appear to vary considerably with development, differentiation, and functional activity. In model cell culture systems, therefore, it is important to try to use nondividing neural cells to identify ethanol-induced responses that are relevant to neurons in the mature nervous system.

Adenosine is a global inhibitory neuromodulator in the nervous system, acting through adenosine $A_1$, $A_2$, and other receptor subtypes in the cell membrane (83). Adenosine modulates calcium channels (338, 371) and inhibits excitatory synaptic transmission by attenuating the release of excitatory transmitters from presynaptic nerve endings (140, 176, 271, 285, 306, 372). Adenosine also acts postsynaptically to diminish the response of dopamine (86) and acetylcholine receptors (51, 269). The extracellular concentration of adenosine increases with neural activity (268, 269), and blockers of adenosine uptake potentiate cellular responses to adenosine (59, 232, 233, 236, 244, 267), suggesting that the physiological effects of adenosine are terminated, in part, by reuptake into the cell.

Neural responses mediated or modulated by adenosine vary depending on the kinds of adenosine transporters and receptors expressed in different brain regions and on different neurons. The ethanol-sensitive adenosine transporter is regionally distributed in the brain (13, 230), suggesting that adenosine will mediate responses to ethanol only in selected neuronal populations expressing an ethanol-sensitive adenosine transporter. Also, these responses are likely to depend on the kinds of adenosine receptors expressed on the target cells. Thus prolonged exposure to ethanol appears to cause heterologous desensitization of cAMP signal transduction in cells expressing adenosine $A_2$ receptors, but experiments in liver cells expressing $A_1$ receptors (133, 234, 235) suggest that hypersensitization of cAMP production will develop in neurons

expressing only adenosine $A_1$ receptors. Moreover, because adenosine $A_1$ and $A_2$ receptors can also be expressed in the same cells (4, 217, 227, 247, 275, 368), possibly with functional and topographic separation in the same cell (163) and on different neurons in the same brain regions (22, 58), the relative expression and functional localization of $A_1$ and $A_2$ receptors would be expected to determine whether ethanol-induced increases in extracellular adenosine leads to desensitization, hypersensitization, or no change in cAMP signal transduction.

Systemic factors also influence the role of adenosine receptors in mediating neural responses to ethanol. Studies by Israel and colleagues (31-33, 251) suggest that ethanol metabolism in the liver causes an accumulation of adenosine in blood that would be expected to exacerbate the acute effects of ethanol on adenosine receptors in the brain. They have reported significant increases in arterial acetate and adenosine levels following the presentation of ethanol to the liver from the gastrointestinal tract (252). The explanation for this observation is that acetate, produced as a consequence of ethanol metabolism in the liver, is readily converted to acetyl CoA, consuming ATP in the process. Breakdown of ATP generates adenosine that is released into the circulation. In addition, they propose that the liver also releases large amounts of acetate that can be metabolized to acetyl CoA, thereby generating adenosine in the brain. Indeed, sedating effects of acetate are blocked by an adenosine receptor antagonist (31). Although the brain does not metabolize ethanol, the studies by Israel and colleagues suggest that the CNS could directly (and indirectly via acetate) be exposed to increased concentrations of adenosine as a consequence of alcohol metabolism in the liver. Because ethanol inhibits adenosine uptake in hepatic cells (233) and in nerve endings (271), and we find ethanol inhibition of adenosine uptake in cultured S49 cells (231, 236), neural cells (231, 236, 305), human lymphocytes (107), and erythrocyte membrane vesicles (unpublished observations), ethanol inhibition of adenosine uptake at synapses in many regions of the brain (66) would be expected to activate nearby adenosine $A_1$, $A_{2a}$ and $A_{2b}$ receptors and potentiate the acute neurological effects of adenosine (and ethanol) in the brain. Consistent with this possibility are reports that ethanol, acetate, and adenosine produce identical neurophysiological responses in hippocampal neurons that are all blocked by an adenosine receptor antagonist (57). Others do not find, however, that acetate affects adenosine receptors in the hippocampus (23) or that an adenosine antagonist blocks acetate depression in neural cells (266). Nevertheless, ethanol potentiation of adenosine responses has been confirmed in the same studies (266).

### C. Ethanol Sensitivity and Protein Phosphorylation

A common theme emerging from recent studies is the possibility that phosphorylation regulates ethanol sensitivity of several proteins, particularly for the ethanol-sensitive adenosine transporter (50, 231), the $GABA_A$ receptor (343), the kainate receptor (79), and the NMDA receptor (320). Other membrane proteins selectively affected by ethanol can be regulated by protein kinases, but the relationship of phosphorylation to ethanol sensitivity has not been determined. These include the opioid receptor (39, 206), the nicotinic acetylcholine receptor (127, 367), a serotonin receptor (303), the GLUT1 glucose transporter (151), and certain calcium (199, 226) and potassium channels (52, 54). The rich cascade of adenylyl cyclases, phospholipases C, protein kinases and phosphatases, and opportunities for "cross-talk" between second messenger pathways suggests that these regulatory mechanisms have the potential to account for diverse and pleiotropic effects of ethanol in many cell systems in the body.

### D. Protein Kinase A

Adenosine 3′,5′-cyclic monophosphate-dependent protein kinase appears to mediate some of the acute and chronic cellular responses to ethanol. In cerebellar Purkinje cells, $\beta$-receptor stimulation, with presumed increases in PKA activity (166), or treatment with 8-bromo-cAMP (93) facilitates acute ethanol potentiation of GABA receptor responses. Also, PKA activity is required for ethanol inhibition of adenosine uptake in S49 (231) and NG108-15 cells (50) and ethanol-induced heterologous desensitization of cAMP signaling (238, 282). Chronic ethanol-induced heterologous desensitization is associated with a reduction of PKA activity in NG108-15 cells (50), and tolerance of the adenosine transporter to ethanol inhibition develops when cAMP-dependent phosphorylation is reduced (50) or absent (231). Recent evidence indicates that some of the chronic effects of ethanol may be due to ethanol-induced translocation of the PKA catalytic subunit, C$\alpha$, to the nucleus of ethanol-treated cells (81). C$\alpha$ remains sequestered in the nucleus as long as ethanol is present. This may account for reduced PKA-mediated phosphorylation of cytoplasmic and membrane proteins and may contribute to the diverse changes in cellular function and gene expression produced by ethanol.

### E. Protein Kinase C

There is substantial evidence that PKC is involved in many cellular responses to ethanol. Protein kinase C has been implicated in the ethanol sensitivity of voltage-dependent calcium channels (19, 205), $GABA_A$ receptors (121, 180, 343, 359), 5-$HT_{1C}$ and muscarinic $M_1$ receptors (303), glutamate receptors (79), and tolerance of the adenosine transporter to ethanol inhibition (unpublished observations). In addition, PKC appears to be required for a transient ethanol-induced decrease in cAMP levels in

human platelets (68) and for phospholipase C activation (146). Anesthetic agents and high concentrations of ethanol inhibit PKC directly (317). The levels of two PKC isozymes, $\delta$ and $\epsilon$, are increased in PC12 cells (292) and in NG108-15 cells (unpublished observations) after chronic exposure to ethanol. Increased activity of specific PKC isozymes may underlie some of the functional consequences of chronic ethanol exposure, as appears to be the case for ethanol's effects on neurite outgrowth.

### F. Protein Kinase C-Dependent Neurite Outgrowth

Prolonged exposure to ethanol increases the growth of dendrites and axons (neurites) in several brain regions of both adult and developing animals (28, 216, 261, 340, 362). Increases in neurite length probably disturb neuronal function by delaying electrical conduction and by interfering with remodeling of synapses during development (277) and learning (7, 259). This kind of synaptic plasticity could contribute to the development of tolerance and dependence (310) as well as cognitive dysfunction in alcoholic adults with dementia and in children with the fetal alcohol syndrome. Using the neural cell line PC12 to study mechanisms by which ethanol regulates neurite growth, Messing et al. (203) found that ethanol markedly enhances neurite outgrowth stimulated by nerve growth factor or basic fibroblast growth factor, apparently via a PKC-dependent stimulation of mitogen-activated protein kinases (291). This enhancement is prevented by inhibitors of PKC or by depleting cells of PKC (293). Chronic exposure to ethanol increases PKC-$\delta$ and PKC-$\epsilon$ isoenzymes, and selective overexpression of PKC-$\epsilon$ mimics the effect of ethanol and promotes neurite outgrowth. Overexpression of PKC-$\delta$ does not (132). In addition, expression of a PKC-$\epsilon$-derived dominant-interfering peptide prevents enhancement of neurite outgrowth by ethanol (R. O. Messing, unpublished observations). These findings suggest that enhancement of growth factor-induced neurite outgrowth is mediated by ethanol-induced increases in PKC-$\epsilon$. It remains to be determined whether upregulation of PKC-$\delta$ contributes to other cellular responses to chronic ethanol exposure, such as chronic ethanol-induced upregulation of calcium channels (see sect. VII*A*).

Current concepts suggest that specific translocation of protein kinases to anchoring proteins may determine the specificity of protein kinase-regulated events (219). Indeed, an important effect of ethanol probably involves PKA (81) and PKC translocation to specific phosphorylation sites (67, 143, 316). It is possible, therefore, that inhibitors of the interaction between specific kinases and anchoring proteins could be developed as therapeutic agents to specifically block adverse CNS responses to ethanol and attenuate some of the neurological complications of alcoholism.

### G. Regulation of Gene Expression

In addition to the acute effects of ethanol on cellular signaling, changes in second messengers and protein kinase activities also could be responsible for longer term regulation of cellular function by altering gene expression. Alcoholics acquire extraordinary tolerance to the intoxicating effects of ethanol, usually associated with physical dependence and uncontrolled craving to continue drinking. In addition, late manifestations of alcoholism include several neurological disorders. Therefore, investigators have begun to search for ethanol-induced changes in gene expression in the nervous system that might underlie some of these adaptive responses to heavy drinking. A reduction in the GTP binding subunit $G_s\alpha$ (220) and/or an increase in $G_i\alpha$ (40) of the heterotrimeric GTP binding proteins appears to account for heterologous desensitization of cAMP signaling caused by chronic exposure to ethanol. Chronic ethanol exposure has also been reported to alter the expression of genes for the major histocompatibility complex antigen (257), proopiomelanocortin (58), glucose transporter (GLUT1) (314), and glial fibrillary acidic protein (88). Recently, Miles et al. (212) have identified an ethanol-responsive gene for a phosducin-like protein with the potential to modulate GTP-binding protein functions and signal transduction (307). Prolonged exposure to ethanol also results in increased expression of the $\delta$- and $\epsilon$-isoforms of PKC (292), another major signaling mechanism. In addition, chronic ethanol-induced decreases in the $\alpha$-subunit of the $GABA_A$ receptor (24, 124, 141, 208, 221) and increases in opioid (37) and NMDA (334) receptors may contribute to tolerance and dependence. Chronic ethanol-induced increases in voltage-dependent calcium channels (199) and tyrosine hydroxylase (98), the rate-limiting enzyme in catecholamine biosynthesis, may account, in part, for CNS hyperactivity during alcohol withdrawal.

Membrane proteins are important targets for ethanol in the nervous system (92, 201, 358). Insertion of proteins into membranes requires specialized cellular mechanisms, including molecular chaperones that regulate protein trafficking. Miles and colleagues (129, 213-215, 365) have discovered that ethanol causes an increase in gene expression for several molecular chaperones, suggesting that ethanol-induced changes in protein trafficking contribute to the adaptive response of the brain to alcohol. This hypothesis is supported by the recent finding that ethanol induces an increase in signal peptidase mRNA levels in brain (313). Specific sequences in the promoter region of ethanol-responsive genes appear to be required for ethanol regulation of gene transcription (214, 346, 365), suggesting that a family of ethanol-responsive genes may be regulated by a common molecular mechanism. This will receive intense investigation as scientists use genetically manipulated animals to study ethanol's actions (357).

These findings open new avenues for potential therapy of alcoholic neurological disorders and the identification of candidate genes that may be altered in genetic alcoholism.

## X. RELEVANCE OF STUDIES IN MODEL SYSTEMS TO ALCOHOLISM

Ethanol-induced changes in cell culture have pathophysiological significance in human alcoholism. Circulating lymphocytes from actively drinking alcoholics exhibit changes similar to those in NG108-15 cells chronically exposed to ethanol (106); there is a marked reduction in cAMP signal transduction in freshly isolated lymphocytes from chronic alcoholics when compared with cells from controls and patients with nonalcoholic liver disease (75). Consistent with these findings, there is decreased prostaglandin $E_1$ receptor-stimulated adenylyl cyclase in platelet membranes isolated from alcoholics (326) and reduced adenylyl cyclase activity in lymphocyte membranes from abstinent alcoholics (345). Also, Nakamura et al. (240) have found reduced $G_s\alpha$ protein in erythrocyte membranes from alcoholics, and Wand and colleagues (345) have reported increased $G\alpha_{i\text{-}2}$ in lymphocyte membranes from abstinent alcoholics.

In addition to heterologous desensitization of cAMP production in circulating lymphocytes (75), we find that adenosine uptake in lymphocytes (107) and sealed erythrocyte membranes (unpublished observations) from alcoholics is insensitive to ethanol, whereas uptake is inhibited by ethanol in nonalcoholic controls. These studies suggest that mechanisms identified in cultured cell lines are relevant to cellular pathophysiology in human alcoholism. Such simple systems may make it possible to develop a sensitive bioassay for heavy drinking.

## XI. GENETICS AND ALCOHOLISM

Genetic factors play a role in the development of alcoholism (9). Alcoholism tends to run in families, and studies of identical twins, alcoholic parents and children, and offspring from alcoholic parents adopted into nondrinking families suggest a genetically transmitted susceptibility for alcoholism. Adoption studies of males who begin drinking at an early age provide the strongest evidence for the heritability of alcoholism. Here, alcoholism in the biologic father is a much greater predictor for alcoholism in the son than is the environment in which the boy is raised (49). Despite compelling clinical evidence, genes responsible for genetic forms of alcoholism have not been identified. An initial report linking alcoholism with a minor allele of the dopamine $D_2$ receptor gene (15) has been confirmed by others (245) but remains inconclusive because the majority of investigators in the field have not replicated these results (48, 87, 100, 101, 128, 241, 337). Indeed, there is no structural mutation in the $D_2$ receptor gene in alcoholism (99). Nevertheless, there is preliminary suggestive evidence that treatment with bromocriptine, a dopaminergic agonist, may benefit alcoholics carrying the minor allele (160). Studies of possible phenotypic markers for genetic alcoholism have been reviewed elsewhere (201).

Schuckit (308) has found that young men with a positive family history for alcoholism have a diminished ataxic response after drinking a test dose of alcohol. This apparent acute tolerance to alcohol appears to predict the development of alcoholism 8 years later (309), raising the possibility that genetic factors may contribute to complex adaptive responses to alcohol in human beings, as reported in many animal studies. All cellular and molecular functions in the brain are under genetic control, and new methodology is being developed to analyze the genetics of complex traits (157). For example, genetic mapping of quantitative trait loci is being used to identify chromosomal locations of genes that influence alcohol-related behavior, such as drinking (197) and tolerance and physical dependence (55). Moreover, selected regions of the brain in different lines of alcohol-preferring rats have fewer serotonin $5\text{-}HT_2$ receptors (190) and increased $5\text{-}HT_{1A}$ receptors (191) or changes in opioid binding (70) and prodynorphin and proenkephalin levels (246). Furthermore, genetically engineered mutant mice lacking the $\gamma$-isoform of PKC show altered behavioral responses to alcohol thought to be related to diminished $GABA_A$ receptor sensitivity (121).

Another approach is to mutate genes at random and search for subjects with altered responses to ethanol. *Drosophila* exhibit alcohol intoxication, tolerance, and withdrawal responses (U. Heberlein, unpublished observations). Regulatory genes are major targets for ethanol, and many are conserved in flies and humans. Therefore, genes identified by random mutation studies in *Drosophila* can be used to identify homologous genes in humans. Mutant flies with genetically induced changes in ethanol tolerance have been isolated, suggesting that the genes responsible for this phenotype will soon be isolated (Heberlein, unpublished observations). Such studies are another exciting advance in our quest for candidate genes that control responses to alcohol and that may also be linked to genetic alcoholism.

## XII. CONCLUSION

The most recent advances in alcohol research indicate that ethanol interacts with highly specific proteins in the membrane of neural cells, affecting ion channels, neurotransmitter receptors, transporters, and signal transduction pathways. Evidence is emerging that phosphorylation of these target proteins may regulate their sensitiv-

ity to ethanol. In addition, ethanol-induced changes in gene expression have also been identified, and genes that regulate acute and chronic responses to ethanol are candidates for genetic alcoholism. Alcohol research has come of age, moving from phenomenology to molecular mechanisms of pathophysiological significance. The next few years will be highlighted by innovative new therapies directed at alcohol-induced changes in signal transduction and genetic alcoholism.

We thank Dr. Robert Messing, Dr. Michael Miles, and Dr. George Siggins for their helpful review of this manuscript and Carol Webb for preparing the manuscript.

This work was supported, in part, by grants from the National Institute on Alcohol Abuse and Alcoholism.

## REFERENCES

1. ACQUAS, E., M. MELONI, AND G. DI CHIARA. Blockade of δ-opioid receptors in the nucleus accumbens prevents ethanol-induced stimulation of dopamine release. *Eur. J. Pharmacol.* 230: 239-241, 1993.
2. AHERN, K. V. B., H. S. LUSTIG, AND D. A. GREENBERG. Enhancement of NMDA toxicity and calcium responses by chronic exposure of cultured cortical neurons to ethanol. *Neurosci. Lett.* 165: 211-214, 1994.
3. ALTSCHULER, H. L., P. E. PHILLIPS, AND D. A. FEINHANDLER. Alteration of ethanol self-administration by naltrexone. *Life Sci.* 26: 679-688, 1980.
4. AMERI, A., AND I. JURNA. Adenosine $A_1$ and non-$A_1$ receptors: intracellular analysis of the actions of adenosine agonists and antagonists in rat hippocampal neurones. *Brain Res.* 546: 69-78, 1991.
5. ANANTHARAM, V., H. BAYLEY, A. WILSON, AND S. N. TREISTMAN. Differential effects of ethanol on electrical properties of various potassium channels expressed in oocytes. *Mol. Pharmacol.* 42: 499-505, 1992.
6. ANGELOTTI, T. P., M. D. UHLER, AND R. L. MACDONALD. Assembly of $GABA_A$ receptor subunits: analysis of transient single-cell expression utilizing a fluorescent substrate/marker gene technique. *J. Neurosci.* 13: 1418-1428, 1993.
7. BAILEY, C. H., AND M. CHEN. Long-term sensitization in *Aplysia* increases the number of presynaptic contacts onto the identified gill motor neuron L7. *Proc. Natl. Acad. Sci. USA* 85: 9356-9359, 1988.
8. BALDUINI, W., F. RENO, L. G. COSTA, AND F. CATTABENI. Developmental neurotoxicity of ethanol: further evidence for an involvement of muscarinic receptor-stimulated phosphoinositide hydrolysis. *Eur. J. Pharmacol.* 266: 283-289, 1994.
9. BALL, D. M., AND R. M. MURRAY. Genetics of alcohol misuse. *Br. Med. Bull.* 50: 18-35, 1994.
10. BENJAMIN, D., E. R. GRANT, AND L. A. POHRECKY. Naltrexone reverses ethanol-induced dopamine release in the nucleus accumbens in awake, freely moving rats. *Brain Res.* 621: 137-140, 1993.
11. BERGAMASCHI, S., F. BATTAINI, M. TRABUCCHI, M. PARENTI, C. M. LOPEZ, AND S. GOVONI. Neuronal differentiation modifies the effect of ethanol exposure on voltage-dependent calcium channels in NG108-15 cells. *Alcohol* 12: 497-503, 1995.
12. BIRNBAUMER, L., K. P. CAMPBELL, W. A. CATTERALL, M. M. HARPOLD, F. HOFMANN, W. A. HORNE, Y. MORI, A. SCHWARTZ, T. P. SNUTCH, T. TANABE, AND R. W. TSIEN. The naming of voltage-gated calcium channels. *Neuron* 13: 505-506, 1994.
13. BISSERBE, J. C., J. PATEL, AND P. J. MARANGOS. Autoradiographic localization of adenosine uptake sites in rat brain using [$^3$H]nitrobenzylthioinosine. *J. Neurosci.* 5: 544-550, 1985.
14. BLANDINA, P., J. GOLDFARB, B. CRADDOCK-ROYAL, AND J. P. GREEN. Release of endogenous dopamine by stimulation of 5-hydroxytryptamine$_3$ receptors in rat striatum. *J. Pharmacol. Exp. Ther.* 251: 803-809, 1989.
15. BLUM, K., E. P. NOBLE, P. J. SHERIDAN, A. MONTGOMERY, T. RITCHIE, P. JAGADEESWARAN, H. NOGAMI, A. H. BRIGGS, AND J. B. COHN. Allelic association of human dopamine $D_2$ receptor gene in alcoholism. *J. Am. Med. Assoc.* 263: 2055-2060, 1990.
16. BODE, D. C., AND P. B. MOLINOFF. Effects of ethanol in vitro on the β-adrenergic receptor-coupled adenylate cyclase system. *J. Pharmacol. Exp. Ther.* 246: 1040-1047, 1988.
17. BONE, G. H. A., E. MAJCHROWICZ, P. R. MARTIN, M. LINNOILA, AND D. J. NUTT. A comparison of calcium antagonists and diazepam in reducing ethanol withdrawal tremors. *Psychopharmacology* 99: 386-388, 1989.
18. BRENNAN, C. H., J. CRABBE, AND J. M. LITTLETON. Genetic regulation of dihydropyridine-sensitive calcium channels in brain may determine susceptibility to physical dependence on alcohol. *Neuropharmacology* 29: 429-432, 1990.
19. BRENNAN, C. H., AND J. M. LITTLETON. Second messengers involved in genetic regulation of the number of calcium channels in bovine adrenal chromaffin cells in culture. *Neuropharmacology* 29: 689-693, 1990.
20. BRODIE, M. S., S. A. SHEFNER, AND T. V. DUNWIDDIE. Ethanol increases the firing rate of dopamine neurons of the rat ventral tegmental area in vitro. *Brain Res.* 508: 65-69, 1990.
21. BRODIE, M. S., R. D. TRIFUNOVIC, AND S. A. SHEFNER. Serotonin potentiates ethanol-induced excitation of ventral tegmental area neurons in brain slices from three different rat strains. *J. Pharmacol. Exp. Ther.* 273: 1139-1146, 1995.
22. BROWN, S. J., S. JAMES, M. REDDINGTON, AND P. J. RICHARDSON. Both $A_1$ and $A_{2a}$ purine receptors regulate striatal acetylcholine release. *J. Neurochem.* 55: 31-38, 1990.
23. BRUNDEGE, J. M., AND T. V. DUNWIDDIE. The role of acetate as a potential mediator of the effects of ethanol in the brain. *Neurosci. Lett.* 186: 214-218, 1995.
24. BUCK, K. J., L. HAHNER, J. SIKELA, AND R. A. HARRIS. Chronic ethanol treatment alters brain levels of γ-aminobutyric $acid_A$ receptor subunit mRNAs: relationship to genetic differences in ethanol withdrawal seizure severity. *J. Neurochem.* 57: 1452-1455, 1991.
25. BUCK, K. J., AND R. A. HARRIS. Benzodiazepine agonist and inverse agonist actions on $GABA_A$ receptor-operated chloride channels. I. Acute effects of ethanol. *J. Pharmacol. Exp. Ther.* 253: 706-712, 1990.
26. BULLER, A. L., H. C. LARSON, R. A. MORRISETT, AND D. T. MONAGHAN. Glycine modulates ethanol inhibition of heteromeric *N*-methyl-D-aspartate receptors expressed in *Xenopus* oocytes. *Mol. Pharmacol.* 48: 717-723, 1995.
27. BURNASHEV, N., R. SCHOEPFER, H. MONYER, J. P. RUPPERSBERG, W. GUNTHER, P. H. SEEBURG, AND B. SAKMANN. Control by asparagine residues of calcium permeability and magnesium blockade in the NMDA receptor. *Science Wash. DC* 257: 1415-1419, 1992.
28. CADETE-LEITE, A., M. A. TAVARES, H. B. M. UYLINGS, AND M. PAULA-BARBOSA. Granule cell loss and dendritic regrowth in the hippocampal dentate gyrus of the rat after chronic alcohol consumption. *Brain Res.* 473: 1-14, 1988.
29. CAMPBELL, A. D., AND W. J. MCBRIDE. Serotonin-3 receptor and ethanol-stimulated dopamine release in the nucleus accumbens. *Pharmacol. Biochem. Behav.* 51: 835-842, 1995.
30. CANDURA, S. M., L. MANZO, AND L. G. COSTA. Inhibition of muscarinic receptor- and G-protein-dependent phosphoinositide metabolism in cerebrocortical membranes from neonatal rats by ethanol. *Neurotoxicology* 13: 281-288, 1992.
31. CARMICHAEL, F. J., Y. ISRAEL, M. CRAWFORD, K. MINHAS, V. SALDIVIA, S. SANDRIN, P. CAMPISI, AND H. ORREGO. Central nervous system effects of acetate: contribution to the central effects of ethanol. *J. Pharmacol. Exp. Ther.* 259: 403-408, 1991.
32. CARMICHAEL, F. J., Y. ISRAEL, V. SALDIVIA, H. G. GILES, S. MEGGIORINI, AND H. ORREGO. Blood acetaldehyde and the ethanol-induced increase in splanchnic circulation. *Biochem. Pharmacol.* 36: 2673-2678, 1987.
33. CARMICHAEL, F. J., V. SALDIVIA, G. A. VARGHESE, Y. ISRAEL, AND H. ORREGO. Ethanol-induced increase in portal blood flow: role of acetate and $A_1$- and $A_2$-adenosine receptors. *Am. J. Physiol.* 255 (*Gastrointest. Liver Physiol.* 18): G417–G423, 1988.

34. CATTERALL, W. A. Structure and function of voltage-gated ion channels. *Annu. Rev. Biochem.* 64: 493-531, 1995.
35. CHANDLER, L. J., H. NEWSOM, C. SUMNERS, AND F. CREWS. Chronic ethanol exposure potentiates NMDA excitotoxicity in cerebral cortical neurons. *J. Neurochem.* 60: 1578-1581, 1993.
36. CHANDLER, L. J., C. SUMNERS, AND F. T. CREWS. Ethanol inhibits NMDA receptor-mediated excitotoxicity in rat primary neuronal cultures. *Alcohol. Clin. Exp. Res.* 17: 54-60, 1993.
37. CHARNESS, M., G. HU, R. H. EDWARDS, AND L. A. QUERIMIT. Ethanol increases $\delta$-opioid receptor gene expression in neuronal cell lines. *Mol. Pharmacol.* 44: 1119-1127, 1993.
38. CHARNESS, M. E., A. S. GORDON, AND I. DIAMOND. Ethanol modulation of opiate receptors in cultured neural cells. *Science Wash. DC* 222: 1246-1248, 1983.
39. CHARNESS, M. E., L. A. QUERIMIT, AND I. DIAMOND. Ethanol increases the expression of functional $\delta$-opioid receptors in neuroblastoma $\times$ glioma NG108-15 hybrid cells. *J. Biol. Chem.* 261: 3164-3169, 1986.
40. CHARNESS, M. E., L. A. QUERIMIT, AND M. HENTELEFF. Ethanol differentially regulates G proteins in neural cells. *Biochem. Biophys. Res. Commun.* 155: 138-143, 1988.
41. CHARNESS, M. E., R. P. SIMON, AND D. A. GREENBERG. Ethanol and the nervous system. *N. Engl. J. Med.* 321: 442-454, 1989.
42. CHEN, C., M. KANO, A. ABELIOVICH, L. CHEN, S. W. BAO, J. J. KIM, K. HASHIMOTO, R. F. THOMPSON, AND S. TONEGAWA. Impaired motor coordination correlates with persistent multiple climbing fiber innervation in PKC$\gamma$ mutant mice. *Cell* 83: 1233-1242, 1995.
43. CHEPKOVA, A. N., N. V. DOREULEE, S. S. TROFIMOV, T. A. GUDASHEVA, R. U. OSTROVSKAYA, AND V. G. SKREBITSKY. Nootropic compound L-pyroglutamyl-D-alanine-amide restores hippocampal long-term potentiation by exposure to ethanol in rats. *Neurosci. Lett.* 188: 163-166, 1995.
44. CHIK, C. L., Q.-Y. LIU, M. GIRARD, E. KARPINSKI, AND A. K. HO. Inhibitory action of ethanol on L-type $Ca^{2+}$ channels and $Ca^{2+}$-dependent guanosine 3′,5′-monophosphate accumulation in rat pinealocytes. *Endocrinology* 131: 1895-1902, 1992.
45. CHU, B., V. ANANTHARAM, AND S. N. TREISTMAN. Ethanol inhibition of recombinant heterometric NMDA channels in the presence and absence of modulators. *J. Neurochem.* 65: 140-148, 1995.
46. CICCOCIOPPO, R., I. PANOCKA, E. STEFANI, G. L. GESSA, AND M. MASSI. Low responsiveness to agents evoking 5-$HT_2$ receptor-mediated behaviors in Sardinian alcohol-preferring rats. *Pharmacology* 51: 21-27, 1995.
47. CLAPHAM, D. E. Calcium signaling. *Cell* 80: 259-268, 1995.
48. CLONINGER, C. R. $D_2$ dopamine receptor gene is associated but not linked with alcoholism. *J. Am. Med. Assoc.* 266: 1833-1834, 1991.
49. CLONINGER, C. R. Neurogenetic adaptive mechanisms in alcoholism. *Science Wash. DC* 236: 410-416, 1987.
50. COE, I. R., D. P. DOHRMAN, I. DIAMOND, AND A. S. GORDON. Activation of cAMP-dependent protein kinase reverses tolerance of the nucleoside transporter to ethanol. *J. Pharmacol. Exp. Ther.* 276: 365-369, 1995.
51. CORREIA-DE, S. P., AND J. A. RIBEIRO. Tonic adenosine $A_{2A}$ receptor activation modulates nicotinic autoreceptor function at the rat neuromuscular junction. *Eur. J. Pharmacol.* 271: 349-355, 1994.
52. COVARRUBIAS, M., AND E. RUBIN. Ethanol selectively blocks a noninactivating $K^+$ current expressed in *Xenopus* oocytes. *Proc. Natl. Acad. Sci. USA* 90: 6957-6960, 1993.
53. COVARRUBIAS, M., T. B. VYAS, L. ESCOBAR, AND A. WEI. Alcohols inhibit a cloned potassium channel at a discrete saturable site. *J. Biol. Chem.* 270: 19408-19416, 1995.
54. COVARRUBIAS, M., A. WEI, L. SALKOFF, AND T. B. VYAS. Elimination of rapid potassium channel inactivation by phosphorylation of the inactivation gate. *Neuron* 13: 1403-1412, 1994.
55. CRABBE, J. C., J. K. BELKNAP, AND K. J. BUCK. Genetic animal models of alcohol and drug abuse. *Science Wash. DC* 264: 1715-1723, 1994.
56. CRISWELL, H. E., P. E. SIMSON, G. E. DUNCAN, T. J. McCOWN, J. S. HERBERT, A. L. MORROW, AND G. R. BREESE. Molecular basis for regionally specific action of ethanol on $\gamma$-aminobutyric acid$_A$ receptors: generalization to other ligand-gated ion channels. *J. Pharmacol. Exp. Ther.* 267: 522-537, 1993.
57. CULLEN, N., AND P. L. CARLEN. Electrophysiological actions of acetate, a metabolite of ethanol, on hippocampal dentate granule neurons: interactions with adenosine. *Brain Res.* 588: 49-57, 1992.
58. CUNHA, R. A., B. JOHANSSON, I. VAN DER PLOEG, A. M. SEBASTIAO, J. A. RIBEIRO, AND B. B. FREDHOLM. Evidence for functionally important adenosine $A_{2a}$ receptors in the rat hippocampus. *Brain Res.* 649: 208-216, 1994.
59. DAR, M. S. Central nervous system effects and behavioral interactions with ethanol of centrally administered dilazep and its metabolites in mice. *Eur. J. Pharmacol.* 164: 303-313, 1989.
60. DAR, M. S. Central adenosinergic system involvement in ethanol-induced motor incoordination in mice. *J. Pharmacol. Exp. Ther.* 255: 1202-1209, 1990.
61. DAR, M. S. Functional correlation between subclasses of brain adenosine receptor affinities and ethanol-induced motor incoordination in mice. *Pharmacol. Biochem. Behav.* 37: 747-753, 1990.
62. DAR, M. S., AND M. CLARK. Tolerance to adenosine's accentuation of ethanol-induced motor incoordination in ethanol-tolerant mice. *Alcohol. Clin. Exp. Res.* 16: 1138-1146, 1992.
63. DAR, M. S., M. JONES, G. CLOSE, S. J. MUSTAFA, AND W. R. WOOLES. Behavioral interactions of ethanol and methylxanthines. *Psychopharmacology* 91: 1-4, 1987.
64. DAVIS-COX, M. I., T. L. FLETCHER, J. N. TURNER, D. SZAROWSKI, AND W. SHAIN. Three-day exposure to low-dose ethanol alters guanine nucleotide binding protein expression in the developing rat hippocampus. *J. Pharmacol. Exp. Ther.* 276: 758-764, 1996.
65. DE BEUN, R., R. SCHNEIDER, A. KLEIN, A. LOHMANN, AND J. DE VRY. Effects of nimodipine and other calcium channel antagonists in alcohol-preferring AA rats. *Alcohol* 13: 263-271, 1996.
66. DECKERT, J., J.-C. BISSERBE, E. KLEIN, AND P. J. MARRANGOS. Adenosine uptake sites in brain: regional distribution of putative subtypes in relationship to adenosine $A_1$-receptors. *J. Neurosci.* 8: 2338-2349, 1988.
67. DEPETRILLO, P. B., AND C. S. LIOU. Ethanol exposure increases total protein kinase C activity in human lymphocytes. *Alcohol. Clin. Exp. Res.* 17: 351-354, 1993.
68. DEPETRILLO, P. B., AND R. M. SWIFT. Ethanol exposure results in a transient decrease in human platelet cAMP levels: evidence for a protein kinase C mediated process. *Alcohol. Clin. Exp. Res.* 16: 290-294, 1992.
69. DEVAUD, L. L., F. D. SMITH, D. R. GRAYSON, AND A. L. MORROW. Chronic ethanol consumption differentially alters the expression of $GABA_A$ receptor subunit mRNAs in rat cerebral cortex: competitive, quantitative RT/PCR analysis. *Mol. Pharmacol.* 48: 861–868, 1995.
70. DE WAELE, J. P., K. KIIANMAA, AND C. GIANOULAKIS. Distribution of the mu and delta opioid binding sites in the brain of the alcohol-preferring AA and alcohol-avoiding ANA lines of rats. *J. Pharmacol. Exp. Ther.* 275: 518-527, 1995.
71. DIAMOND, I. Alcohol neurotoxicity. Diseases of the nervous system. *Clin. Neurobiol.* 2: 1259-1273, 1992.
72. DIAMOND, I. Alcoholism and alcohol abuse. In: *Cecil's Textbook of Medicine*, edited by J. B. Wyngaarden, L. H. Smith, Jr., and F. Plum. Philadelphia, PA: Saunders, 1996, vol. 20, p. 47-49.
73. DIAMOND, I., AND A. S. GORDON. The role of adenosine in mediating cellular and molecular responses to ethanol. In: *Toward a Molecular Basis of Alcohol Use and Abuse. 86th Nobel Symposium*, edited by B. Jansson, H. Jornvall, U. Rydberg, L. Terenius, and B. L. Vallee. Stockholm: Karolinska Institute, 1994, p. 175-184.
74. DIAMOND, I., L. NAGY, D. MOCHLY-ROSEN, AND A. GORDON. The role of adenosine and adenosine transport in ethanol-induced cellular tolerance and dependence. In: *Molecular and Cellular Mechanisms of Alcohol and Anesthetics*, edited by E. Rubin, K. W. Miller, and S. H. Roth. New York: Ann. NY Acad. Sci., 1991, vol. 625, p. 473-487, 1991.
75. DIAMOND, I., B. WRUBEL, E. ESTRIN, AND A. S. GORDON. Basal and adenosine receptor-stimulated levels of cAMP are reduced in lymphocytes from alcoholic patients. *Proc. Natl. Acad. Sci. USA* 84: 1413-1416, 1987.
77. DIANA, M., M. PISTIS, A. MUNTONI, AND G. GESSA. Mesolimbic

dopaminergic reduction outlasts ethanol withdrawal syndrome: evidence of protracted abstinence. *Neuroscience* 71: 411-415, 1996.
78. DILDY, J. E., AND S. W. LESLIE. Ethanol inhibits NMDA-induced increases in free intracellular $Ca^{2+}$ in dissociated brain cells. *Brain Res.* 499: 383-387, 1989.
79. DILDY-MAYFIELD, J. E., AND R. A. HARRIS. Ethanol inhibits kainate responses of glutamate receptors expressed in *Xenopus* oocytes: role of calcium and protein kinase C. *J. Neurosci.* 15: 3162-3171, 1995.
80. DILDY-MAYFIELD, J. E., T. MACHU, AND S. W. LESLIE. Ethanol and voltage- or receptor-mediated increases in cytosolic $Ca^{2+}$ in brain cells. *Alcohol* 9: 63-69, 1991.
81. DOHRMAN, D. P., I. DIAMOND, AND A. S. GORDON. Ethanol causes translocation of cAMP-dependent protein kinase catalytic subunit to the nucleus. *Proc. Natl. Acad. Sci. USA.* In press.
82. DOLIN, S. J., AND H. J. LITTLE. Are changes in neuronal calcium channels involved in ethanol tolerance? *J. Pharmacol. Exp. Ther.* 250: 985-991, 1989.
83. DUNWIDDIE, T. V. *The Physiological Role of Adenosine in the Central Nervous System.* Denver, CO: Academic, 1985, vol. 27, p. 63-139.
84. DYR, W., W. J. MCBRIDE, L. LUMENG, T. K. LI, AND J. M. MURPHY. Effects of $D_1$ and $D_2$ dopamine receptor agents on ethanol consumption in the high-alcohol-drinking (HAD) line of rats. *Alcohol* 10: 207-212, 1993.
85. EBERT, B., K. A. WAFFORD, P. J. WHITING, P. KROGSGAARD-LARSEN, AND J. A. KEMP. Molecular pharmacology of $\gamma$-aminobutyric acid type A receptor agonists and partial agonists in oocytes injected with different $\alpha$, $\beta$, and $\gamma$ receptor subunit combinations. *Mol. Pharmacol.* 46: 957-963, 1994.
86. FERRE, S., G. VON EULER, B. JOHANSSON, B. B. FREDHOLM, AND K. FUXE. Stimulation of high-affinity adenosine $A_2$ receptors decreases the affinity of dopamine $D_2$ receptors in rat striatal membranes. *Proc. Natl. Acad. Sci. USA* 88: 7238-7241, 1991.
87. FINCKH, U., O. VON WIDDERN, V. GIRALDO, M. J. PODSCHUS, P. DUFEU, T. SANDER, H. HARMS, L. G. SCHMIDT, H. ROMMEL-SPACHER, AND A. ROLFS. No association of the structural dopamine $D_2$ receptor (DRD2) variant 311Cys with alcoholism. *Alcohol. Clin. Exp. Res.* 20: 528-532, 1996.
88. FLETCHER, T. L., AND W. SHAIN. Ethanol-induced changes in astrocyte gene expression during rat central nervous system development. *Alcohol. Clin. Exp. Res.* 17: 993-1001, 1993.
89. FORREST, D., M. YUZAKI, H. D. SOARES, L. NG, D. C. LUK, M. SHENG, C. L. STEWART, J. I. MORGAN, J. A. CONNOR, AND T. CURRAN. Targeted disruption of NMDA receptor 1 gene abolishes NMDA response and results in neonatal death. *Neuron* 13: 325-338, 1994.
90. FRANKS, N. P., AND W. R. LIEB. Mapping of general anaesthetic target sites provides a molecular basis for cutoff effects. *Nature Lond.* 316: 349-351, 1985.
91. FRANKS, N. P., AND W. R. LIEB. Stereospecific effects of inhalational general anesthetic optical isomers on nerve ion channels. *Science Wash. DC* 254: 427-430, 1991.
92. FRANKS, N. P., AND W. R. LIEB. Molecular and cellular mechanisms of general anesthesia. *Nature Lond.* 367: 607-614, 1994.
93. FREUND, R. K., AND M. R. PALMER. 8-Bromo-cAMP mimics $\beta$-adrenergic sensitization of GABA responses to ethanol in cerebellar Purkinje neurons in vivo. *Alcohol. Clin. Exp. Res.* 20: 408-412, 1996.
94. FROEHLICH, J. C., J. HARTS, L. LUMENG, AND T.-K. LI. Naloxone attenuates voluntary ethanol intake in rats selectively bred for high ethanol preference. *Pharmacol. Biochem. Behav.* 35: 385-390, 1990.
95. GALLIMBERTI, L., M. FERRI, S. D. FERRARA, F. FADDA, AND G. L. GESSA. Gamma-hydroxybutyric acid in the treatment of alcohol dependence: a double-blind study. *Alcohol. Clin. Exp. Res.* 16: 673-676, 1992.
96. GARDELL, L. R., C. L. HUBBELL, AND L. D. REID. Naltrexone persistently reduces rats' intake of a palatable alcoholic beverage. *Alcohol. Clin. Exp. Res.* 20: 584-588, 1996.
97. GATTO, G. J., W. J. MCBRIDE, J. M. MURPHY, L. LUMENG, AND T.-K. LI. Ethanol self-infusion into the ventral tegmental area by alcohol-preferring rats. *Alcohol* 11: 557-564, 1994.
98. GAYER, G. G., A. GORDON, AND M. F. MILES. Ethanol increases tyrosine hydroxylase gene expression in N1E-115 neuroblastoma cells. *J. Biol. Chem.* 266: 22279-22284, 1991.
99. GEJMAN, P. V., A. RAM, J. GELERNTER, E. FRIEDMAN, Q. CAO, D. PICKAR, K. BLUM, E. P. NOBLE, H. R. KRANZLER, S. O'MALLEY, D. H. HAMER, F. WHITSITT, P. RAO, L. E. DELISI, M. VIRKKUNEN, M. LINNOILA, D. GOLDMAN, AND E. S. GERSHON. No structural mutation in the dopamine $D_2$ receptor gene in alcoholism or schizophrenia. *J. Am. Med. Assoc.* 271: 204-208, 1994.
100. GELERNTER, J., D. GOLDMAN, AND N. RISCH. The A1 allele at the $D_2$ dopamine receptor gene and alcoholism. *J. Am. Med. Assoc.* 269: 1673-1678, 1993.
101. GELERNTER, J., S. O'MALLEY, N. RISCH, H. R. KRANZLER, J. KRYSTAL, K. MERIKANGAS, J. L. KENNEDY, AND K. K. KIDD. No association between an allele at the $D_2$ dopamine receptor gene (DRD2) and alcoholism. *J. Am. Med. Assoc.* 266: 1801-1807, 1991.
102. GEORGE, S. R., T. FAN, G. Y. NG, S. Y. JUNG, B. F. O'DOWD, AND C. A. NARANJO. Low endogenous dopamine function in brain predisposes to high alcohol preference and consumption: reversal by increasing synaptic dopamine. *J. Pharmacol. Exp. Ther.* 273: 373-379, 1995.
103. GIVENS, B., AND K. MCMAHON. Ethanol suppresses the induction of long-term potentiation in vivo. *Brain Res.* 688: 27-33, 1995.
104. GOLDSTEIN, D. B. Ethanol-induced adaptation in biological membranes. *Ann. NY Acad. Sci.* 492: 103-111, 1986.
105. GOLDSTEIN, D. B., AND J. H. CHIN. Interaction of ethanol with biological membranes. *Federation Proc.* 40: 2073-2076, 1981.
106. GORDON, A. S., K. COLLIER, AND I. DIAMOND. Ethanol regulation of adenosine receptor-stimulated cAMP levels in a clonal neural cell line: an in vitro model of cellular tolerance to ethanol. *Proc. Natl. Acad. Sci. USA* 83: 2105-2108, 1986.
107. GORDON, A. S., S. W. KRAUSS, L. NAGY, AND I. DIAMOND. Nucleoside transport in lymphocytes from alcoholics and non-alcoholics. In: *Advances in Experimental Medicine and Biology. Purine and Pyrimidine Metabolism in Man VII.* New York: Plenum, 1991, vol. 309A, p. 387-390.
108. GORDON, A. S., D. MOCHLY-ROSEN, AND I. DIAMOND. Alcoholism: a possible G-protein disorder. *G Proteins* 8: 191-216, 1992.
109. GOTO, M., J. J. LEMASTERS, AND R. G. THURMAN. Activation of voltage-dependent calcium channels in Kupffer cells by chronic treatment with alcohol in the rat. *J. Pharmacol. Exp. Ther.* 267: 1264-1268, 1993.
110. GRANT, A. J., G. KOSKI, AND S. N. TREISTMAN. Effect of chronic ethanol on calcium currents and calcium uptake in undifferentiated PC12 cells. *Brain Res.* 600: 280-284, 1993.
111. GRANT, K. A., AND J. E. BARRETT. Blockade of the discriminative stimulus effects of ethanol with 5-$HT_3$ receptor antagonists. *Psychopharmacology* 104: 451-456, 1991.
112. GULYA, K., K. A. GRANT, P. VALVERIUS, P. L. HOFFMAN, AND B. TABAKOFF. Brain regional specificity and time-course of changes in the NMDA receptor-ionophore complex during ethanol withdrawal. *Brain Res.* 547: 129-134, 1991.
113. GUPPY, L. J., J. C. CRABBE, AND J. M. LITTLETON. Time course and genetic variation in the regulation of calcium channel antagonist binding sites in rodent tissues during the induction of ethanol physical dependence and withdrawal. *Alcohol Alcohol.* 30: 607-615, 1995.
114. HABUCHI, Y., T. FURUKAWA, H. TANAKA, L. L. LU, J. MORIKAWA, AND M. YOSHIMURA. Ethanol inhibition of $Ca^{2+}$ and $Na^+$ currents in the guinea-pig heart. *Eur. J. Pharmacol.* 292: 143-149, 1995.
115. HALL, A. C., W. R. LIEB, AND N. P. FRANKS. Insensitivity of P-type calcium channels to inhalational and intravenous general anesthetics. *Anesthesiology* 81: 117-123, 1994.
116. HALLIDAY, G., K. BAKER, AND C. HARPER. Serotonin and alcohol-related brain damage. *Metab. Brain Dis.* 10: 25-30, 1995.
117. HALLIDAY, G., J. ELLIS, R. HEARD, D. CAINE, AND C. HARPER. Brain stem serotonergic neurons in chronic alcoholics with and without the memory impairment of Korsakoff's psychosis. *J. Neuropathol. Exp. Neurol.* 52: 567-579, 1993.
118. HARPER, C., AND J. KRIL. Patterns of neuronal loss in the cerebral cortex in chronic alcoholic patients. *J. Neurol. Sci.* 92: 81-89, 1989.
119. HARRIS, R. A. Transfected cells for study of alcohol actions on $GABA_A$ receptors. *Addict. Biol.* 1: 157-163, 1996.

120. HARRIS, R. A., R. BURNETT, S. McQUILKIN, A. McCLARD, AND F. R. SIMON. Effects of ethanol on membrane order: fluorescence studies. *Alcohol Cell* 492: 125-133, 1987.
121. HARRIS, R. A., S. J. McQUILKIN, R. PAYLOR, A. ABELIOVICH, S. TONEGAWA, AND J. M. WEHNER. Mutant mice lacking the $\gamma$ isoform of protein kinase C show decreased behavioral actions of ethanol and altered function of $\gamma$-aminobutyrate type A receptors. *Proc. Natl. Acad. Sci. USA* 92: 3658-3662, 1995.
122. HARRIS, R. A., W. R. PROCTOR, S. J. McQUILKIN, R. L. KLEIN, M. P. MASCIA, V. WHATLEY, P. J. WHITING, AND T. V. DUNWIDDIE. Ethanol increases $GABA_A$ responses in cells stably transfected with receptor subunits. *Alcohol. Clin. Exp. Res.* 19: 226-232, 1995.
123. HIJIOKA, T., M. GOTO, J. J. LEMASTERS, AND R. G. THURMAN. Effect of short-term ethanol treatment on voltage-dependent calcium channels in Kupffer cells. *Hepatology* 18: 400-405, 1993.
124. HIROUCHI, M., T. HASHIMOTO, AND K. KURIYAMA. Alteration of $GABA_A$ receptor $\alpha_1$-subunit mRNA in mouse brain following continuous ethanol inhalation. *Eur. J. Pharmacol.* 247: 127-130, 1993.
125. HOFFMAN, P. L., K. R. IORIO, L. D. SNELL, AND B. TABAKOFF. Attenuation of glutamate-induced neurotoxicity in chronically ethanol-exposed cerebellar granule cells by NMDA receptor antagonists and ganglioside $GM_1$. *Alcohol. Clin. Exp. Res.* 19: 721-726, 1995.
126. HOFFMAN, P. L., C. S. RABE, F. MOSES, AND B. TABAKOFF. *N*-methyl-D-aspartate receptors and ethanol: inhibition of calcium flux and cyclic GMP production. *J. Neurochem.* 52: 1937-1940, 1989.
127. HOFFMAN, P. W., A. RAVINDRAN, AND R. L. HUGANIR. Role of phosphorylation in desensitization of acetylcholine receptors expressed in *Xenopus* oocytes. *J. Neurosci.* 14: 4185-4195, 1994.
128. HOLDEN, C. A cautionary genetic tale: the sobering story of $D_2$. *Science Wash. DC* 264: 1696, 1994.
129. HSIEH, K.-P., N. WILKE, A. HARRIS, AND M. F. MILES. Interaction of ethanol with inducers of glucose-regulated stress proteins: ethanol potentiates inducers of grp78 transcription. *J. Biol. Chem.* 271: 2709-2716, 1996.
130. HU, G., L. A. QUERIMIT, L. A. DOWNING, AND M. E. CHARNESS. Ethanol differentially increases $\alpha_2$-adrenergic and muscarinic acetylcholine receptor gene expression in NG108-15 cells. *J. Biol. Chem.* 268: 23441-23447, 1993.
131. HUANG, G.-J., AND J. J. McARDLE. Chronic ingestion of ethanol increases the number of $Ca^{2+}$ channels of hippocampal neurons of long-sleep but not short-sleep mice. *Brain Res.* 615: 328-330, 1993.
132. HUNDLE, B., T. McMAHON, J. DADGAR, AND R. O. MESSING. Overexpression of $\epsilon$-protein kinase C enhances nerve growth factor-induced phosphorylation of mitogen-activated protein kinases and neurite outgrowth. *J. Biol. Chem.* 270: 30134-30140, 1995.
133. ILES, K. E., AND L. E. NAGY. Chronic ethanol feeding increases the quantity of Galphas-protein in rat liver plasma membranes. *Hepatology* 21: 1154-1160, 1995.
134. IORIO, K. R., L. REINLIB, B. TABAKOFF, AND P. L. HOFFMAN. Chronic exposure of cerebellar granule cells to ethanol results in increased *N*-methyl-D-aspartate receptor function. *Mol. Pharmacol.* 41: 1142-1148, 1992.
135. JANKOWSKA, E., AND W. KOSTOWSKI. The effect of tropisetron injected into the nucleus accumbens septi on ethanol consumption in rats. *Alcohol* 12: 195-198, 1995.
136. JENAB, S., B. KEST, S. O. FRANKLIN, AND C. E. INTURRISI. Quantitative distribution of the delta opioid receptor mRNA in the mouse and rat CNS. *Life Sci.* 56: 2343-2355, 1995.
137. JOHNSON, B. A., G. M. CAMPLING, P. GRIFFITHS, AND P. J. COWEN. Attenuation of some alcohol-induced mood changes and the desire to drink by $5\text{-}HT_3$ receptor blockade: a preliminary study in healthy male volunteers. *Psychopharmacology* 112: 142-144, 1993.
138. JULIUS, D. Molecular biology of serotonin receptors. *Annu. Rev. Neurosci.* 14: 335-360, 1991.
139. KANO, M., K. HASHIMOTO, C. CHEN, A. ABELIOVICH, A. AIBA, H. KURIHARA, M. WATANABE, Y. INOUE, AND S. TONEGAWA. Impaired synapse elimination during cerebellar development in PKCgamma mutant mice. *Cell* 83: 1223-1231, 1995.
140. KARUNANITHI, S., N. A. LAVIDIS, AND M. R. BENNETT. The effect of adenosine on spontaneous and evoked quantal secretion from different release sites of amphibian motor-nerve terminals. *Neurosci. Lett.* 147: 49-52, 1992.
141. KEIR, W. J., AND A. L. MORROW. Differential expression of $GABA_A$ receptor subunit mRNAs in ethanol-naive withdrawal seizure resistant (WSR) vs. withdrawal seizure prone (WSP) mouse brain. *Mol. Brain Res.* 25: 200-208, 1994.
142. KELLY, E., P. K. HARRISON, AND R. J. WILLIAMS. Effects of acute and chronic ethanol on cyclic AMP accumulation in NG108-15 cells: differential dependence of changes on extracellular adenosine. *Br. J. Pharmacol.* 114: 1433-1441, 1995.
143. KHARBANDA, S., T. NAKAMURA, AND D. KUFE. Induction of the c-*jun* proto-oncogene by a protein kinase C-dependent mechanism during exposure of human epidermal keratinocytes to ethanol. *Biochem. Pharmacol.* 45: 675-681, 1993.
144. KIIANMAA, K., M. NURMI, I. NYKÄNEN, AND J. D. SINCLAIR. Effect of ethanol on extracellular dopamine in the nucleus accumbens of alcohol-preferring AA and alcohol-avoiding ANA rats. *Pharmacol. Biochem. Behav.* 52: 29-34, 1995.
145. KIM, W.-K., M. H. HAWTHORN, AND R. A. RABIN. Chronic ethanol exposure potentiates muscarinic receptor and $\alpha_2$-adrenoceptor-mediated inhibition of cAMP accumulation in PC12 cells. *Eur. J. Pharmacol.* 247: 89-92, 1993.
146. KISS, Z., AND N. GARAMSZEGI. Overexpression of protein kinase C-$\epsilon$ enhances the stimulatory effect of ethanol on phospholipase C-mediated hydrolysis of phosphatidylethanolamine in NIH 3T3 fibroblasts. *FEBS Lett.* 333: 229-232, 1993.
147. KOPPI, S., G. EBERHARDT, R. HALLER, AND P. KÖNIG. Calcium-channel blocking agent in the treatment of acute alcohol withdrawal-caroverine versus meprobamate in a randomized double-blind study. *Neuropsychobiology* 17: 49-52, 1987.
148. KOSTOWSKI, W., W. DYR, AND P. KZR. The abilities of $5\text{-}HT_3$ receptor antagonist ICS 205-930 to inhibit alcohol preference and withdrawal seizures in rats. *Alcohol* 10: 369-373, 1993.
149. KOVACS, K. A., T. J. KAVANAGH, AND L. G. COSTA. Ethanol inhibits muscarinic receptor-stimulated phosphoinositide metabolism and calcium mobilization in rat primary cortical cultures. *Neurochem. Res.* 20: 939-949, 1995.
150. KRAUS, J. E., G.-C. YEH, D. W. BONHAUS, J. V. NADLER, AND J. O. McNAMARA. Kindling induces the long-lasting expression of a novel population of NMDA receptors in hippocampal region CA3. *J. Neurosci.* 14: 4196-4205, 1994.
151. KRAUSS, S. W., I. DIAMOND, AND A. S. GORDON. Selective inhibition by ethanol of the type I facilitative glucose transporter (GLUT1). *Mol. Pharmacol.* 45: 1281-1286, 1994.
152. KRAUSS, S. W., R. B. GHIRNIKAR, I. DIAMOND, AND A. S. GORDON. Inhibition of adenosine uptake by ethanol is specific for one class of nucleoside transporters. *Mol. Pharmacol.* 44: 1021-1026, 1993.
153. KRISHNAN-SARIN, S., S. L. JING, D. L. KURTZ, M. ZWEIFEL, P. S. PORTOGHESE, T. K. LI, AND J. C. FROEHLICH. The delta opioid receptor antagonist naltrindole attenuates both alcohol and saccharin intake in rats selectively bred for alcohol preference. *Psychopharmacology* 120: 177-185, 1995.
154. KRISHNAN-SARIN, S., P. S. PORTOGHESE, T. K. LI, AND J. C. FROEHLICH. The delta2-opioid receptor antagonist naltriben selectively attenuates alcohol intake in rats bred for alcohol preference. *Pharmacol. Biochem. Behav.* 52: 153-159, 1995.
155. KUMAR, K. N., N. TILAKARATNE, P. S. JOHNSON, A. E. ALLEN, AND E. K. MICHAELIS. Cloning of cDNA for the glutamate-binding subunit of an NMDA receptor complex. *Nature Lond.* 354: 70-73, 1991.
156. KUTSUWADA, T., K. SAKIMURA, T. MANABE, C. TAKAYAMA, N. KATAKURA, E. KUSHIYA, R. NATSUME, M. WATANABE, Y. INOUE, T. YAGI, S. AIZAWA, M. ARAKAWA, H. MORI, AND M. MISHINA. Impairment of suckling response, trigeminal neuronal pattern formation, and hippocampal LTD in NMDA receptor $\epsilon 2$ subunit mutant mice. *Neuron* 16: 333-344, 1996.
157. LANDER, E. S., AND N. J. SCHORK. Genetic dissection of complex traits. *Science Wash. DC* 265: 2037-2048, 1994.
158. LARSSON, C., P. SIMONSSON, J. B. HOEK, AND C. ALLING. Ethanol inhibits the peak of muscarinic receptor-stimulated formation of inositol 1,4,5-trisphosphate in neuroblastoma SH-SY5Y cells. *Biochem. Pharmacol.* 50: 647-654, 1995.
159. LAURIE, D. J., W. WISDEN, AND P. H. SEEBURG. The distribution of thirteen $GABA_A$ receptor subunit mRNAs in the rat brain. III.

Embryonic and postnatal development. *J. Neurosci.* 12: 4151-4172, 1992.
160. LAWFORD, B. R., R. M. YOUNG, J. A. ROWELL, J. QUALICHEFSKI, B. H. FLETCHER, K. SYNDULKO, T. RITCHIE, AND E. P. NOBLE. Bromocriptine in the treatment of alcoholics with $D_2$ dopamine receptor A1 allele. *Nature Med.* 1: 337-341, 1995.
161. LE, F., P. A. WILCE, D. A. HUME, AND B. C. SHANLEY. Involvement of $\gamma$-aminobutyric acid and *N*-methyl-D-aspartate receptors in the inhibitory effect of ethanol on pentylenetetrazole-induced c-*fos* expression in rat brain. *J. Neurochem.* 59: 1309-1315, 1992.
162. LEE, R. S., S. S. SMITH, J. K. CHAPIN, B. D. WATERHOUSE, N. SHIMIZU, B. N. MADDUX, AND D. J. WOODWARD. Effects of systemic and local ethanol on responses of rat cerebellar Purkinje neurons to iontophoretically applied gamma-aminobutyric acid. *Brain Res.* 687: 1-11, 1995.
163. LEVIER, D. G., D. E. MCCOY, AND W. S. SPIELMAN. Functional localization of adenosine receptor-mediated pathways in the LLC-$PK_1$ renal cell line. *Am. J. Physiol.* 263 (*Cell Physiol.* 32): C729–C735, 1992.
164. LI, C., R. W. PEOPLES, AND F. F. WEIGHT. Alcohol action on a neuronal membrane receptor: evidence for a direct interaction with the receptor protein. *Neurobiology* 91: 8200-8204, 1994.
165. LIMA-LANDMAN, M. T. R., AND E. X. ALBUQUERQUE. Ethanol potentiates and blocks NMDA-activated single-channel currents in rat hippocampal pyramidal cells. *FEBS Lett.* 247: 61-67, 1989.
166. LIN, A. M.-Y., R. K. FREUND, B. J. HOFFER, AND E. AL. Ethanol-induced depressions of cerebellar Purkinje neurons are potentiated by $\beta$-adrenergic mechanisms in rat brain. *J. Pharmacol. Exp. Ther.* 271: 1175-1180, 1994.
167. LITTLE, H. J. Mechanisms that may underlie the behavioural effects of ethanol. *Prog. Neurobiol.* 36: 171-194, 1991.
168. LITTLE, H. J., S. J. DOLIN, AND M. J. HALSEY. Calcium channel antagonists decrease the ethanol withdrawal syndrome. *Life Sci.* 39: 2059-2065, 1986.
169. LOVINGER, D. M. Developmental decrease in ethanol inhibition of *N*-methyl-D-aspartate receptors in rat neocortical neurons: relation to the actions of ifenprodil. *J. Pharmacol. Exp. Ther.* 274: 164-172, 1995.
170. LOVINGER, D. M. Ethanol potentiation of 5-$HT_3$ receptor-mediated ion current in NCB-20 neuroblastoma cells. *Neurosci. Lett.* 122: 57-60, 1991.
171. LOVINGER, D. M. Excitotoxicity and alcohol-related brain damage. *Alcohol. Clin. Exp. Res.* 17: 19-27, 1993.
172. LOVINGER, D. M. High ethanol sensitivity of recombinant AMPA-type glutamate receptors expressed in mammalian cells. *Neurosci. Lett.* 159: 83-87, 1993.
173. LOVINGER, D. M., AND G. WHITE. Ethanol potentiation of 5-hydroxytryptamine$_3$ receptor-mediated ion current in neuroblastoma cells and isolated adult mammalian neurons. *Mol. Pharmacol.* 40: 263-270, 1991.
174. LOVINGER, D. M., G. WHITE, AND F. F. WEIGHT. Ethanol inhibits NMDA-activated ion current in hippocampal neurons. *Science Wash. DC* 243: 1721-1724, 1989.
175. LOVINGER, D. M., AND Q. ZHOU. Alcohols potentiate ion current mediated by recombinant 5-$HT_3$RA receptors expressed in a mammalian cell line. *Neuropharmacology* 33: 1567-1572, 1994.
176. LUPICA, C. R., W. R. PROCTOR, AND T. V. DUNWIDDIE. Presynaptic inhibition of excitatory synaptic transmission by adenosine in rat hippocampus: analysis of unitary EPSP variance measured by whole-cell recording. *J. Neurosci.* 12: 3753-3764, 1992.
177. LUSTIG, H. S., J. CHAN, AND D. A. GREENBERG. Ethanol inhibits excitotoxicity in cerebral cortical cultures. *Neurosci. Lett.* 135: 259-261, 1992.
178. LUSTIG, H. S., K. L. VON BRAUCHITSCH, J. CHAN, AND D. A. GREENBERG. Ethanol and excitotoxicity in cultured cortical neurons: differential sensitivity of *N*-methyl-D-aspartate and sodium nitroprusside toxicity. *J. Neurochem.* 59: 2193-2200, 1992.
179. LYNCH, M. A., E. R. ARCHER, AND J. M. LITTLETON. Increased sensitivity of transmitter release to calcium in ethanol tolerance. *Biochem. Pharmacol.* 35: 1207-1209, 1986.
180. MACDONALD, R. L. Ethanol, $\gamma$-aminobutyrate type A receptors, and protein kinase C phosphorylation. *Proc. Natl. Acad. Sci. USA* 92: 3633-3635, 1995.
181. MADAMBA, S. G., M. HSU, P. SCHWEITZER, AND G. R. SIGGINS. Ethanol enhances muscarinic cholinergic neurotransmission in rat hippocampus in vitro. *Brain Res.* 685: 21-32, 1995.
182. MADAMBA, S. G., P. SCHWEITZER, W. ZIEGLGANSBERGER, AND G. R. SIGGINS. Acamprosate (calcium acetylhomotaurinate) enhances the *N*-methyl-D-aspartate component of excitatory neurotransmission in rat hippocampal Ca1 neurons in vitro. *Alcohol. Clin. Exp. Res.* In press.
183. MALENKA, R. C. LTP and LTD: dynamic and interactive processes of synaptic plasticity. *Neuroscientist* 1: 35-42, 1995.
184. MALETIC-SAVATIC, M., N. J. LENN, AND J. S. TRIMMER. Differential spatiotemporal expression of $K^+$ channel polypeptides in rat hippocampal neurons developing in situ and in vitro. *J. Neurosci.* 15: 3840-3851, 1995.
185. MARFAING-JALLET, P., D. MICELI, AND J. LE MAGNEN. Decrease in ethanol consumption by naloxone in naive and dependent rats. *Pharmacol. Biochem. Behav.* 18: 537-539, 1983.
186. MARSZALEC, W., Y. KURATA, B. J. HAMILTON, D. B. CARTER, AND T. NARAHASHI. Selective effects of alcohols on gamma-aminobutyric acid A receptor subunits expressed in human embryonic kidney cells. *J. Pharmacol. Exp. Ther.* 269: 157-163, 1994.
187. MARTIN, D., M. I. TAYYEB, AND H. S. SWARTZWELDER. Ethanol inhibition of AMPA and kainate receptor-mediated depolarizations of hippocampal area CA1. *Alcohol. Clin. Exp. Res.* 19: 1312-1316, 1995.
188. MASOOD, K., C. WU, U. BRAUNEIS, AND F. F. WEIGHT. Differential ethanol sensitivity of recombinant *N*-methyl-D-asparate receptor subunits. *Mol. Pharmacol.* 45: 324-329, 1993.
189. MCBRIDE, W. J., E. CHERNET, W. DYR, L. LUMENG, AND T.-K. LI. Densities of dopamine $D_2$ receptors are reduced in CNS regions of alcohol-preferring P rats. *Alcohol* 10: 387-390, 1993.
190. MCBRIDE, W. J., E. CHERNET, J. A. RABOLD, L. LUMENG, AND T.-K. LI. Serotonin-2 receptors in the CNS of alcohol-preferring and -nonpreferring rats. *Pharmacol. Biochem. Behav.* 46: 631-636, 1993.
191. MCBRIDE, W. J., X.-M. GUAN, E. CHERNET, L. LUMENG, AND T.-K. LI. Regional serotonin$_{1A}$ receptors in the CNS of alcohol-preferring and -nonpreferring rats. *Pharmacol. Biochem. Behav.* 49: 7-12, 1994.
192. MCCOOL, B. A., AND D. M. LOVINGER. Ifenprodil inhibition of the 5-hydroxytryptamine 3 receptor. *Neuropharmacology* 34: 621-629, 1995.
193. MCKERNAN, R. M., K. QUIRK, R. PRINCE, P. A. COX, N. P. GILLARD, C. I. RAGAN, AND P. WHITING. $GABA_A$ receptor subtypes immunopurified from rat brain with a subunit-specific antibodies have unique pharmacological properties. *Neuron* 7: 667-676, 1991.
194. MCKERNAN, R. M., AND P. J. WHITING. Which $GABA_A$-receptor subtypes really occur in the brain? *Trends Neurosci.* 19: 139-143, 1996.
195. MCMILLEN, B. A., S. WALTER, H. L. WILLIAMS, AND R. D. MYERS. Comparison of the action of the 5-$HT_2$ antagonists amperozide and trazodone on preference for alcohol in rats. *Alcohol* 11: 203-206, 1994.
196. MEHTA, A. K., AND M. K. TICKU. Ethanol potentiation of GABAergic transmission in cultured spinal cord neurons involves $\gamma$-aminobutyric acid$_A$-gated chloride channels. *J. Pharmacol. Exp. Ther.* 246: 558-564, 1988.
197. MELO, J. A., J. SHENDURE, K. POCIASK, AND L. M. SILVER. Identification of sex-specific quantitative trait loci controlling alcohol preference in C57BL/6 mice. *Nature Genet.* 13: 147-153, 1996.
198. MENDELSON, J. H., B. T. WOODS, T.-M. CHIU, N. K. MELLO, S. E. LUKAS, S. K. TEOH, P. SINTAVANARONG, J. COCHIN, M. A. HOPKINS, AND M. DOBROSIELSKI. In vivo proton magnetic resonance spectroscopy of alcohol in human brain. *Alcohol* 7: 443-447, 1990.
199. MESSING, R. O., C. L. CARPENTER, I. DIAMOND, AND D. A. GREENBERG. Ethanol regulates calcium channels in clonal neural cells. *Proc. Natl. Acad. Sci. USA* 83: 6213-6215, 1986.
201. MESSING, R. O., AND I. DIAMOND. Molecular biology of alcohol dependence. In: *The Molecular and Genetic Basis of Neurological Disease*, edited by R. N. Rosenberg, S. B. Prusiner, S. DiMauro, R. L. Barchi, and L. M. Kunkel. Boston, MA: Butterworth-Heinemann, 1993, p. 129-142.

202. MESSING, R. O., AND I. DIAMOND. Molecular biology of alcohol dependence. In: *The Molecular and Genetic Basis of Neurological Disease*, edited by R. N. Rosenberg, S. B. Prusiner, S. DiMauro, R. L. Barchi, and L. M. Kunkel. Boston, MA: Butterworth-Heinemann. In press.
203. MESSING, R. O., M. HENTELEFF, AND J. J. PARK. Ethanol enhances growth factor-induced neurite formation in PC12 cells. *Brain Res.* 565: 301-311, 1991.
204. MESSING, R. O., P. J. PETERSEN, AND C. J. HENRICH. Chronic ethanol exposure increases levels of protein kinase C $\delta$ and $\epsilon$ and protein kinase C-mediated phosphorylation in cultured neural cells. *J. Biol. Chem.* 266: 23428-23432, 1991.
205. MESSING, R. O., A. B. SNEADE, AND B. SAVIDGE. Protein kinase C participates in up-regulation of dihydropyridine-sensitive calcium channels by ethanol. *J. Neurochem.* 55: 1383-1389, 1990.
206. MESTEK, A., J. H. HURLEY, L. S. BYE, A. D. CAMPBELL, Y. CHEN, M. TIAN, J. LIU, H. SCHULMAN, AND L. YU. The human $\mu$ opioid receptor: modulation of functional desensitization by calcium/calmodulin-dependent protein kinase and protein kinase C. *J. Neurosci.* 15: 2396-2406, 1995.
207. MHATRE, M., AND M. K. TICKU. Chronic ethanol treatment upregulates the GABA receptor beta subunit expression. *Brain Res.* 23: 246-252, 1994.
208. MIIATRE, M. C., G. PENA, W. SIEGHART, AND M. K. TICKU. Antibodies specific for $GABA_A$ receptor $\alpha$ subunits reveal that chronic alcohol treatment down-regulates $\alpha$-subunit exprcssion in rat brain regions. *J. Neurochem.* 61: 1620-1625, 1993.
209. MHATRE, M. C., AND M. K. TICKU. Chronic ethanol administration alters $\gamma$-aminobutyric $acid_A$ receptor gene expression. *Mol. Pharmacol.* 42: 415-422, 1992.
210. MICHAELIS, E. K., W. J. FREED, N. GALTON, J. FOYE, M. L. MICHAELIS, I. PHILLIPS, AND J. E. KLEINMAN. Glutamate receptor changes in brain synaptic membranes from human alcoholics. *Neurochem. Res.* 15: 1055-1063, 1990.
211. MICHAELIS, M. L., AND E. K. MICHAELIS. Effects of ethanol on NMDA receptors in brain: possibilities for $Mg^{2+}$-ethanol interactions. *Alcohol. Clin. Exp. Res.* 18: 1069-1075, 1994.
212. MILES, M., S. BARHITE, M. SGANGA, AND M. ELLIOTT. Phosducin-like protein: an ethanol-responsive potential modulator of guanine nucleotide-binding protein function. *Proc. Natl. Acad. Sci. USA* 90: 10831-10835, 1993.
213. MILES, M. F., J. E. DIAZ, AND V. DEGUZMAN. Ethanol-responsive gene expression in neural cell cultures. *Biochim. Biophys. Acta* 1138: 268-274, 1992.
214. MILES, M. F., J. E. DIAZ, AND V. S. DEGUZMAN. Mechanisms of neuronal adaptation to ethanol. *J. Biol. Chem.* 266: 2409-2414, 1991.
215. MILES, M. F., N. WILKE, M. ELLIOT, W. TANNER, AND S. SHAH. Ethanol-responsive genes in neural cells include the 78-kilodalton glucose-regulated protein (GRP78) and 94-kilodalton glucose-regulated protein (GRP94) molecular chaperones. *Mol. Pharmacol.* 46: 873-879, 1994.
216. MILLER, M. W., N. L. NICHOLAS, AND R. W. RHOADES. Intracellular recording and injection study of corticospinal neurons in the rat somatosensory cortex: effect of prenatal exposure to ethanol. *J. Comp. Neurol.* 297: 91-105, 1990.
217. MILLS, I., AND H. GEWIRTZ. Cultured vascular smooth muscle cells from porcine coronary artery possess A1 and A2 adenosine receptor activity. *Biochem. Biophys. Res. Commun.* 168: 1297-1302, 1990.
218. MIRSHAHI, T., AND J. J. WOODWARD. Ethanol sensitivity of heteromeric NMDA receptors: effects of subunit assembly, glycine and NMDAR1 $Mg^{2+}$-insensitive mutants. *Neuropharmacology* 34: 347-355, 1995.
219. MOCHLY-ROSEN, D. Localization of protein kinases by anchoring proteins: a theme in signal transduction. *Science Wash. DC* 268: 247-251, 1995.
220. MOCHLY-ROSEN, D., F.-H. CHANG, L. CHEEVER, M. KIM, I. DIAMOND, AND A. S. GORDON. Chronic ethanol causes heterologous desensitization of receptors by reducing $\alpha_s$ messenger RNA. *Nature Lond.* 333: 848-850, 1988.
221. MONTPIED, P., A. L. MORROW, J. W. KARANIAN, E. I. GINNS, B. M. MARTIN, AND S. M. PAUL. Prolonged ethanol inhalation decreases $\gamma$-aminobutyric $acid_A$ receptor $\alpha$ subunit mRNAs in the rat cerebral cortex. *Mol. Pharmacol.* 39: 157-163, 1991.
222. MORRISETT, R. A., AND H. S. SWARTZWELDER. Attenuation of hippocampal long-term potentiation by ethanol: a patch-clamp analysis of glutamatergic and GABAergic mechanisms. *J. Neurosci.* 13: 2264-2272, 1993.
223. MORROW, A. L., P. MONTPIED, A. LINGFORD-HUGHES, AND S. M. PAUL. Chronic ethanol and pentobarbital administration in the rat: effects on $GABA_A$ receptor function and expression in brain. *Alcohol* 7: 237-244, 1990.
224. MULLIKIN-KILPATRICK, D., N. D. MEHTA, J. D. HILDEBRANDT, AND S. N. TREISTMAN. $G_i$ is involved in ethanol inhibition of L-type calcium channels in undifferentiated but not differentiated PC-12 cells. *Mol. Pharmacol.* 47: 997-1005, 1995.
225. MULLIKIN-KILPATRICK, D., AND S. N. TREISTMAN. Inhibition of dihydropyridine-sensitive $Ca^{2+}$ channels by ethanol in undifferentiated and nerve growth factor-treated PC12 cells: interaction with the inactivated state. *J. Pharmacol. Exp. Ther.* 272: 489-497, 1995.
226. MUNDINA-WEILENMANN, C., C. F. CHANG, L. M. GUTIERREZ, AND M. M. HOSEY. Demonstration of the phosphorylation of dihydropyridine-sensitive calcium channels in chick skeletal muscle and the resultant activation of the channels after reconstitution. *J. Biol. Chem.* 266: 4067-4073, 1991.
227. MURPHY, M. G., AND Z. BYCZKO. Effects of adenosine analogues on basal, prostaglandin $E_1$- and forskolin-stimulated cyclic AMP formation in intact neuroblastoma cells. *Biol. Pharmacol.* 38: 3289-3295, 1989.
228. MYERS, R. D., S. BORG, AND R. MOSSBERG. Antagonism by naltrexone of voluntary alcohol selection in the chronically drinking macaque monkey. *Alcohol* 3: 383-388, 1986.
229. NADLER, J. V., D. MARTIN, M. A. BOWE, R. A. MORRISETT, AND J. O. MCNAMARA. Kindling, prenatal exposure to ethanol and postnatal development selectively alter responses of hippocampal pyramidal cells to NMDA. *Adv. Exp. Med. Biol.* 268: 407-417, 1990.
230. NAGY, J. I., J. D. GEIGER, AND P. E. DADDONA. Adenosine uptake sites in rat brain: identification using [$^3$H]nitrobenzylthioinosine and co-localization with adenosine deaminase. *Neurosci. Lett.* 55: 47-53, 1985.
231. NAGY, L., I. DIAMOND, AND A. S. GORDON. cAMP-dependent protein kinse regulates inhibition of adenosine transport by ethanol. *Mol. Pharmacol.* 40: 812-817, 1991.
232. NAGY, L. E. Ethanol metabolism and inhibition of nucleoside uptake leads to increased extracellular adenosine in hepatocytes. *Am. J. Physiol.* 262 (*Cell Physiol.* 31): C1175–C1180, 1992.
233. NAGY, L. E. Effects of ethanol-induced changes in adenosine transport on cAMP production in rat hepatocytes. *Alcohol Alcoholism Suppl.* 2: 419-423, 1993.
234. NAGY, L. E., AND S. E. F. DESILVA. Ethanol increases receptor-dependent cyclic AMP production in cultured hepatocytes by decreasing $G_i$-mediated inhibition. *Biochem. J.* 286: 681-686, 1992.
235. NAGY, L. E., AND S. E. F. DESILVA. Adenosine $A_1$ receptors mediate chronic ethanol-induced increases in receptor-stimulated cyclic AMP in cultured hepatocytes. *Biochem. J.* 304: 205-210, 1994.
236. NAGY, L. E., I. DIAMOND, D. J. CASSO, C. FRANKLIN, AND A. S. GORDON. Ethanol increases extracellular adenosine by inhibiting adenosine uptake via the nucleoside transporter. *J. Biol. Chem.* 265: 1946-1951, 1990.
237. NAGY, L. E., I. DIAMOND, K. COLLIER, L. LOPEZ, B. ULLMAN, AND A. S. GORDON. Adenosine is required for ethanol-induced heterologous desensitization. *Mol. Pharmacol.* 36: 744-748, 1989.
238. NAGY, L. E., I. DIAMOND, AND A. S. GORDON. cAMP-dependent protein kinase regulates inhibition of adenosine transport by ethanol. *Mol. Pharmacol.* 40: 812-817, 1991.
239. NAKAMURA, J. Ethanol-induced reduction of the amount of stimulatory GTP-binding regulatory protein, $G_s$, in wild-type S49 murine lymphoma cells: effect of cycloheximide and puromycin. *Biochim. Biophys. Acta* 1209: 111–116, 1994.
240. NAKAMURA, J., S. HARADA, AND N. TANAKA. Relationship between alcohol consumpion and the activity of GTP-binding regulatory proteins in human erythrocyte membranes. *Clin. Chim. Acta* 215: 1-7, 1993.
241. NEISWANGER, K., B. B. KAPLAN, AND S. Y. HILL. What can the

DRD2/alcoholism story teach us about association studies in psychiatric genetics? *Am. J. Med. Genet.* 60: 272-275, 1995.
242. NETZEBAND, J. G., AND D. L. GRUOL. Modulatory effects of acute ethanol on metabotropic glutamate responses in cultured Purkinje neurons. *Brain Res.* 688: 105-113, 1995.
243. NIE, Z., S. G. MADAMBA, AND G. R. SIGGINS. Ethanol inhibits glutamatergic neurotransmission in nucleus accumbens neurons by multiple mechanisms. *J. Pharmacol. Exp. Ther.* 271: 1566-1573, 1994.
244. NIMIT, Y., P. SKOLNICK, AND J. W. DALY. Adenosine and cyclic AMP in rat cerebral cortical slices: effects of adenosine uptake inhibitors and adenosine deaminase inhibitors. *J. Neurochem.* 36: 908-912, 1981.
245. NOBLE, E. P. The gene that rewards alcoholism. *Sci. Am.* 3: 52-60, 1996.
246. NYLANDER, I., P. HYYTIA, O. FORSANDER, AND L. TERENIUS. Differences between alcohol-preferring (AA) and alcohol avoiding (ANA) rats in the prodynorphin and proenkephalin systems. *Alcohol. Clin. Exp. Res.* 18: 1272-1279, 1994.
247. OLIVERA, A., M. TOMAS, AND J. M. LOPEZ-NOVOA. Effect of adenosine $A_1$ and $A_2$ agonists and antagonists on cAMP and $Ca^{2+}$ in cultured rat mesangial cells. *Am. J. Physiol.* 262 (*Cell Physiol.* 31): C840–C844, 1992.
248. OLSEN, R. W., AND A. J. TOBIN. Molecular biology of $GABA_A$ receptors. *FASEB J.* 4: 1469-1480, 1990.
249. O'MALLEY, S. S., A. J. JAFFE, G. CHANG, S. RODE, R. SCHOTTENFELD, R. E. MEYER, AND B. ROUNSAVILLE. Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. *Arch. Gen. Psychiatry* 53: 217-224, 1996.
250. O'MALLEY, S. S., A. J. JAFFE, G. CHANG, R. S. SCHOTTENFELD, R. E. MEYER, AND B. ROUNSAVILLE. Naltrexone and coping skills therapy for alcohol dependence. *Arch. Gen. Psychiatry* 49: 881-887, 1992.
251. ORREGO, H., F. J. CARMICHAEL, AND Y. ISRAEL. New insights on the mechanism of the alcohol-induced increase in portal blood flow. *Can. J. Pharmacol.* 66: 1-9, 1988.
252. ORREGO, H., F. J. CARMICHAEL, V. SALDIVIA, H. G. GILES, S. SANDRIN, AND Y. ISRAEL. Ethanol-induced increase in portal blood flow: role of adenosine. *Am. J. Physiol.* 255 (*Gastrointest. Liver Physiol.* 18): G495–G501, 1988.
253. PAILLE, F. M., J. D. GUELFI, A. C. PERKINS, R. J. ROYER, L. STERU, AND P. PAROT. Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. *Alcohol Alcohol.* 30: 239-247, 1995.
254. PALMER, M. R., C. G. VAN HORNE, J. T. HARLAN, AND E. A. MOORE. Antagonism of ethanol effects on cerebellar Purkinje neurons by the benzodiazepine inverse agonist Ro 15-4513 and FG 7142: electrophysiological studies. *J. Pharmacol. Exp. Ther.* 247: 1018-1024, 1988.
255. PANOCKA, I., R. CICCOCIOPPO, M. MOSCA, C. POLIDORI, AND M. MASSI. Effects of dopamine $D_1$ receptor antagonist SCH 39166 on the ingestive behaviour of alcohol-preferring rats. *Psychopharmacology* 120: 227-235, 1995.
256. PANOCKA, I., R. CICCOCIOPPO, P. POMPEI, AND M. MASSI. 5-$HT_2$ receptor antagonists do not reduce ethanol preference in sardinian alcohol-preferring (sP) rats. *Pharmacol. Biochem. Behav.* 46: 853-856, 1993.
257. PARENT, L. J., R. EHRLICH, L. MATIS, AND D. S. SINGER. Ethanol: an enhancer of major histocompatibility complex antigen expression. *FASEB J.* 1: 469-473, 1987.
258. PARKER, E. S., J. M. MORIHISA, R. J. WYATT, B. L. SCHWARTZ, H. WEINGARTNER, AND R. C. STILLMAN. The alcohol facilitation effect on memory: a dose-response study. *Psychopharmacology* 74: 88-92, 1981.
259. PATEL, S. N., AND M. G. STEWART. Changes in the number and structure of dendritic spines 25 hours after passive avoidance training in the domestic chick, *Gallus domesticus*. *Brain Res.* 449: 34-36, 1988.
260. PELLEGRINO, S. M., J. M. WOODS, AND M. J. DRUSE. Effects of chronic ethanol consumption on G protein in brain areas associated with the nigrostriatal and mesolimbic dopamine systems. *Alcohol. Clin. Exp. Res.* 17: 1247-1253, 1993.
261. PENTNEY, R. J., AND L. J. QUACKENBUSH. Dendritic hypertrophy in Purkinje neurons of old Fischer 344 rats after long-term ethanol treatment. *Alcohol. Clin. Exp. Res.* 14: 878-886, 1990.
262. PEOPLES, R. W., AND F. F. WEIGHT. Cutoff in potency implicates alcohol inhibition of *N*-methyl-D-aspartate receptors in alcohol intoxication. *Proc. Natl. Acad. Sci. USA* 92: 2825-2829, 1995.
263. PEREZ-VELAZQUEZ, J. L., AND K. J. ANGELIDES. Assembly of $GABA_A$ receptor subunits determines sorting and localization in polarized cells. *Nature Lond.* 361: 457-460, 1993.
264. PEREZ-VELAZQUEZ, J. L., T. A. VALIANTE, AND P. L. CARLEN. Changes in calcium currents during ethanol withdrawal in a genetic mouse model. *Brain Res.* 649: 305-309, 1994.
265. PETROFF, O. A. C., E. J. NOVOTNY, T. OGINO, M. AVISON, AND J. W. PRICHARD. In vivo measurements of ethanol concentration in rabbit brain by $^1H$ magnetic resonance spectroscopy. *J. Neurochem.* 54: 1188-1195, 1990.
266. PHILLIS, J. W., M. H. O'REGAN, AND L. M. PERKINS. Actions of ethanol and acetate on rat cortical neurons: ethanol/adenosine interactions. *Alcohol* 9: 541-546, 1992.
267. PHILLIS, J. W., M. H. O'REGAN, AND G. A. WALTER. Effects of two nucleoside transport inhibitors, dipyridamole and soluflazine, on purine release from the rat cerebral cortex. *Brain Res.* 481: 309-316, 1989.
268. PHILLIS, J. W., AND P. H. WU. The role of adenosine and its nucleotides in central synaptic transmission. *Prog. Neurobiol.* 16: 187-239, 1981.
269. PITCHFORD, S., J. W. DAY, A. GORDON, AND D. MOCHLY-ROSEN. Nicotinic acetylcholine receptor desensitization is regulated by activation-induced extracellular adenosine accumulation. *J. Neurosci.* 12: 4540-4544, 1992.
270. PLAGEMANN, P. G. W., R. M. WOHLHEUTER, AND C. WOFFENDIN. Nucleoside and nucleobase transporter in animal cells. *Biochim. Biophys. Acta* 947: 405-443, 1988.
271. PRINCE, D. A., AND C. F. STEVENS. Adenosine decreases neurotransmitter release at central synapses. *Proc. Natl. Acad. Sci. USA* 89: 8586-8690, 1992.
272. PROCTOR, W. R., A. M. ALLAN, AND T. V. DUNWIDDIE. Brain region-dependent sensitivity of $GABA_A$ receptor-mediated responses to modulation by ethanol. *Alcohol. Clin. Exp. Res.* 16: 480-489, 1992.
273. PROCTOR, W. R., AND T. V. DUNWIDDIE. Behavioral sensitivity to purinergic drugs parallels ethanol sensitivity in selectively bred mice. *Science Wash. DC* 224: 519-522, 1984.
274. PROCTOR, W. R., B. L. SOLDO, A. M. ALLAN, AND T. V. DUNWIDDIE. Ethanol enhances synaptically evoked $GABA_A$ receptor-mediated responses in cerebral cortical neurons in rat brain slices. *Brain Res.* 595: 220-227, 1992.
275. PROLL, M. A., R. B. CLARK, AND R. W. BUTCHER. $A_1$ and $A_2$ adenosine receptors regulate adenylate cyclase in cultured human lung fibroblasts. *Mol. Cell. Endocrinol.* 44: 211-217, 1986.
276. PULVIRENTI, L., AND G. F. KOOB. Dopamine receptor agonists, partial agonists and psychostimulant addiction. *Trends Pharmacol. Sci.* 15: 374-379, 1994.
277. PURVES, D., AND J. W. LICHTMAN. *Principles of Neural Development.* Sunderland, MA: Sinauer, 1985.
278. RABE, C. S., P. R. GIRI, P. L. HOFFMAN, AND B. TABAKOFF. Effect of ethanol on cyclic AMP levels in intact PC12 cells. *Biochem. Pharmacol.* 40: 565-571, 1990.
279. RABIN, R. A. Chronic ethanol exposure of PC 12 cells alters adenylate cyclase activity and intracellular cyclic AMP content. *J. Pharmacol. Exp. Ther.* 252: 1021-1027, 1990.
280. RABIN, R. A. Direct effects of chronic ethanol exposure on $\beta$-adrenergic and adenosine-sensitive adenylate cyclase activities and cyclic AMP content in primary cerebellar cultures. *J. Neurochem.* 55: 122-128, 1990.
281. RABIN, R. A. Ethanol-induced desensitization of adenylate cyclase: role of the adenosine receptor and GTP-binding proteins. *J. Pharmacol. Exp. Ther.* 264: 977-983, 1993.
282. RABIN, R. A., A. M. EDELMAN, AND J. A. WAGNER. Activation of protein kinase A is necessary but not sufficient for ethanol-induced desensitization of cyclic AMP production. *J. Pharmacol. Exp. Ther.* 262: 257-262, 1992.
283. RABIN, R. A., D. FIORELLA, AND D. G. L. VAN WYLEN. Role of

extracellular adenosine in ethanol-induced desensitization of cyclic AMP production. *J. Neurochem.* 60: 1012-1017, 1992.
284. RANDALL, A., AND R. W. TSIEN. Pharmacological dissection of multiple types of $Ca^{2+}$ channel currents in rat cerebellar granule neurons. *J. Neurosci.* 15: 2995-3012, 1995.
285. REYNOLDS, J. D., AND J. F. BRIEN. The role of adenosine $A_1$ receptor activation in ethanol-induced inhibition of stimulated glutamate release in the hippocampus of the fetal and adult guinea pig. *Alcohol* 12: 151-157, 1995.
286. REYNOLDS, J. N., A. PRASAD, AND J. F. MACDONALD. Ethanol modulation of GABA receptor-activated $Cl^-$ currents in neurons of the chick, rat and mouse central nervous system. *Eur. J. Pharmacol.* 224: 173-181, 1992.
287. REZVANI, A. H., D. H. OVERSTREET, AND Y. W. LEE. Attenuation of alcohol intake by Ibogaine in three strains of alcohol-preferring rats. *Pharmacol. Biochem. Behav.* 52: 615-620, 1995.
288. RICHELSON, E., S. STENSTROM, C. FORRAY, L. ENLOE, AND M. PFENNING. Effects of chronic exposure to ethanol on the prostaglandin $E_1$ receptor-mediated response and binding in a murine neuroblastoma clone (N1E-115). *J. Pharmacol. Exp. Ther.* 239: 687-692, 1986.
289. RIPLEY, T. L., AND H. J. LITTLE. Ethanol withdrawal hyperexcitability in vitro is selectively decreased by a competitive NMDA receptor antagonist. *Brain Res.* 699: 1-11, 1995.
290. RIPLEY, T. L., AND H. J. LITTLE. Nitrendipine prevents the decrease caused by chronic ethanol intake in the maintenance of tetanic long-term potentiation. *Exp. Brain Res.* 103: 1-8, 1995.
291. ROIVAINEN, R., B. HUNDLE, AND R. O. MESSING. Ethanol enhances growth factor activation of mitogen-activated protein kinases by a protein kinase C-dependent mechanism. *Proc. Natl. Acad. Sci. USA* 92: 1891-1895, 1995.
292. ROIVAINEN, R., B. HUNDLE, AND R. O. MESSING. Protein kinase C and adaptation to ethanol. In: *Toward a Molecular Basis of Alcohol Use and Abuse*, edited by B. Jansson, H. Jornval, U. Rydberg, L. Terenius, and B. L. Ballee. Basel: Birkhauser Verlag, 1994, p. 29-38.
293. ROIVAINEN, R., T. MCMAHON, AND R. O. MESSING. Protein kinase C isozymes that mediate enhancement of neurite outgrowth by ethanol and phorbol esters in PC12 cells. *Brain Res.* 624: 85-93, 1993.
294. ROSSETTI, Z. L., AND S. CARBONI. Ethanol withdrawal is associated with increased extracellular glutamate in the rat striatum. *Eur. J. Pharmacol.* 283: 177-183, 1995.
295. ROSSETTI, Z. L., Y. HMAIDAN, AND G. L. GESSA. Marked inhibition of mesolimbic dopamine release: a common feature of ethanol, morphine, cocaine and amphetamine abstinence in rats. *Eur. J. Pharmacol.* 221: 227-234, 1992.
296. ROTHMAN, S. M., AND J. W. OLNEY. Excitotoxicity and the NMDA receptor: still lethal after eight years. *Trends Neurosci.* 18: 57-58, 1995.
297. ROTTENBERG, H. Membrane solubility of ethanol in chronic alcoholism: the effect of ethanol feeding and its withdrawal on the protection by alcohol of rat red blood cells from hypnotic hemolysis. *Biochim. Biophys. Acta* 855: 211-222, 1986.
298. ROTTENBERG, H., R. BITTMAN, AND H.-L. LI. Resistance to ethanol disordering of membranes from ethanol-fed rats is conferred by all phospholipid classes. *Biochim. Biophys. Acta* 1123: 282-290, 1992.
299. RYABININ, A. E., K. R. MELIA, M. COLE, F. E. BLOOM, AND M. C. WILSON. Alcohol selectively attenuates stress-induced c-*fos* expression in rat hippocampus. *J. Neurosci.* 15: 721-730, 1995.
300. SAKIMURA, K., T. KUTSUWADA, I. ITO, T. MANABE, C. TAKAYAMA, E. KUSHIYA, T. YAGI, S. AIZAWA, Y. INOUE, H. SUGLYAMA, AND M. MISHINA. Reduced hippocampal LTP and spatial learning in mice lacking NMDA receptor $\epsilon 1$ subunit. *Nature Lond.* 373: 151-155, 1995.
301. SAMSON, H. H., AND T. F. DOYLE. Oral ethanol self-administration in the rat: effect of naloxone. *Pharmacol. Biochem. Behav.* 22: 91-99, 1985.
302. SAMSON, H. H., C. W. HODGE, G. A. TOLLIVER, AND M. HARAGUCHI. Effect of dopamine agonist and antagonist on ethanol-reinforced behavior: the involvement of the nucleus accumbens. *Brain Res. Bull.* 30: 133-141, 1993.
303. SANNA, E., J. E. DILDY-MAYFIELD, AND A. HARRIS. Ethanol inhibits the function of 5-hydroxytryptamine type 1c and muscarinic $M_1$ G protein-linked receptors in *Xenopus* oocytes expressing brain mRNA: role of protein kinase C. *Mol. Pharmacol.* 1994: 1004-1012, 1994.
304. SANNA, E., M. SERRA, A. COSSU, G. COLOMBO, AND P. FOLLESA. Chronic ethanol intoxication induces differential effects on $GABA_A$ and NMDA receptor function in the rat brain. *Alcohol. Clin. Exp. Res.* 17: 115-123, 1993.
305. SAPRU, M. K., I. DIAMOND, AND A. S. GORDON. Adenosine receptors mediate cellular adaptation to ethanol in NG108-15 cells. *J. Pharmacol. Exp. Ther.* 271: 542-548, 1994.
306. SCHOLZ, K. P., AND R. J. MILLER. Inhibition of quantal transmitter release in the absence of calcium influx by a G protein-linked adenosine receptor at hippocampal synapses. *Neuron* 8: 1139-1150, 1992.
307. SCHROEDER, S., AND M. J. LOHSE. Inhibition of G-protein $\beta\gamma$-subunit functions by phosducin-like protein. *Proc. Natl. Acad. Sci. USA* 1996: 2100-2104, 1996.
308. SCHUCKIT, M. A. Low level of response to alcohol as a predictor of future alcoholism. *Am. J. Psychiatry* 151: 184-189, 1994.
309. SCHUCKIT, M. A., AND T. L. SMITH. An 8-year follow-up of 450 sons of alcoholic and control subjects. *Arch. Gen. Psychiatry* 53: 202-210, 1996.
310. SELF, D. W., AND E. J. NESTLER. Molecular mechanisms of drug reinforcement and addiction. *Annu. Rev. Neurosci.* 18: 463-495, 1995.
311. SELLERS, E. M., T. TONEATTO, M. K. ROMACH, G. R. SOMER, L. C. SOBELL, AND M. B. SOBELL. Clinical efficacy of the $5\text{-}HT_3$ antagonist ondansetron in alcohol abuse and dependence. *Alcohol. Clin. Exp. Res.* 18: 879-885, 1994.
312. SIGEL, E., R. BAUR, AND P. MALHERBE. Recombinant $GABA_A$ receptor function and ethanol. *FEBS Lett.* 324: 140-142, 1993.
313. SIGNS, S. A., AND R. JACQUET. Induction of ethanol dependence increases signal peptidase mRNA levels in rat brain. *Mol. Cell. Biochem.* 139: 21-26, 1994.
314. SINGH, S. P., K. S. SRIVENUGOPAL, X.-H. YUAN, F. JIANG, AND A. K. SNYDER. Effects of ethanol ingestion on glucose transporter-1 protein and mRNA levels in rat brain. *Life Sci.* 53: 1811-1819, 1993.
315. SKATTEBOL, A., AND R. A. RABIN. Effects of ethanol on $^{45}Ca^{2+}$ uptake in synaptosomes and in PC12 cells. *Biochem. Pharmacol.* 36: 2227-2229, 1987.
316. SKWISH, S., AND W. SHAIN. Ethanol and diolein stimulate PKC translocation in astroglial cells. *Life Sci.* 47: 1037-1042, 1990.
317. SLATER, S. J., K. J. A. COX, J. V. LOMBARDI, C. HO, M. B. KELLY, E. RUBIN, AND C. D. STUBBS. Inhibition of protein kinase C by alcohols and anaesthetics. *Nature Lond.* 364: 82-84, 1993.
318. SMITH, G. B., AND R. W. OLSEN. Functional domains of $GABA_A$ receptors. *Trends Physiol. Sci.* 16: 162-168, 1995.
319. SNELL, L. D., B. TABAKOFF, AND P. L. HOFFMAN. Radioligand binding to the *N*-methyl-D-aspartate receptor/ionophore complex: alterations by ethanol in vitro and by chronic in vivo ethanol ingestion. *Brain Res.* 602: 91-98, 1993.
320. SNELL, L. D., B. TABAKOFF, AND P. L. HOFFMAN. Involvement of protein kinase C in ethanol-induced inhibition of NMDA receptor function in cerebellar granule cells. *Alcohol. Clin. Exp. Res.* 18: 81-85, 1994.
321. STERNWEIS, P. C., AND A. V. SMRCKA. Regulation of phospholipase C by G proteins. *Trends Biochem. Sci.* 17: 502-506, 1992.
322. SUGIURA, M., Y. SHOYAMA, H. SAITO, AND K. ABE. Crocin (crocetin di-gentiobiose ester) prevents the inhibitory effect of ethanol on long-term potentiation in the dentate gyrus in vivo. *J. Pharmacol. Exp. Ther.* 271: 703-707, 1994.
323. SUN, G. Y., H.-M. HUANG, D.-Z. LEE, AND A. Y. SUN. Increased acidic phospholipids in rat brain membranes after chronic ethanol administration. *Life Sci.* 35: 2127-2133, 1984.
324. SUZDAK, P. D., J. R. GLOWA, J. N. CRAWLEY, R. D. SCHWARTZ, P. SKOLNICK, AND S. M. PAUL. A selective imidazobenzodiazepine antagonist of ethanol in the rat. *Science Wash. DC* 234: 1243-1247, 1986.
325. SUZDAK, P. D., R. D. SCHWARTZ, P. SKOLNICK, AND S. M. PAUL. Ethanol stimulates $\gamma$-aminobutyric acid receptor-mediated chloride

transport in rat brain synaptoneurosomes. *Proc. Natl. Acad. Sci. USA* 83: 4071-4075, 1986.
326. TABAKOFF, B., P. L. HOFFMAN, J. M. LEE, T. SAITO, B. WILLARD, AND F. DE LEON-JONES. Differences in platelet enzyme activity between alcoholics and nonalcoholics. *N. Engl. J. Med.* 318: 134-139, 1988.
327. TABAKOFF, B., J. P. WHELAN, L. OVCHINNIKOVA, P. NHAMBURO, M. YOSHIMURA, AND P. L. HOFFMAN. Quantitative changes in G proteins do not mediate ethanol-induced downregulation of adenylyl cyclase in mouse cerebral cortex. *Alcohol. Clin. Exp. Res.* 19: 187-194, 1995.
328. TAN, X. X., AND L. G. COSTA. Postnatal development of muscarinic receptor-stimulated phosphoinositide metabolism in mouse cerebral cortex: sensitivity to ethanol. *Brain Res.* 86: 348-353, 1995.
329. TARASCHI, T. F., J. S. ELLINGSON, A. WU, R. ZIMMERMAN, AND E. RUBIN. Phosphatidylinositol from ethanol-fed rats confers membrane tolerance to ethanol. *Proc. Natl. Acad. Sci. USA* 83: 9398-9402, 1986.
330. TECOTT, L. H., A. V. MARICQ, AND D. JULIUS. Nervous system distribution of the serotonin 5-$HT_3$ receptor mRNA. *Proc. Natl. Acad. Sci. USA* 90: 1430-1434, 1993.
331. TECOTT, L. H., L. M. SUN, S. F. AKANA, A. M. STRACK, D. H. LOWENSTEIN, M. F. DALLMAN, AND D. JULIUS. Eating disorder and epilepsy in mice lacking 5-$HT_{2C}$ serotonin receptors. *Nature Lond.* 374: 542-546, 1995.
332. TIIHONEN, J., J. KUIKKA, K. BERGSTRÖM, P. HAKOLA, J. KARHU, O. P. RYYNÄNEN, AND J. FÖHR. Altered striatal dopamine re-uptake site densities in habitually violent and non-violent alcoholics. *Nature Med.* 1: 654-657, 1995.
333. TOMKINS, D. M., A. D. LE, AND E. M. SELLERS. Effect of the 5-$HT_3$ antagonist ondansetron on voluntary ethanol intake in rats and mice maintained on a limited access procedure. *Psychopharmacology* 117: 479-485, 1995.
334. TREVISAN, L., L. W. FITZGERALD, N. BROSE, G. P. GASIC, S. F. HEINEMANN, R. S. DUMAN, AND E. J. NESTLER. Chronic ingestion of ethanol up-regulates NMDAR1 receptor subunit immunoreactivity in rat hippocampus. *J. Neurochem.* 62: 1635-1638, 1994.
335. TWOMBLY, D. A., M. D. HERMAN, C. H. KYE, AND T. NARAHASHI. Ethanol effects on two types of voltage-activated calcium channels. *J. Pharmacol. Exp. Ther.* 254: 1029-1037, 1990.
336. TYNDALE, R. F., T. G. HALES, R. W. OLSEN, AND A. J. TOBIN. Distinctive patterns of $GABA_A$ receptor subunit mRNAs in 13 cell lines. *J. Neurosci.* 14: 5417-5428, 1994.
337. UHL, G., K. BLUM, E. NOBLE, AND S. SMITH. Substance abuse vulnerability and $D_2$ receptor genes. *Trends Neurosci.* 16: 83-88, 1993.
338. UMEMIYA, M., AND A. J. BERGER. Activation of adenosine $A_1$ and $A_2$ receptors differentially modulates calcium channels and glycinergic synaptic transmission in rat brain stem. *Neuron* 13: 1439-1446, 1994.
339. VICTOR, M., R. D. ADAMS, AND G. H. COLLINS. *The Wernicke-Korsakoff Syndrome and Related Neurologic Disorders Due to Alcoholism and Malnutrition. Contemporary Neurology Series.* Philadelphia, PA: Davis, 1989, vol. 3.
340. VOLK, B. Neurohistological and neurobiological aspects of fetal alcohol syndrome in the rat. In: *Neurobehavioral Teratology*, edited by J. Yanai. Amsterdam: Elsevier, 1984, p. 163-193.
341. VOLPICELLI, J. R., A. I. ALTERMAN, M. HAYASHIDA, AND C. P. O'BRIEN. Naltrexone in the treatment of alcohol dependence. *Arch. Gen. Psychiatry* 49: 876-880, 1992.
342. WAFFORD, K. A., D. M. BURNETT, N. J. LEIDENHEIMER, D. R. BURT, J. G. WANG, P. KOFUJI, T. V. DUNWIDDIE, R. A. HARRIS, AND J. M. SIKELA. Ethanol sensitivity of the $GABA_A$ receptor expressed in *Xenopus* oocytes requires 8 amino acids contained in the $\gamma$2L subunit. *Neuron* 7: 1-20, 1991.
343. WAFFORD, K. A., AND P. J. WHITING. Ethanol potentiation of $GABA_A$ receptors requires phosphorylation of the alteratively spliced variant of the gamma 2 subunit. *FEBS Lett.* 313: 113-117, 1992.
344. WAHLESTEDT, C., E. GOLANOV, S. YAMAMOTO, F. YEE, H. ERICSON, H. YOO, C. E. INTURRISI, AND D. J. REIS. Antisense oligodeoxynucleotides to NMDA-R1 receptor channel protect cortical neurons from excitotoxicity and reduce focal ischaemic infarctions. *Nature Lond.* 363: 260-263, 1993.
345. WALTMAN, C., M. A. LEVINE, M. E. MCCAUL, D. S. SVIKIS, AND G. S. WAND. Enhanced expression of the inhibitory protein $G_{i2}\alpha$ and decreased activity of adenylyl cyclase in lymphocytes of abstinent alcoholics. *Alcohol. Clin. Exp. Res.* 17: 315-320, 1993.
346. WALTON, C. M., G. Y. WU, C. A. PETRUFF, S. H. CLARK, A. C. LICHTLER, AND C. H. WU. A collagen enhancer-promoter construct in transgenic mice is markedly stimulated by ethanol administration. *Hepatology* 23: 310-315, 1996.
347. WAN, F.-J., F. BERTON, S. G. MADAMBA, W. FRANCESCONI, AND G. R. SIGGINS. Low ethanol concentrations enhance GABAergic postsynaptic in hippocampal pyramidal neurons only after block of $GABA_B$ receptors. *Proc. Natl. Acad. Sci. USA* 193: 5049–5054, 1996.
348. WAND, G. S., A. M. DIEHL, M. A. LEVINE, D. WOLFGANG, AND S. SAMY. Chronic ethanol treatment increases expression of inhibitory G-proteins and reduces adenylyl cyclase activity in the central nervous system of two lines of ethanol-sensitive mice. *J. Biol. Chem.* 268: 2595-2601, 1993.
349. WAND, G. S., AND M. A. LEVINE. Hormonal tolerance to ethanol is associated with decreased expression of the GTP-binding protein, $G_s\alpha$, and adenylyl cyclase activity in ethanol-treated mice. *Alcohol. Clin. Exp. Res.* 15: 705-710, 1991.
350. WANG, D.-C., T. F. TARASCHI, E. RUBIN, AND N. JANES. Configurational entropy is the driving force of ethanol action on membrane architecture. *Biochim. Biophys. Acta* 1145: 141-148, 1993.
351. WANG, X., G. DAYANITHI, J. R. LEMOS, J. J. NORDMANN, AND S. N. TREISTMAN. Calcium currents and peptide release from neurohypophysial terminals are inhibited by ethanol. *J. Pharmacol. Exp. Ther.* 259: 705-711, 1991.
352. WANG, X., J. R. LEMOS, G. DAYANITHI, J. J. NORDMANN, AND S. N. TREISTMAN. Ethanol reduces vasopressin release by inhibiting calcium currents in nerve terminals. *Brain Res.* 551: 338-341, 1991.
353. WANG, X., G. WANG, J. R. LEMOS, AND S. N. TREISTMAN. Ethanol directly modulates gating of a dihydropyridine-sensitive $Ca^{2+}$ channel in neurohypophysial terminals. *J. Neurosci.* 14: 5453-5460, 1994.
354. WANNAMAKER, V. L., AND L. E. NAGY. Equilibrative adenosine transport in rat hepatocytes after chronic ethanol feeding. *Alcohol. Clin. Exp. Res.* 19: 735-740, 1995.
355. WAYNER, M. J., J. L. POLAN-CURTAIN, S. C. CHIU, AND D. S. ARMSTRONG. Losartan reduces ethanol intoxication in the rat. *Alcohol* 11: 343-346, 1994.
356. WEGELIUS, K., AND E. R. KORPI. Ethanol inhibits NMDA-induced toxicity and trophism in cultured cerebellar granule cells. *Acta Physiol. Scand.* 154: 25-34, 1995.
357. WEHNER, J. M., AND B. J. BOWERS. Use of transgenics, null mutants, and antisense approaches to study ethanol's actions. *Alcohol. Clin. Exp. Res.* 19: 811-820, 1995.
358. WEIGHT, F. F. Cellular and molecular physiology of alcohol action in the nervous system. *Int. Rev. Neurobiol.* 33: 289-348, 1992.
359. WEINER, J. L., L. ZHANG, AND P. L. CARLEN. Potentiation of $GABA_A$-mediated synaptic current by ethanol in hippocampal CA1 neurons: possible role of protein kinase C. *J. Pharmacol. Exp. Ther.* 268: 1388-1395, 1994.
360. WEISS, F., M. T. LORANG, F. E. BLOOM, AND G. F. KOOB. Oral alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: genetic and motivational determinants. *J. Pharmacol. Exp. Ther.* 267: 250-258, 1993.
361. WEISS, F., L. H. PARSONS, G. SCHULTEIS, P. HYYTIA, M. T. LORANG, F. E. BLOOM, AND G. F. KOOB. Ethanol self-administration restores withdrawal-associated deficiencies in accumbal dopamine and 5-hydroxytryptamine release in dependent rats. *J. Neurosci.* 16: 3474-3485, 1996.
362. WEST, J. R., C. A. HODGES, AND A. C. J. BLACK. Prenatal exposure to ethanol alters the organization of hippocampal mossy fibers in rats. *Science Wash. DC* 211: 957-959, 1981.
363. WHITTINGTON, M. A., J. D. LAMBERT, AND H. J. LITTLE. Increased NMDA receptor and calcium channel activity underlying ethanol withdrawal hyperexcitability. *Alcohol Alcohol.* 30: 105-114, 1995.
364. WIDDOWSON, P. S., AND R. B. HOLMAN. Ethanol-induced increase

in endogenous dopamine release may involve endogenous opiates. *J. Neurochem.* 59: 157-163, 1992.

365. WILKE, N., M. SGANGA, S. BARHITE, AND M. F. MILES. Effects of alcohol on gene expression in neural cells. In: *Toward a Molecular Basis of Alcohol Use and Abuse*, edited by B. Jansson, H. Hornvall, Y. Rydberg, L. Ternius, and B. L. Vallee. Basal: Birkhauser Verlag, 1994, p. 49-59.
366. WILLIAMS, R. J., M. A. VEALE, P. HORNE, AND E. KELLY. Ethanol differentially regulates guanine nucleotide-binding protein $\alpha$ subunit expression in NG108-15 cells independently of extracellular adenosine. *Mol. Pharmacol.* 43: 158-166, 1993.
367. WOOD, S. C., P. H. TONNER, A. J. DE ARMENDI, B. BEGGE, AND K. W. MILLER. Channel inhibition by alkanols occurs at a binding site on the nicotinic acetylcholine receptor. *Mol. Pharmacol.* 47: 121-130, 1995.
368. WOODS, M. D., R. I. FRESHNEY, S. G. BALL, AND P. F. T. VAUGHAN. Regulation of cyclic AMP formation in cultures of human foetal astrocytes by $\beta_2$-adrenergic and adenosine receptors. *J. Neurochem.* 53: 864-869, 1989.
369. WOZNIAK, K. M., A. PERT, AND M. LINNOILA. Antagonism of 5-$HT_3$ receptors attenuates the effects of ethanol on extracellular dopamine. *Eur. J. Pharmacol.* 187: 287-289, 1990.
370. WU, C. H., A. FROSTHOLM, A. L. DE BLAS, AND A. ROTTER. Differential expression of $GABA_A$/benzodiazepine receptor subunit mRNAs and ligand binding sites in mouse cerebellar neurons following in vivo ethanol administration: an autoradiographic analysis. *J. Neurochem.* 65: 1229-1239, 1995.
371. WU, L.-G., AND P. SAGGUA. Adenosine inhibits evoked synaptic transmission primarily by reducing presynatpic calcium influx in area CA1 of hippocampus. *Neuron* 12: 1139-1148, 1994.
372. YOON, K. W., AND S. M. ROTHMAN. Adenosine inhibits excitatory but not inhibitory synaptic transmission in the hippocampus. *J. Neurosci.* 11: 1375-1380, 1991.
373. YOSHIMOTO, K., W. J. MCBRIDE, L. LUMENG, AND T.-K. LI. Ethanol enhances the release of dopamine and serotonin in the nucleus accumbens of HAD and LAD lines of rats. *Alcohol. Clin. Exp. Res.* 16: 781-785, 1992.
374. YOSHIMURA, M., AND B. TABAKOFF. Selective effects of ethanol on the generation of cAMP by particular members of the adenylyl cyclase family. *Alcohol. Clin. Exp. Res.* 19: 1435-1440, 1995.
375. ZHANG, Y., H. SAITO, N. NISHIYAMA, AND K. ABE. Effects of DX-9386, a traditional Chinese medicinal prescription, on long-term potentiation in the dentate gyrus in rats. *Biol. Pharm. Bull.* 17: 1337-1340, 1994.