The Neural Correlate of Consciousness and the Mechanisms of General Anaesthesia

H. Flohr, U. Glade, D. Motzko

Brain Research Institute, University of Bremen, Germany

Introduction

Previous attempts to explain the mechanism of action of general anaesthetics have mainly focussed on the cellular and molecular effects of these agents. Despite an immense amount of experimental data collected over the past decades, a convincing theory of general anaesthesia has not yet emerged. The anaesthetic state remains a mystery. After all, it might appear questionable whether anaesthetic action can be understood at this *level of description*.

General anaesthesia consists in a loss of consciousness, i.e. the absence of subjective phenomenal states such as perceptions, feelings, thoughts, sensations, memories etc. A theory of anaesthesia must therefore explain how phenomenal states are suppressed as a result of the action of anaesthetic agents on brain function. The explanandum of such a theory is not (only) to identify the variety of targets and physiological effects of anaesthetic agents, but to prove as to whether and why (some) of these actions are causally relevant for the loss of consciousness. This, however, presupposes a concept on the neurophysiological conditions and mechanisms underlying consciousness, a scientific theory on the mind-brain relationship. For many decades the problem of consciousness has been regarded as intractable. It was either claimed that consciousness is not a natural phenomenon which is explicable in scientific terms or, even if considered to belong to the domain of natural phenomena, it was argued that the relation between brain processes and consciousness was beyond our cognitive grasp and could not be made intelligible. This traditional skepticism is essentially the reason why a theory of anaesthesia could not have been developed.

Higher-order Representation Theories of Consciousness

The last decade, however, has brought a remarkable change to this skeptic attitude. It appears that finally some genuine progress has been made in demystifying the

notion of consciousness. Some novel theoretical concepts have been developed that might lead to new and concrete hypotheses on the physiological basis of consciousness. Such hypotheses could also be a point of departure for understanding the phenomenon of anaesthesia.

One important position in the current debate is that conscious states are, or consist in, a specific class of mental representations, namely higher-order representations (HORs). HORs are conceived as complex representational structures by which an information processing system represents its actual inner state as its own state. Being conscious means that an information processing system generates either perceptions or thoughts about its own current state. The higher-order representation paradigm has a long history in the philosophy of mind that dates back to John Locke, Gottfried Wilhelm Leibniz, Immanuel Kant, William James and Franz Brentano. Modern versions have been worked out by D. Armstrong (1980), P. Churchland (1985), D. Rosenthal (1986, 1990, 1993a, 1993b) and T. Metzinger (1993).

The attractive feature of the HOR idea is that it leads to concrete hypotheses on the realisation of consciousness in brains and possibly in other information processing systems. The neurosciences have developed a concept on how mental representations could be physiologically realized. This is the concept of the cell assembly originally proposed by Donald Hebb. In brief, Hebb suggested that the physiological substrate of a mental representation consists in the activity pattern of a *cell assembly*, i.e. a group of neurons preferentially interconnected and firing in a coordinated fashion. It was also Hebb's idea that such assemblies will be automatically formed in neural nets, if a specific plastic synapse is present that strengthens synaptic connections between concurrently activated presynaptic and postsynaptic neurons. More recently, a hypothesis on the specific physiological mechanisms involved in the realisation of higher-order representations has been proposed (Flohr, 1991, 1992 and 1995a). It was suggested (a) that HORs are instantiated by a special class or subset of large and complex cell assemblies, (b) that the formation of such assemblies requires a specific mechanism for the modification of synaptic links and (c) that this particular binding mechanism is effected by the cortical NMDA synapse.

NMDA Receptor-dependent Plasticity, Higher-order Representations and the Mechanism of Anaesthesia

One unique feature of the NMDA synapse (Fig. 1) is that it is both voltage-dependent and ligand-gated. The receptor-associated ion channel opens under two conditions. Firstly, the presynapse must release the transmitter glutamate and, secondly, the postsynaptic membrane must be depolarized to about -35 mV. At membrane potentials around the resting potential the channel is blocked by a magnesium ion that binds in a voltage-dependent manner to a site in the lumen of the channel. This blockade will be removed, if the membrane is depolarized. This mechanism qualifies the NMDA synapse as a Hebbian coincidence detector that detects coincident pre- and postsynaptic activity. The occurrence of pre- and postsynaptic activity induces diverse changes in the connection strength between simul-

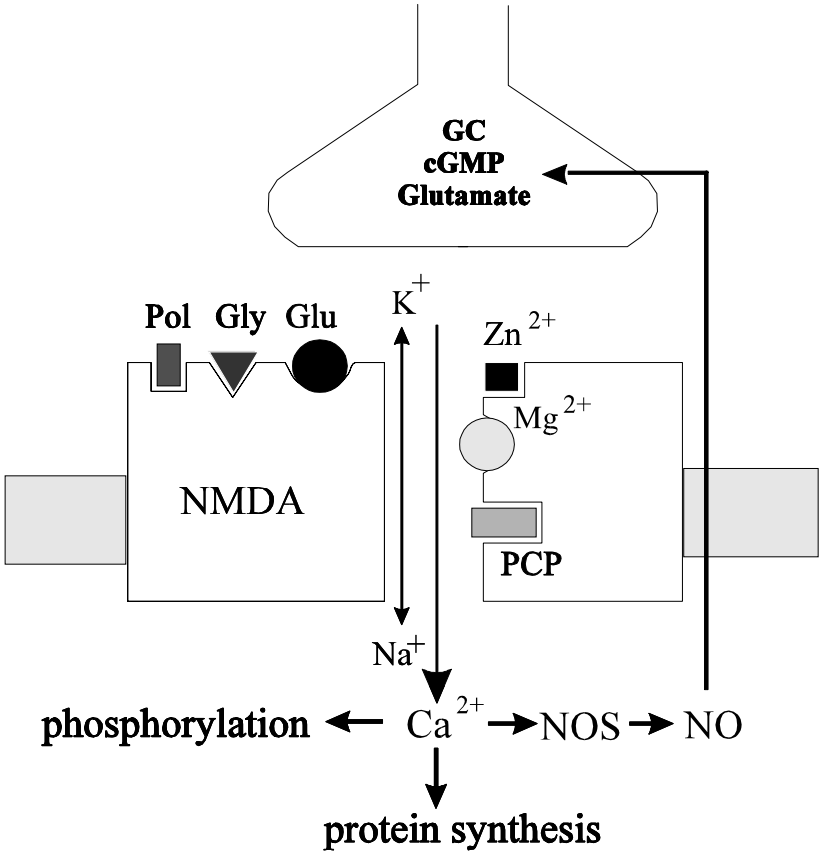

Fig. 1: Schematic representation of the NMDA synapse and its multiple sites for drug action. Dissociative anaesthetics bind to a receptor (PCP) within the channel. Glu: the agonist recognition site at which glutamate analogues act as competitive antagonists. Gly: glycine binding site. Pol: polyamine binding site. Two additional binding sites for Mg^{2+} and Zn^{2+} are also shown. NOS: nitric oxide synthase.

taneously active neurons. The NMDA channel is permeable to Na^+, K^+ and Ca^{2+} ions. As soon as the activation threshold is reached this synapse is switched on in addition to already active non-NMDA connections converging at the postsynaptic membrane. This means that non-NMDA receptor-mediated depolarisations that exceed a critical voltage or frequency are amplified and a rapid change in the interaction between simultaneously active neurons takes place. The activity of these neurons is enhanced and coordinated via positive feedback loops resulting in reverberatory excitatory activity in a pool of interconnected neurons. In addition, Ca^{2+} acts as a second messenger and triggers a cascade of reactions in the postsynaptic terminal. It activates the enzyme NO-synthase that catalyzes the production of nitric oxide (NO). NO is a gas which rapidly diffuses through the cell membrane.

Acting as a retrograde messenger, it induces changes in both, presynaptic transmitter release and postsynaptic sensitivity to the transmitter. Again, this mechanism leads to rapid modifications in synaptic weight and in the interaction of simultaneously firing neurons. In addition to such rapid and transient changes, Ca^{2+} triggers post-translational changes of neuronal proteins and changes in protein synthesis. These effects are presumably responsible for persistent alterations in synaptic connectivity and the formation of permanent memory traces. Thus it appears that the NMDA synapse possesses a repertoire of different mechanisms to bring about Hebbian plastic changes of synaptic efficacy. It controls both fast and transient changes as well as slow and permanent ones. It enables the formation of cell assemblies with different lifetimes.

Following the activation by glutamate, the NMDA receptor channel complex remains in an activated state for several hundred milliseconds. This endows the postsynaptic membrane with a relatively long memory for the detection of temporarily correlated activity. This feature is presumably crucial for the specific role of this synapse in the formation of HORs. A large time window is necessary for detecting distributed correlated activity and for establishing plastic modifications in long-distance cortico-cortical connections. The NMDA receptor appears to be ideally suited to control the organisation of large, spatially extended neuronal assemblies that bind and integrate widely distributed activities and thereby to produce those global representational structures to which higher-order representations belong. The activation state of the cortical NMDA receptor determines the size and the complexity of the representational structures that can be built up in a given period of time. Large and complex assemblies will automatically develop, if the plastic changes are accomplished at a critical rate, i.e. if the potential of the postsynaptic membrane is near its threshold. If the cortical NMDA system is inactivated, such distributed representational states cannot be generated. This is equivalent to a loss of consciousness.

Recently, a theory of anaesthesia has been derived from these hypotheses (Flohr, 1995b). The core of this theory consists of the assumption that a disruption of the NMDA-dependent representational processes is the common mechanism of action of anaesthetic agents. Anaesthetics are agents that *directly* or *indirectly* interfere with these computational processes. This hypothesis leads to concrete predictions that can be experimentally tested. If it is true, it will follow, firstly, that *all* agents that directly inactivate the NMDA synapse, necessarily have anaesthetic properties; secondly, anaesthetic agents that do not act upon the NMDA synapse directly, but primarily have other targets, will exert their anaesthetic action if and only if, they inhibit the NMDA-dependent processes indirectly.

The NMDA Synapse as a Target for Anaesthetics

The NMDA synapse is a potential target for many different drugs. Consequently a variety of possibilities exists to test these predictions.

1. The receptor-associated ion channel contains a binding site (PCP receptor) for non-competitive antagonists. When these substances bind to the PCP receptor, the influx of Na^+ and Ca^{2+} is blocked. As a consequence the Na^+-dependent depolarisation and the Ca^{2+}-regulated changes are inhibited. Mg^{2+} also binds in a voltage-dependent manner to a site located within the channel. An increase of the extracellular Mg^{2+} concentration increases the probability that the open channel is blocked and should produce similar effects as non-competitive NMDA antagonists.
2. The glutamate receptor can be blocked by specific competitive NMDA antagonists;
3. A strychnine-insensitive glycine binding site, the co-activation of which is necessary for receptor activation, can be blocked by specific glycine antagonists;
4. A polyamine binding site can be blocked by polyamine antagonists;
5. Downstream from the channel the enzyme nitric oxide synthase (NOS) can be inactivated by NOS inhibitors;
6. As the NMDA synapse is both, ligand-gated and voltage-dependent, the working conditions of the receptor channel complex can be changed *indirectly* by all influences that alter the postsynaptic membrane potential. In particular, the working conditions of the receptor can be modified by inhibitory and excitatory synapses located in the vicinity of the receptor. AMPA and $GABA_A$ synapses are co-localized with NMDA receptors which suggests that the two types of excitatory amino acid receptors and the inhibitory $GABA_A$ receptor may act in concert.

Anaesthetic Effects of Drugs that Primarily Interact with the NMDA Synapse

It appears that *any* of the possible *direct* interventions that block the activation of the NMDA receptor or the subsequent processes triggered by Ca^{2+} inevitably produce an anaesthetic effect. Fig. 2 summarizes what is currently known about these processes.

Non-competitive NMDA antagonists, like ketamine or phencyclidine, cause severe disturbances of consciousness. Administered in low doses, they induce psychedelic states. Patients experience sensory illusions, visual and auditory hallucinations, and disorganized thought. The body image is distorted. In particular, they report ego-disorders that resemble schizophrenic states. Typically, they experience a loosening of ego-boundaries that may end up in a feeling of merging with the cosmos. They experience the loss of control over their thought processes. In high doses that lead to a blockade of a large fraction of cortical NMDA receptors, non-competitive NMDA antagonists produce general anaesthesia. This anaesthetic state is different from that caused by most other anaesthetic agents. It is characterized by a rather selective loss of conscious functions, whereas other functions, such as most protective reflexes, remain intact. Based upon electroencephalic studies, Corssen and Domino (1966) assigned the special features of this state to a depression of activity

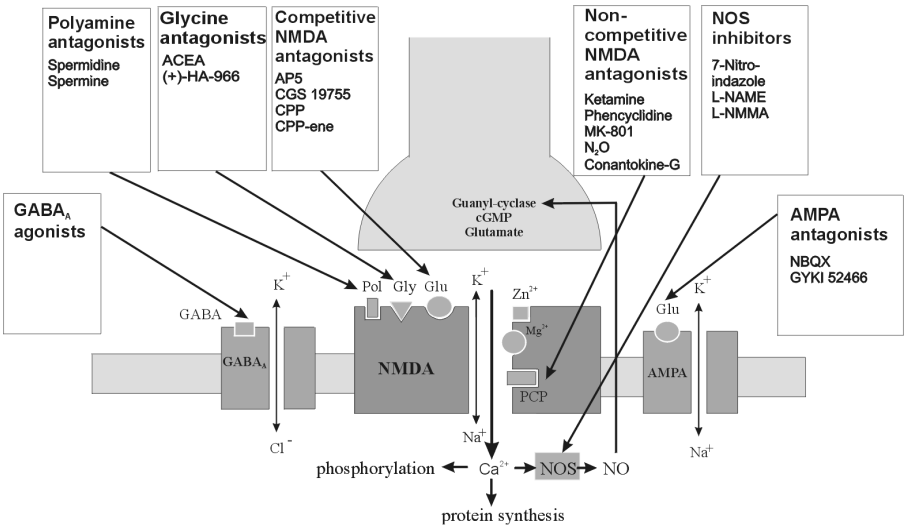

Fig. 2: The NMDA synapse as a target for anaesthetics. Schematic representation of the NMDA receptor channel complex with its regulatory sites and neighbouring AMPA and $GABA_A$ receptors which can influence the working conditions of the NMDA receptor. All agents mentioned in this scheme possess anaesthetic properties. Arrows indicate possible interaction sites.

in the cortical association areas and to a selective inhibition of "higher associative functions".

Most non-competitive NMDA antagonists are not fully selective, but also interact with other components of the central nervous system. But these side effects are not able to fully account for the anaesthetic or psychotomimetic properties. On the contrary, there are good reasons to assume that both effects are caused by their NMDA antagonism. Firstly, *all* substances that bind within the NMDA channel produce a dissociative anaesthetic state. One of them is MK-801, which is an antagonist that displays a high selectivity for the PCP binding site (Koek et al., 1989; Scheller et al., 1989; Daniell, 1990; Löscher et al., 1991; Irifune et al., 1992; Perkins and Morrow, 1992a). Secondly, the anaesthetic potency of these compounds is highly correlated with their relative affinity for the PCP binding site (Koek et al., 1989; Perkins and Morrow, 1992b). Ketamine exists in two enantiomers, R- and S-ketamine. S-ketamine has a three times higher affinity for the PCP recognition site than R-ketamine. This agrees well with the anaesthetic potency of the two isomers. S-ketamine possesses high hypnotic and analgesic potency. R-ketamine is much less effective (Marietta et al., 1977; Ryder et al., 1978; White et al., 1980). The subjective psychoactive effects of the non-competitive antagonists, as indicated by animal discrimination studies, are also correlated with their affinity for the PCP receptor (Martin and Lodge, 1988). The same is true for the psychotomimetic effects in humans and in particular for the ego-disorders observed after the administration of subanaesthetic doses. For instance, S-ketamine causes pronounced ego-disorders whereas R-ketamine does not (Vollenweider, 1998). Thirdly, the anaesthetic effects

of the non-competitive antagonists can be changed by modifying their binding kinetics. Agonists of the glutamate and glycine receptors enhance the opening-time of the channel and thereby the dissociation of ligands bound inside. Both agonists reduce the anaesthetic effects of channel blockers. This antianaesthetic effect can be reversed again by selective glutamate and glycine antagonists (Irifune et al., 1992).

Mg^{2+} ions block the open NMDA channel in a voltage-dependent manner. When the Mg^{2+} concentrations in the extracellular fluid are normal and membrane potentials are close to the resting potential the channel will be blocked. As mentioned above, an increase of the Mg^{2+} concentration in the extracellular fluid increases the probability that the open channel is blocked and should have similar effects as the administration of non-competitive NMDA antagonists. In fact, an anaesthetic action of high Mg^{2+} concentrations has been shown by Irifune et al. (1992). $MgCl_2$ dose-dependently enhances the effect of non-competitive NMDA antagonists in mice. Interestingly, the first general anaesthesia in man with magnesium sulphate was performed in 1916 (Peck and Meltzer, 1916).

Competitive NMDA antagonists that block the glutamate receptor like AP5, CPP, CGS 19755 and D-CPP-ene have also been shown to possess anaesthetic potencies (Koek et al., 1986; Boast and Pastor, 1988; Woods, 1989; France et al., 1990; Daniell, 1991; Irifune et al., 1992; Perkins and Morrow, 1992a; Kuroda et al., 1993). They either reduce the MAC for volatile anaesthetics or increase the sleeping time of other intravenous anaesthetics. The same is true for agents acting on the polyamine site, like spermine and spermidine (Daniell, 1992), or on the glycine site (McFarlane et al., 1995). Recently it was found that N_2O inhibits the ionic currents mediated through the NMDA receptor (Jevtovic-Todorovic et al., 1998). The findings suggest a mixed competitive/non-competitive mechanism of inhibition. N_2O has almost no effect on GABA-activated currents. These observations would also explain the specific psychopharmacological profile of laughing gas as similar to ketamine.

The potential role of the NO-signalling pathway in general anaesthesia is suggested by several recent observations. Originally it was reported that the inhibition of NO synthesis by the unspecific NOS inhibitor nitro^{G}-L-arginine methyl ester (L-NAME) potentiates the effects of halothane, isoflurane and alcohol (Johns et al., 1992; Adams et al., 1994; Ichinose et al., 1995). More recently, it was shown that the brain-selective NOS inhibitor 7-nitro-indazole (7-Ni) dose-dependently prolongs the duration of barbiturate narcosis (Motzko et al., 1998) and also reduces the isoflurane MAC in the rat (Pajewski et al., 1996). Nitric oxide is an important component in the Hebbian plastic processes controlled by the NMDA synapse. Subsequent to the activation of the NMDA receptor channel, NO is produced and acts as a retrograde messenger. It induces changes in both presynaptic transmitter release and postsynaptic sensitivity to the released transmitter. In the presynaptic terminal it acts through the activation of the soluble guanyl-cyclase to produce cyclic GMP which subsequently has multiple effects on presynaptic transmitter release. The formation of cGMP in response to stimulation by glutamate and NMDA can be suppressed by ketamine (Gonzales et al., 1995). The involvement of the NO-cGMP pathway has also been shown for a number of other anaesthetics, such as

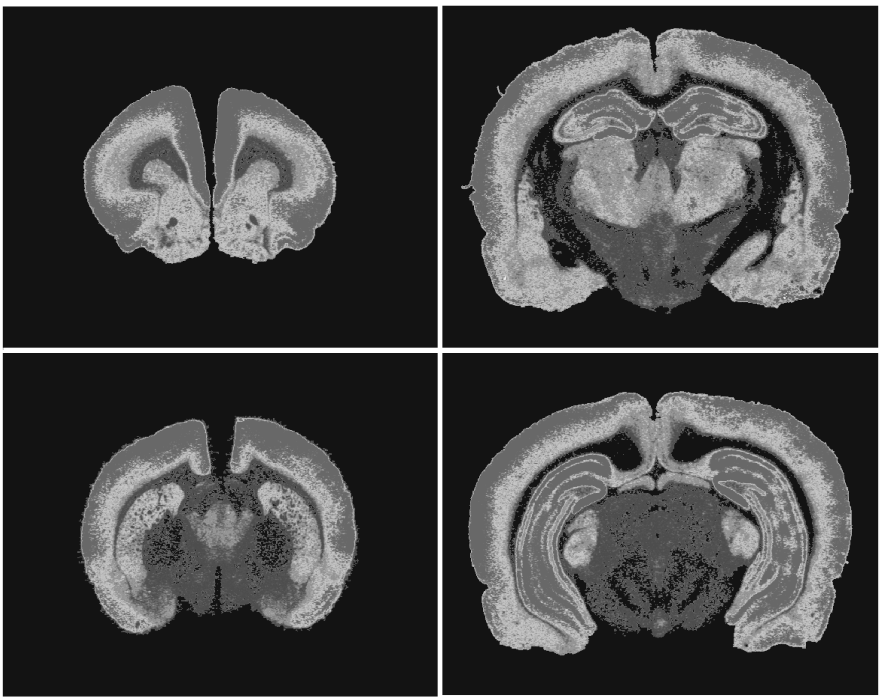

Fig. 3: In vivo uptake of [^{3}H]MK-801 in the rat brain under awake conditions. [^{3}H]MK-801 was dissolved in saline solution and injected through a vene catheter at a dose of 600 μCi/kg. The experimental animals were sacrificed by swift decapitation 1 min after the administration of the tracer, i.e. before equilibrium conditions were reached. The brains were rapidly removed and frozen. Frozen sections were washed with TRIS maleate buffer to minimize non-receptor-associated bindings in the sections and subsequently air-dried. The sections were juxtaposed to [^{3}H]Hyperfilm (Amersham, Buchler) for 60 days.

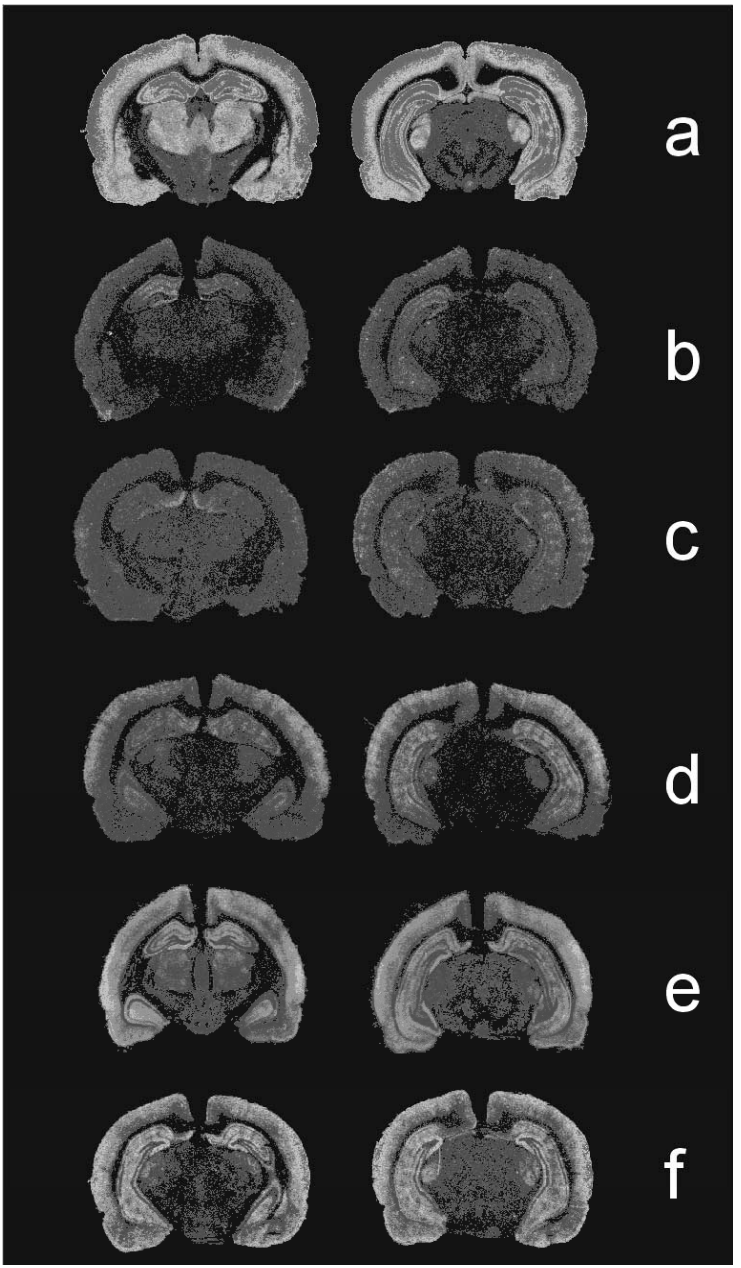

Fig. 4: In vivo uptake of [^{3}H]MK-801 in (b) ketamine (175 mg/kg), (c) Na-pentobarbital (110 mg/kg), (d) halothane, (e) ethanol (4 g/kg); and (f) propofol (180 mg/kg) anaesthesia. Compared to the awake condition (a) the cortical indicator uptake is reduced in all forms of anaesthesia.

halothane, enflurane and isoflurane (Zuo et al., 1996; Zuo and Johns, 1995; Tonner et al., 1997), barbiturates (Morgan et al., 1991; Terasako et al., 1994), and alpha-2-adrenergic agonists (Vuilliemoz et al., 1996).
Taken together it appears that the first of the previously stated predictions is correct: Any of the various possible *direct* pharmacological interventions that block the activation of the NMDA receptor channel complex, or the subsequent plastic processes triggered by Ca^{2+}, inevitably do cause anaesthetic effects.

Indirect Effects of Anaesthetics that Primarily Act Upon other Targets on the NMDA Synapse

It is known for a large number of anaesthetics that they do not act upon the NMDA synapse directly. However, according to what has been said above, it is possible that these agents exert an *indirect* effect on the working conditions of the NMDA receptor. It is therefore possible that the anaesthetic action of anaesthetics known to primarily interact with other targets in the CNS results from an *indirect* effect on the NMDA receptor. In particular, this could be the case for $GABA_A$ agonists that comprise a large group of anaesthetics (Metherate and Ashe, 1995).
In fact such indirect effects can be demonstrated. Fig. 3 shows an attempt to directly visualize the activation state of the cortical NMDA synapse in the rat under *in vivo* conditions by means of an autoradiographic technique. This technique is based on the following considerations: Radioactively labeled non-competitive NMDA antagonists, such as MK-801, have access to their binding sites within the channel only if the channel displays an open conformation. The rate at which the indicator is bound under non-equilibrium conditions depends on the number of activated channels and on the mean opening times of the individual channels.
In the awake rat (Fig. 3) the binding sites labeled *in vivo* are unevenly distributed with highest densities in the cortex and the hippocampal formation. Most of the cortical NMDA synapses are labeled when the animal is awake. This means that, in this condition, most of the NMDA synapses have been active during the time period in which the indicator was available in the extracellular space. In ketamine narcosis (Fig. 4b) the indicator uptake in the cortex is considerably reduced, which is not surprising because ketamine acts as a channel blocker. A very similar pattern, however, is obtained in barbiturate (Fig. 4c), and propofol (Fig. 4f) narcosis where the cortical NMDA synapse is obviously suppressed by GABAergic inhibition. The same is true for halothane (Fig. 4d) and alcohol (Fig. 4e). Thus it appears that the second prediction mentioned above can also be supported by experimental evidence: The anaesthetic action of anaesthetics that do not primarily affect the NMDA synapse such as $GABA_A$ agonists, can be a consequence of indirect effects.

Conclusions

All agents that directly inactivate the NMDA synapse or the subsequent plastic processes possess anaesthetic properties. The anaesthetic action of agents that

primarily act upon other targets can be explained as an indirect effect on the NMDA receptor. Thus current experimental evidence supports the hypothesis that a disruption of NMDA-dependent processes is the final common pathway of anaesthetic action. The data also support the hypothesis outlined above on the key role of the NMDA synapse in the neural mechanisms underlying consciousness. Consciousness critically depends on a specific class of computational processes mediated by the cortical NMDA synapse.

References

Adams ML, Meyer ER, Sewing BN, Cicero TJ (1994) Effects of nitric oxide-related agents on alcohol narcosis. Alcohol clin exp Res 18: 969-975

Armstrong D (1980) The nature of mind and other essays. Cornell University Press, Ithaca, NY

Boast CH, Pastor G (1988) Characterisation of motor activity patterns induced by N-methyl-D-aspartate antagonists in gerbils. J Pharmacol Exp Ther 247: 556-561

Churchland P (1985) Reduction qualia and the direct introspection of brain states. J Phil 82 (1): 2-28

Corssen G, Domino EF (1966) Dissociative anesthesia: Further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. Anesth Analg 45: 29-40

Daniell LC (1990) The non-competitive NMDA antagonists MK 801, phencyclidine and ketamine increase the potency of general anesthetics. Pharmacol Biochem Behav 36: 111-115

Daniell LC (1991) Effects of CGS 19755, a competitive N-methyl-D-aspartate antagonist, on general anesthetic potency. Pharmacol Biochem Behav 40: 767-769

Daniell LC (1992) Alteration of general anesthetic potency by agonists and antagonists of the polyamine binding site of the N-methyl-D-aspartate receptor. J Pharmacol exp Ther 261: 304-310

Flohr H (1991) Brain processes and phenomenal consciousness. A new and specific hypothesis. Theory and Psychology 1: 245-262

Flohr H (1992) Qualia and brain processes. In: Beckermann A, Flohr H, Kim J (Eds.) Emergence or Reduction. De Gruyter, Berlin, New York, pp. 220-238

Flohr H (1995a) Sensations and brain processes. Behav Brain Res 71: 157-161

Flohr H (1995b) An information processing theory of anaesthesia. Neuropsychologia 33: 1169-1180

France CP, Winger GD, Woods JH (1990) Analgesic, anesthetic and respiratory effects of the competitive N-methyl-D-aspartate (NMDA) antagonist CGS 19755 in rhesus monkeys. Brain Res 526: 355-358

Gonzales JM, Loeb AL, Reichard PS, Irvine S (1995) Ketamine inhibits glutamate-, N-methyl-D-aspartate-, and quisqualate-stimulated cGMP production in cultured cerebral neurons. Anesthesiology 82: 205-213

Ichinose F, Huang PL, Zapol WD (1995) Effects of targeted neuronal nitric oxide synthase gene disruption and nitro^{G}-L-arginine methylester on the threshold for isoflurane anesthesia. Anesthesiology 83: 101-108

Irifune M, Shimizu T, Nomoto M, Fukuda T (1992) Ketamine-induced anesthesia involves the N-methyl-D-aspartate receptor-channel complex in mice. Brain Res 596: 1-9

Jevtovic-Todorovic V, Todorovic SM, Mennerick S, Powell S, Dikranian K, Benshoff N, Zorumski CF, Olney JW (1998) Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nature Medicine 4: 460-463

Johns RA, Moscicki JC, DiFazio CA (1992) Nitric oxide synthase inhibitor dose-dependently and reversibly reduces the threshold for halothane anesthesia. Anesthesiology 77: 779-784

Koek WJ, Woods H, Ornstein P (1986) Phencyclidine-like behavioral effects in pigeons induced by systemic administration of the excitatory amino acid antagonist, 2-amino-5-phosphono-valerate. Life Sci 39: 973-978

Koek W, Colpaert FC, Woods JH, Kamenka JM (1989) The phencyclidine (PCP) analog N-[1-(2-Benzo (B)thiophenyl)cyclohexyl] piperidine shares cocaine-like but not other characteristic behavioral effects with PCP, ketamine and MK 801. J Pharmacol exp Ther 250: 1019-1027

Kuroda Y, Strebel S, Rafferty C, Bullock R (1993) Neuroprotective doses of N-methyl-D-aspartate receptor antagonists profoundly reduce the minimum alveolar anaesthetic concentration (MAC) for isoflurane in rats. Anesth Analg 77: 795-800

Löscher W, Fredow G, Ganter M (1991) Comparison of pharmacodynamic effects of the non-competitive NMDA receptor antagonists MK 801 and ketamine in pigs. Eur J Pharmacol 192: 377-382

Marietta MP, Way WL, Castagnoli N, Trevor AJ (1977) On the pharmacology of the ketamine enantiomorphs in the rat. J Pharmacol Exp Ther 202: 157-165

Martin D, Lodge D (1988) Phencyclidine receptors and N-methyl-D-aspartate antagonism: Electrophysiologic data correlate with known behaviors. Pharmacol Biochem Behav 31: 279-286

McFarlane C, Warner DS, Nader A, Dexter F (1995) Glycine receptor antagonism. Effects of ACEA 1021 on the minimum alveolar concentration for halothane in the rat. Anesthesiology 82: 961-968

Metherate R, Ashe JH (1995) GABAergic suppression prevents the appearance and subsequent fatigue of an NMDA receptor-mediated potential in the neocortex. Brain Res 699: 221-230

Metzinger T (1993) Subjekt und Selbstmodell. Schöningh Verlag, Paderborn

Morgan WW, Bermudez J, Chang X (1991) The relative potency of pentobarbital in suppressing the kainic acid- or the N-methyl-D-aspartate acid-induced enhancement of cGMP in cerebellar cells. Eur J Pharmacol 204: 335-338

Motzko D, Glade U, Tober C, Flohr H (1998) 7-nitro indazole enhances methohexital anesthesia. Brain Res 788: 353-355

Pajewski TN, DiFazio CA, Moscicki JC, Johns RA (1996) Nitric oxide synthase inhibitors, 7-nitro indazole and nitro^{G}-L-arginine methyl ester, dose dependently reduce the threshold for isoflurane anesthesia. Anesthesiology 85: 1111-1119

Peck CH, Meltzer SJ (1916) Anesthesia in human beings by intravenous injection of magnesium sulphate. JAMA 67: 1131-1133

Perkins WJ, Morrow DR (1992a) A dose-dependent reduction in halothane MAC in rats with a competitive N-methyl-D-aspartate (NMDA) receptor antagonist. Anesth Analg 74: 233

Perkins WJ, Morrow DR (1992b) Correlation between anesthetic potency and receptor binding constant for non-competitive N-methyl-D-aspartate receptor antagonists. Anesthesiology 77: A742

Rosenthal D (1986) Two concepts of consciousness. Philosophical Studies 49: 329-359

Rosenthal D (1990) A theory of consciousness. Report No. 40/1990 on mind and brain, perspectives in theoretical psychology and the philosophy of mind. ZiF, University of Bielefeld

Rosenthal D (1993a) Thinking that one thinks. In: Davies M, Humphreys G (Eds.) Consciousness. Blackwell, Cambridge, MA, pp. 197-223
Rosenthal D (1993b) Higher-order thoughts and the appendage theory of consciousness. Philosophical Psychology 6: 155-166
Ryder S, Way WL, Trevor AJ (1978) Comparative pharmacology of the optical isomers of ketamine in mice. Eur J Pharmacol 49: 15-23
Scheller MS, Zornow MH, Fleischer JE, Shearman GT, Greber TF (1989) The noncompetitive NMDA receptor antagonist, MK 801, profoundly reduces volatile anesthetic requirements in rabbits. Neuropharmacology 28: 677-681
Terasako K, Nakamura K, Miyawaki I, Toda H, Kakuyuma M, Kenjiro M (1994) Inhibitory effects of anesthetics on cyclic guanosine monophosphate (cGMP) accumulation in rat cerebellar slices. Anesth Analg 78: 823-830
Tonner PH, Scholz J, Lamberz L, Schlamp N, Schulte am Esch J (1997) Inhibition of nitric oxide synthase decreases anesthetic requirements of intravenous anesthetics in Xenopus laevis. Anesthesiology 87: 1479-1485
Vollenweider FX (1998) Advances and pathophysiological models of halucinogenic drug action in humans: A preamble to schizophrenia research. Pharmacopsychiat 31: 92-103
Vuilliemoz Y, Shen H, Virag L (1996) Alpha-2-adrenoreceptor agonists decrease cyclic guanosine 3', 5'-monophosphate in the mouse brain. Anesthesiology 85: 544-550
White PF, Ham J, Way WL, Trevor AJ (1980) Pharmacology of ketamine isomers in surgical patients. Anesthesiology 52: 231-239
Woods JM (1989) Consciousness. Pharmacol Biochem Behav 32: 1081
Zuo Z, Johns RA (1995) Halothane, enflurane, and isoflurane do not affect the basal or agonist-stimulated activity of partially isolated soluble and particulate guanyl cyclases of rat brain. Anesthesiology 83: 395-404
Zuo Z, De Vente J, Johns RA (1996) Halothane and isoflurane dose-dependently inhibit the cyclic GMP increase caused by N-methyl-D-aspartate in rat cerebellum: Novel localisation and quantitation by in vitro autoradiography. Neuroscience 74: 1069-1075