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Reciprocal autoreceptor and heteroreceptor control of serotonergic, dopaminergic and noradrenergic transmission in the frontal cortex: relevance to the actions of antidepressant agents

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The frontal cortex (FCX) plays a key role in processes that control mood, cognition and motor behaviour, functions which are compromised in depression, schizophrenia and other psychiatric disorders. In this regard, there is considerable evidence that a perturbation of monoaminergic input to the FCX is involved in the pathogenesis of these states. Correspondingly, the modulation of monoaminergic transmission in the FCX and other corticolimbic structures plays an important role in the actions of antipsychotic and antidepressant agents. In order to further understand the significance of monoaminergic systems in psychiatric disorders and their treatment, it is essential to characterize mechanisms underlying their modulation. Within this framework, the present commentary focuses on our electrophysiological and dialysis analyses of the complex and reciprocal pattern of auto- and heteroreceptor mediated control of dopaminergic, noradrenergic and serotonergic transmission in the FCX. The delineation of such interactions provides a framework for an interpretation of the influence of diverse classes of antidepressant agent upon extracellular levels of dopamine, noradrenaline and serotonin in FCX. Moreover, it also generates important insights into strategies for the potential improvement in the therapeutic profiles of antidepressant agents.

Key words: antidepressant; depression; dopamine; frontal cortex; monoamines; mood; noradrenaline; selective serotonin reuptake inhibitor; serotonin; tricyclic

Monoamines and psychiatric disorders

A perturbation of corticolimbic serotonergic, dopaminergic and noradrenergic transmission is implicated in the aetiology of depression, schizophrenia and other psychiatric disorders (Caldecott-Hazard *et al.*, 1991; Willner, 1995; Deakin, 1996; Brunello, 1997; Frazer, 1997; Leonard, 1997; Bonhomme and Esposito, 1998; Goodnick and Goldstein, 1998a,b; Malison *et al.*, 1998; Murphy *et al.*, 1998) (Fig. 1). Correspondingly, the therapeutic actions of currently employed antipsychotic and antidepressant agents are generally attributed to their ability to modulate the activity of monoaminergic networks and to restore an appropriate pattern of functional interrelationships amongst them. Indeed, the discovery of five subtypes of dopaminergic receptor, nine subtypes of noradrenergic receptor (AR) and 15 subtypes of serotonergic receptor has provided a broad palette of potential targets for the improved treatment of psychiatric disorders via monoaminergic mechanisms (Boess and Martin, 1994; Sokoloff and Schwartz, 1995; Hieble and Ruffolo, 1996, 1997). Clearly, however, for the successful implementation of such strategies, it is necessary to further our understanding of the functional roles of individual receptor types and to clarify their implication in the aetiology and management of depressive and psychotic states. A related and equally important goal is to characterize the complex and reciprocal pattern of functional interactions amongst monoaminergic networks.

Frontocortical monoaminergic transmission and depressive states

In this light, the present commentary focuses on our recent studies of interrelationships amongst serotonergic, dopaminergic and noradrenergic pathways projecting to the frontal cortex (FCX) (Figs 1 and 2) and the possible significance of such interactions for the management of depressive states. Several considerations prompted selection of the FCX for these studies. First, it plays a crucial role (Fig. 1) in processes involved in the control of mood, cognition–attention and motor performance, functions compromised in depressive (and other psychiatric) disorders (Kotrla and Weinberger, 1995; Goodwin, 1997; Mayberg *et al.*, 1997; Soares and Mann, 1997; Beauregard *et al.*, 1998; Mielke *et al.*, 1998; Nolde *et al.*, 1998; Rogers *et al.*, 1998; Steffens and

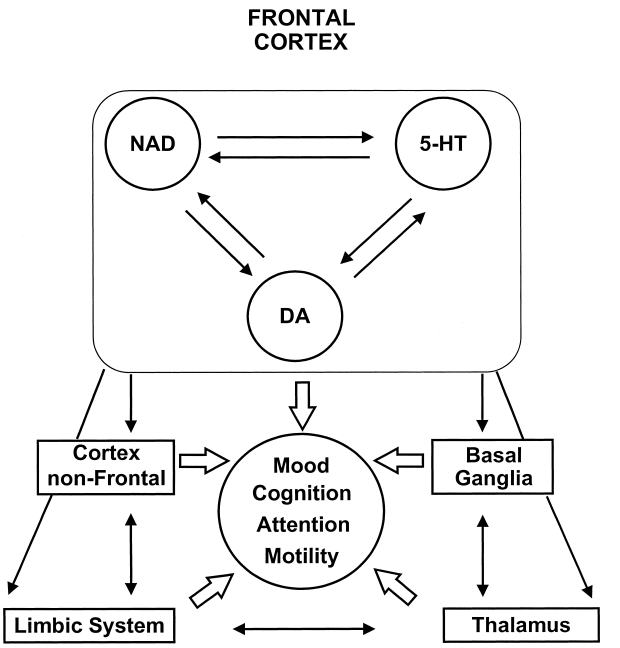

Figure 1 Schematic representation of the role of the frontal cortex in relation to other cortical and subcortical regions in the control of mood, cognition/attention and motor behaviour, functions compromised in depressive states and other psychiatric disorders

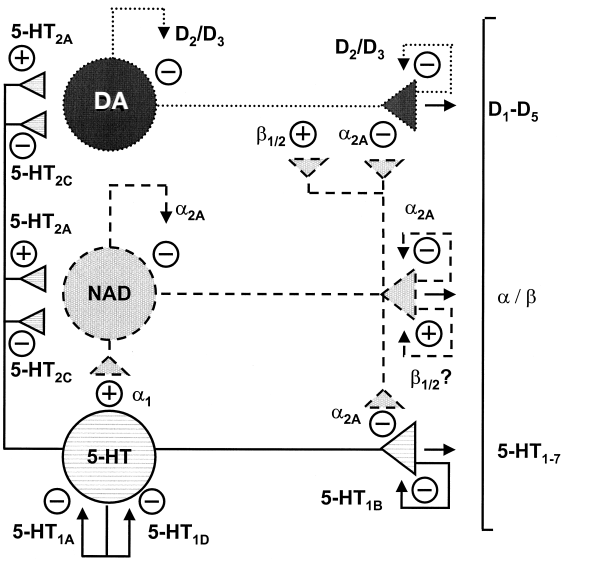

Figure 2 Schematic representation of the role of diverse classes of monoaminergic auto- and heteroreceptor in the modulation of the activity of serotonergic, dopaminergic and noradrenergic pathways innervating the frontal cortex. Note that the excitatory influence of 5-HT_{2A} receptors is probably not expressed at the level of dopaminergic and noradrenergic cell bodies, but rather their terminals. The inhibitory influence of 5-HT_{2C} receptors upon dopaminergic and noradrenergic cell bodies is likely indirect, via activation of GABAergic interneurons

Krishnan, 1998). Second, monoaminergic mechanisms in the FCX are strongly implicated in the regulation of these functions (Le Moal and Simon, 1991; Arnsten, 1997; Goldman-Rakic and Selemon, 1997; Darracq *et al.*, 1998). Third, antidepressant agents modify frontocortical monoaminergic transmission (Tanda *et al.*, 1994; Jordan *et al.*, 1994; Gobert *et al.*, 1997a,b). Fourth, although fragmentary, there are data indicative of functional interactions amongst monoaminergic pathways innervating the FCX (see Gobert *et al.*, 1998). Fifth, both the FCX – and the nuclei from which serotonergic, dopaminergic and noradrenergic projections originate, the dorsal raphe nucleus (DRN), ventrotegmental area (VTA), and locus coeruleus (LC), respectively – express a diversity of monoaminergic receptor types (Boess and Martin, 1994; Gobert *et al.*, 1998; Lee *et al.*, 1998a; Levant, 1998). Finally, as described below, we have developed a technique which allows for the simultaneous determination of extracellular levels of serotonin (5-HT), dopamine and noradrenaline (NAD) in single dialysis samples of the FCX.

Aims of studies: questions addressed herein

The principal issues addressed in the present review are as follows. First, the identity and activity (tonic or phasic) of autoreceptors underlying the feedback control of serotonergic, dopaminergic and noradrenergic transmission. Second, the role of postsynaptic serotonergic receptors in the modulation of dopaminergic and noradrenergic transmission. Third, reciprocally, the influence of noradrenergic and dopaminergic mechanisms upon serotonergic and dopaminergic/noradrenergic-pathways. Fourth, the influence of diverse classes of antidepressant agent upon extracellular levels of 5-HT as compared to dopamine and NAD in FCX. Finally, the potential modulation of these actions of antidepressant agents by ligands acting at various classes of auto- and heteroreceptor.

Multidisciplinary experimental strategy

Several complementary approaches were employed, technical details of which are given elsewhere (Lejeune *et al.*, 1997b; Lejeune and Millan, 1998; Gobert *et al.*, 1998; Millan *et al.*, 1998c). First, determination of the binding profiles of all ligands employed at 5-HT, dopamine and NAD receptor subtypes modulating monoaminergic transmission in FCX. Although binding data are not shown here, it should be emphasized that the present studies employed the most selective auto- and hetero-receptor ligands currently available. Second, the use of a highly sensitive system of concentric dialysis and high performance liquid chromatography/coulometric detection which permits the simultaneous quantification of 5-HT, dopamine and NAD levels in single dialysate samples of the FCX freely moving rats. Third, inasmuch as the influence of systemic drug injection upon FCX levels of monoamines does not indicate whether effects are integrated at the level of monoaminergic terminals in the FCX itself, or at their cell bodies of origin, the electrical activity of serotonergic, dopaminergic and noradrenergic perikarya in the DRN, VTA and LC, respectively, was recorded.

Autoreceptor control of 5-HT release (Table 1)

The prototypical 5-HT_{1A} receptor agonist, 8-OH-DPAT, inhibits the activity of ascending serotonergic pathways via the

Table 1 Summary of the influence of ligands at multiple serotonergic receptor types upon FCX levels of 5-HT, DA and NAD and their elevation by the SSRI, fluoxetine

			Vehicle			Fluoxetine		
Drug	Class	Dose	5-HT	DA	NAD	5-HT	DA	NAD
Vehicle	–	–	0	0	0	↑	↑	↑
8-OH-DPAT	5-HT_{1A} ago	0.16	↓	↑	↑	0	↑↑	↑↑
WAY100,635	5-HT_{1A} ant	0.16	0	0	0	↑↑	↑	↑
GR46,611	5-$HT_{1B/1D}$ ago	10.0	↓	0	0	0	↑	↑
GR127,935	5-$HT_{1B/1D}$ ant	2.5	0	0	0	↑↑	↑	↑
SB224,289	5-HT_{1B} ant	2.5	0	0	0	↑↑	↑	↑
BRL15,572[a]	5-HT_{1D} ant	10.0	0	0	0	↑	↑	↑
DOI[b]	5-HT_{2A} ago	2.5	0	↑	↑	–	–	–
BW723C86	5-HT_{2B} ago	2.5	0	0	0	–	–	–
Ro60–0075	5-HT_{2C} ago	2.5	0	↓	↓	–	–	–
MDL100,907	5-HT_{2A} ant	0.04	0	0	0	↑	↑	↑
SB204,741	5-HT_{2B} ant	2.5	0	0	0	–	–	–
SB206,553	5$HT_{2B/2C}$ ant	2.5	0	↑	↑	↑	↑↑	↑↑
SB242,084	5-HT_{2C} ant	2.5	0	↑	↑	–	–	–
Ondansetron	5-HT_3 ant	0.16	0	0	0	↑	↑	↑
GR125,487[a]	5-HT_4 ant	0.16	0	0	0	↑	↑	↑

Fluoxetine or vehicle administered at a dose of 10.0 mg/kg s.c. and vehicle or drug was given 20 min prior to fluoxetine. Drug effects are expressed relative to vehicle/vehicle or vehicle/fluoxetine semi-quantitatively for the 60-min period after fluoxetine/vehicle administration. The doses employed (mg/kg, base, s.c. or [a]i.p.) are those at which drugs express their actions selectively at the particular receptor specified. [b]Note that DOI is a mixed agonist at 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors, but that its 5-HT_{2A} agonist properties predominate in its intrinsic influence upon FCX levels of dopamine (DA) and NAD (Gobert and Millan, 1999a). Ago, agonist; ant, antagonist; 0, no effect; ↑, increase; ↑↑, , additive increase; ↓, decrease; –, not evaluated. Results are derived exclusively from data acquired by the present authors under identical test conditions for all drugs (Gobert *et al.*, 1998; Millan *et al.*, 1998b; Gobert and Millan, 1999a).

engagement of inhibitory, dendritic 5-HT_{1A} autoreceptors. This influence is reflected in a parallel suppression of cerebral 5-HT turnover, a reduction in extracellular levels of 5-HT in the FCX (Table 1) and a diminution in the electrical activity of DRN-localized serotonergic neurons (Hjorth *et al.*, 1982; Aghajanian *et al.*, 1988; Hjorth and Sharp, 1991; Gobert *et al.*, 1995a; Lejeune *et al.*, 1997b). Other high efficacy 5-HT_{1A} agonists, such as flesinoxan and S14671, as well as the partial agonist, buspirone, act similarly (Millan *et al.*, 1992; Bosker *et al.*, 1996; Gobert *et al.*, 1999b). Notably, S15535, a highly selective 5-HT_{1A} receptor ligand possessing low intrinsic activity, mimicked these inhibitory actions upon serotonergic pathways (Millan *et al.*, 1997b), consistent with the high receptor reserve/sensitivity of 5-HT_{1A} autoreceptors relative to their postsynaptic counterparts (Meller *et al.*, 1990). The actions of each of the above ligands was reversible by the highly selective 5-HT_{1A} antagonist, WAY100,635 (Fletcher *et al.*, 1996; Lejeune *et al.*, 1997b; Lejeune and Millan, 1998; Gobert *et al.*, 1998, 1999b), which alone does not affect 5-HT levels, suggesting that 5-HT_{1A} autoreceptors are not tonically active.

Dendrites of serotonergic cell bodies also bear 5-HT_{1D} autoreceptors, for which an inhibitory influence upon serotonergic transmission has been suggested (Davidson and Stamford, 1995; Pineyro *et al.*, 1995, 1996). However, the closely related 5-HT_{1B} receptor, localized principally on the terminals of serotonergic neurons, appears to play a more prominent role than 5-HT_{1D} sites in the inhibition of serotonergic pathways (Sharp *et al.*, 1989; Saito *et al.*, 1996; Roberts *et al.*, 1997; Trillat *et al.*, 1997; Gaster *et al.*, 1998; Hjorth, 1998; Tingley *et al.*, 1998; Sari *et al.*, 1999). Correspondingly, the 5-$HT_{1B/1D}$ agonist, GR46,611, reduced dialysate levels of 5-HT in the FCX, and its effect was abolished by the 5-$HT_{1B/1D}$ antagonist, GR127,935, and by the selective 5-HT_{1B} antagonist, SB224,289 (Skingle *et al.*, 1995; Gobert *et al.*, 1998), but not by the selective 5-HT_{1D} antagonist, BRL15,572 (Price *et al.*, 1997). These observations are consistent with a predominant role of 5-HT_{1B} rather than 5-HT_{1D} autoreceptors in the inhibition of FCX release of 5-HT. In these studies, GR127,935, SB224,289, BRL15,572 and other antagonists at 5-HT_{1B} and/or 5-HT_{1D} sites did not themselves increase levels of 5-HT – and similar data have generally been obtained *in vitro* (e.g. Schilder *et al.*, 1997; Hjorth, 1998). This suggests that, in analogy to 5-HT_{1A} autoreceptors, there is a low degree of tonic activity at 5-$HT_{1B/1D}$ autoreceptors (Gobert *et al.*, 1998). It might be argued that a stimulatory influence of antagonists at tonically active 5-$HT_{1B/1D}$ or 5-HT_{1A} sites might be immediately compensated for by an increased degree of feedback inhibition by 5-HT at their vacant counterparts (Starkey and Skingle, 1994; Trillat *et al.*, 1997; Ramboz *et al.*, 1998). However, even combined administration of WAY100,635 plus GR127,935 or SB224,289 failed to elevate FCX levels of 5-HT, suggesting that this objection is not valid (Gobert *et al.*, 1997c, 1998). Furthermore, this lack of facilitatory influence of SB224,289 suggest that its 'inverse agonist' properties, which are apparent at cloned, human (h)5-HT_{1B} receptors *in vitro* (Gaster *et al.*, 1998; Audinot *et al.*, 1999), may not translate into actions opposite to those of 5-HT_{1B} autoreceptor agonists *in vivo*. This issue was recently discussed in detail elsewhere (Millan *et al.*, 1999c).

There is some evidence that 5-HT_{2C} and/or 5-HT_{2A} receptor ligands may modulate the electrical activity of DRN-localized serotonergic neurons and the *in vitro* release of 5-HT in certain cerebral tissues. However, concentrations required are high and their effects are resistant to antagonists (Pennington, 1996; Craven *et al.*, 1997). Furthermore, there is little anatomical support for such findings (Pompeiano *et al.*, 1994, but see also Cheung *et al.*, 1998). Indeed, employing highly selective agonists and antagonists, we (Millan *et al.*, 1998b; Gobert and Millan, 1999a; Gobert *et al.*, in press b), and other groups (Thorn and Routledge, 1997; Ichikawa *et al.*, 1998), have not observed alterations in FCX levels of 5-HT upon administration of selective agonists or antagonists at 5-HT_{2A}, 5-HT_{2B} or 5-HT_{2C} receptors.

Table 2 Summary of the influence of ligands at multiple dopaminergic and noradrenergic receptor types upon FCX levels of 5-HT, dopamine (DA) and NAD and their elevation by the SSRI, fluoxetine

			Vehicle			Fluoxetine		
Drug	Class	Dose	5-HT	DA	NAD	5-HT	DA	NAD
Vehicle	–	–	0	0	0	↑	↑	↑
Cirazoline	α_1 ago	0.63	0	0	0	–	–	–
Prazosin	α_1 ant	0.63	↓	0	0	–	–	–
Clenbuterol	$\beta_{1/2}$ ago	2.5	0	↑	↑	↑	↑	↑
Betaxolol	β_1 ant	10.0	0	↓	0	↑	↑	↑
ICI118,551	β_2 ant	10.0	0	0	0	↑	↑	↑
Guanfacine	α_{2A} ago	0.63	↓	↓	↓	–	–	–
Atipamezole	α_2 ant	0.16	0	↑	↑	↑↑	↑↑	↑↑
BRL44408	α_{2A} ant	10.0	0	↑	↑	–	–	–
PD128,907	$D_3 > D_2$ ago	0.16	0	↓	0	–	–	–
Raclopride	D_2/D_3 ant	0.16	0	↑	0	↑	↑	↑
L741,626	D_2 ant	10.0	0	↑	0	–	–	–
GR218,231	D_3 ant	0.16	0	0	0	–	–	–
S18126	D_4 ant	0.16	0	0	0	–	–	–

Fluoxetine or vehicle was administered at a dose of 10.0 mg/kg s.c. and vehicle or drug was given 20 min prior to fluoxetine. Drug effects are expressed relative to vehicle/vehicle or vehicle/fluoxetine semi-quantitatively for the 60-min period after fluoxetine/vehicle administration. The doses employed (mg/kg, base, s.c.) are those at which drugs express their actions selectively at the particular receptor specified. Note, however, that prazosin also behaves as an antagonist at α_{2B}- and α_{2C}- adrenoceptors. Ago, agonist; ant, antagonist; 0, no effect; ↑, increase; ↑↑, , additive increase; ↓, decrease; –, not evaluated. Results are derived exclusively from data acquired by the present authors under identical test conditions for all drugs (Gobert *et al.*, 1996, 1997a, 1998; Millan *et al.*, 1998d; Lejeune *et al.*, 1998; Gobert and Millan, 1999b).

Autoreceptor control of dopamine release: role of D_2 versus D_3 receptors (Table 2)

There is a consensus that the activity of dopaminergic neurons is subject to a tonic, inhibitory control by spontaneously released dopamine (Carlsson, 1975; Jackson and Westlind-Danielsson, 1994; Gobert *et al.*, 1995b; Cragg and Greenfield, 1997) – assuming that stimulatory effects of antagonists upon dopamine release do not reflect inverse agonist actions, which is unlikely (Griffon *et al.*, 1996; Hall and Strange, 1997; Malmberg *et al.*, 1998; Newman-Tancredi *et al.*, 1999). However, a much-debated question is whether inhibitory dopaminergic autoreceptors are exclusively of the D_2 type, or whether D_3 autoreceptors may also be implicated. Several lines of evidence support a role of D_3 receptors. First, a minor population of (mRNA encoding) D_3 receptors is detectable in dopaminergic cell bodies (Valerio *et al.*, 1992; Meador-Woodruff *et al.*, 1994; Diaz *et al.*, 1995; Richtand *et al.*, 1995; Kessler *et al.*, 1998; Khan *et al.*, 1998; Levant, 1998; Suzuki *et al.*, 1998; Gurevich and Joyce, 1999). Second, the potency of preferential D_3 versus D_2 agonists in suppressing the synthetic and electrical activity of dopaminergic neurons is correlated with their affinity at hD_3 but not hD_2 receptors (Gobert *et al.*, 1995b; Kreiss *et al.*, 1995). It should be noted, however, that such analyses do not account for differential drug absorption and metabolism. Third, the inhibitory influence of the preferential D_3 agonist, PD128,907, upon dopamine release in FCX and upon the electrical activity of dopaminergic neurons is blocked by the selective D_3 antagonists, S14297, GR218 231 and S33084 (Lejeune and Millan, 1995; Rivet *et al.*, 1994; Gobert *et al.*, 1996; Millan *et al.*, in press a). Fourth, neutralization of D_3 receptors with specific antisense probes may likewise abrogate the inhibitory influence of dopaminergic agonists upon dopamine release (Nissbrandt *et al.*, 1995; Tepper *et al.*, 1997; Ekman *et al.*, 1998). Fifth, D_3 receptors inhibit dopamine release in clonal cell lines (Tang *et al.*, 1994). These observations collectively suggest that D_3 autoreceptors may contribute to the phasic suppression of dopaminergic input to the FCX and other regions. Interestingly, studies in knockout mice lacking D_3 receptors, while corroborating a phasic, inhibitory role of D_3 receptors, suggested that they may be localized postsynaptically and exert a short-loop feedback, inhibitory influence on dopaminergic neurons (Koeltzow *et al.*, 1998). In contrast to the above findings, the absence of an inhibitory influence of 'preferential' D_3 agonists upon dopaminergic neurons in transgenic mice lacking D_2 receptors was taken as evidence that D_2 autoreceptors can fully account for the actions of dopaminergic agonists (Mercuri *et al.*, 1997; L'hirondel *et al.*, 1998).

PD128 907 has only a limited preference for D_3 versus D_2 sites (Audinot *et al.*, 1998), and a further reason underlying such discrepant data may be that 'selective' D_3 antagonists actually block D_2 receptors due to poor selectivity *in vivo*. Another possible explanation for divergent data is species differences (notably in studies in transgenic mice versus pharmacological and antisense studies in rats). Compensatory mechanisms in knockout mice may also be implicated: for example, mice lacking D_2 receptors do not show alterations in dopamine turnover (Baik *et al.*, 1995; Kelly *et al.*, 1998). It has also been suggested that D_3 receptors predominantly control dopamine release rather than turnover (Gainetdinov *et al.*, 1996, but see also Ekman *et al.*, 1998). Overall, the high concentration of D_2 receptors in dopaminergic neurons underpins the contention that they play a key role in the tonic inhibition of dopaminergic activity, and that their blockade underlies the facilitatory actions of dopaminergic antagonists (Jackson and Westlind-Danielsson, 1994; Sesack *et al.*, 1994; Mercuri *et al.*, 1997; L'hirondel *et al.*, 1998). Furthermore, although data from D_3 antisense and gene knockout studies are inconsistent, our studies with selective D_3 antagonists suggest that blockade of D_3 sites does not markedly influence dopaminergic transmission: this indicates that D_3 receptors are not major participants in the tonic control of dopaminergic neurons (Rivet *et al.*, 1994; Gobert *et al.*, 1995b, 1996; Tepper *et al.*, 1997; Koeltzow *et al.*, 1998**;** Ekman *et al.*, 1998; Millan *et al.*, in press a). On the

other hand, the apparent, phasic role of D_3 autoreceptors, or postsynaptic D_3 receptors, in the inhibition of the activity of dopaminergic neurons requires further study.

Feedback control of noradrenergic neurons (Table 2)

In analogy to dopaminergic networks, a tonic, inhibitory feedback influence of NAD upon cerebral noradrenergic transmission has been documented (Svensson *et al.*, 1975; Van Veldhuizen *et al.*, 1993; Millan *et al.*, 1994; Kiss *et al.*, 1995; Lee *et al.*, 1998a). Although it might be argued that inverse agonist actions of α_2-AR antagonists account for increases in the activity of noradrenergic neurons (e.g. Tian *et al.*, 1993), there is no evidence for such actions *in vivo*. Both neuroanatomical, pharmacological and gene knockout analyses converge upon the conclusion that the inhibitory autoreceptor role is principally fulfilled by the α_{2A}-AR subtype, which is localized at both the dendritic and terminal level (Zeng and Lynch, 1991; Trendelenburg *et al.*, 1993; Millan *et al.*, 1994; Kiss *et al.*, 1995; Hunter *et al.*, 1997; Lakhlani *et al.*, 1997; Lee *et al.*, 1998a). Correspondingly, the preferential α_{2A}-AR agonists, guanabenz and guanfacine, both suppressed FCX levels of NAD (Gobert *et al.*, 1998). Furthermore, the facilitatory influence of α_2-AR antagonists, such as atipamezole, upon FCX levels of NAD, was mimicked by the preferential α_{2A}-AR antagonist, BRL44408, whereas the preferential $\alpha_{2B/C}$- versus α_{2A}-AR subtype antagonist, prazosin, was ineffective (Millan *et al.*, 1994; Renouard *et al.*, 1994; Gobert *et al.*, 1998). With respect to other α_2-AR subtypes, recent anatomical studies have identified α_{2C}-ARs in the LC (Rosin *et al.*, 1996; Lee *et al.*, 1998b), while studies of monoamine turnover in transgenic mice lacking α_{2C}-ARs were interpreted as indicative that α_{2C}-ARs may contribute to the modulation of noradrenergic transmission (Sallinen *et al.*, 1997). However, changes in the latter study were minor and α_{2A}-ARs are indubitably the key subtype of autoreceptor inhibitory to noradrenergic transmission.

Studies both *in vitro* and *in vivo* have suggested that activation of β-AR receptors enhances the FCX release and synthesis of NAD, and both β_1- and β_2-ARs may be involved in these actions. This influence is exerted phasically inasmuch as β_1- and/or β_2-AR antagonists are ineffective alone (Misu and Kubo, 1986; O'Donnell, 1993; Murugaiah and O'Donnell, 1995). In line with these observations, the mixed $\beta_{1/2}$-AR agonist, clenbuterol, elevated FCX levels of NAD, whereas the β_1- and β_2-AR antagonists, betaxolol and ICI118,551, respectively, failed to modify FCX levels of NAD (Lejeune *et al.*, 1998; Gobert and Millan, 1999b). Interestingly, both β_1- and β_2-ARs contribute to the facilitatory influence of (–)-pindolol, which possesses partial agonist properties at these sites, upon FCX levels of NAD (Gobert and Millan, 1999b; Millan and Gobert, 1999). In the periphery, β_2-ARs are localized on sympathetic neurons and, in the FCX, it is possible that they are similarly localized on the terminals of noradrenergic fibres (Misu and Kubo, 1986; Nicholas *et al.*, 1993). Similarly β_1-ARs, which are enriched in FCX, may be situated on noradrenergic terminals themselves (Nicholas *et al.*, 1993). However, ionotropic, glutamatergic receptors facilitate FCX release of NAD, and β-ARs enhance frontocortical release of glutamate (Ruzicka and Jhamandas, 1993; Herrero and Sanchez-Prieto, 1996). Thus, an indirect, excitatory influence of β-ARs upon FCX release of NAD might be mediated via glutamatergic mechanisms.

Facilitation of frontocortical dopaminergic and noradrenergic transmission by 5-HT_{1A} receptors (Table 1)

There are essentially two loci via which serotonergic mechanisms may modulate the activity of dopaminergic and noradrenergic networks projecting to the FCX. First, at the level of their terminals in the FCX itself and, second, at the level of their cell bodies of origin in the VTA and LC. In both cases, direct actions on dopaminergic/noradrenergic neurons and indirect effects, which are likely mediated by [γ-aminobutyric acid (GABA)ergic] interneurons, require consideration.

There is evidence that 5-HT_{1B} receptors, via an interaction with GABAergic interneurons at the level of cell bodies, and possibly terminals, facilitate mesolimbic and nigrostriatal dopaminergic transmission (Johnson *et al.*, 1992; Galloway *et al.*, 1993; Cameron and Williams, 1994; Stanford and Lacey, 1996; Boulenguez *et al.*, 1998; Sari *et al.*, 1999). Furthermore, the local infusion of 5-HT_{1B} agonists was reported to enhance dialysate levels of dopamine in FCX – probably via a mechanism independent of GABAergic interneurons (Iyer and Bradberry, 1996). With respect to noradrenergic transmission, activation of 5-HT_{1B} receptors has been documented to inhibit synaptic potentials in the LC (Bobker and Williams, 1989). However, in our studies of systemic drug administration to conscious rats, selective agonists and antagonists at 5-HT_{1B} and/or 5-HT_{1D} receptors exerted little or no significant influence upon dialysate levels of dopamine or NAD in FCX, suggesting that 5-$HT_{1B/1D}$ receptors do not play a major role in the modulation of frontocortical dopaminergic and noradrenergic transmission.

In accordance with previous observations demonstrating a preferential, facilitatory influence of 5-HT_{1A} receptor agonists upon frontocortical versus subcortical release of dopamine (Arborelius *et al.*, 1993; Tanda *et al.*, 1994), selective 5-HT_{1A} receptor agonists elicited a pronounced elevation in extracellular levels of dopamine (and NAD) in FCX (Millan *et al.*, 1997b; Gobert *et al.*, 1998). Inasmuch as 5-HT_{1A} agonists also elicited burst firing, and accelerated the firing rate of VTA-localized dopaminergic neurons, this facilitatory influence of 5-HT_{1A} agonists upon dopaminergic transmission was clearly integrated at the cell body level (Lejeune *et al.*, 1997b; Lejeune and Millan, 1998). Similarly, the concomitant induction of NAD release probably reflects an activation of noradrenergic perikarya in the LC (Bobker and Williams, 1989; Done and Sharp, 1994; Millan *et al.*, 1997b; Gobert *et al.*, 1998; Haddjeri *et al.*, 1998). However, it remains unclear whether the population of 5-HT_{1A} sites implicated is localized in the VTA itself (postsynaptic) or in the DRN (presynaptic). This issue is discussed in detail elsewhere (Lejeune and Millan, 1998). Evidence in support of a role of postsynaptic 5-HT_{1A} sites includes the observation that 20-fold higher doses of 5-HT_{1A} agonists are required to activate VTA-localized dopaminergic neurons compared to doses inhibiting DRN serotonergic neurons (Lejeune *et al.*, 1997b; Lejeune and Millan, 1998): this may correspond to the lower receptor reserve/sensitivity of post- versus presynaptic 5-HT_{1A} receptors (Meller *et al.*, 1990). Postsynaptic 5-HT_{1A} receptors would, presumably,

disinhibit mesocortical dopaminergic projections by hyperpolarizing GABAergic and other classes of interneuron in the VTA, although direct evidence for this remain to be provided (Pessia *et al.*, 1994; Westerink *et al.*, 1996; Cameron *et al.*, 1997). However, the density of 5-HT_{1A} receptors in the VTA is low (Pazos and Palacios, 1985). Furthermore, even 5-HT_{1A} ligands which possess low intrinsic activity at 5-HT_{1A} receptors, and which act as antagonists and agonists at postsynaptic and presynaptic 5-HT_{1A} receptors, respectively, inhibit serotonergic pathways and concomitantly accelerate release of dopamine (and NAD) in FCX (Millan *et al.*, 1997b; Lejeune and Millan, 1998). Furthermore, the ability of 5-HT_{1A} agonists to excite frontocortical dopaminergic neurons is abolished by neurochemical lesions of serotonergic neurons (Prisco *et al.*, 1994; Chen and Reith, 1995). Functional data indicating that activation of 5-HT_{1A} autoreceptors in the DRN stimulates the activity of mesocortical (and mesolimbic) dopaminergic pathways has also been presented (Fletcher, 1991). Overall, the balance of data (see Lejeune and Millan., 1998), favours the argument that it is predominantly the activation of presynaptic 5-HT_{1A} receptors which facilitates dopaminergic and noradrenergic input to the FCX. This hypothesis implies that suppression of serotonergic transmission by the engagement of 5-HT_{1A} autoreceptors must relieve a tonic, inhibitory influence of 5-HT upon mesocortical dopaminergic and noradrenergic pathways.

Facilitation and inhibition of frontocortical dopaminergic and noradrenergic transmission by 5-HT_{2A} and 5-HT_{2C} receptors, respectively (Table 1)

From the above discussion, the question arises as to which 5-HT receptor subtype mediates this tonic, inhibitory influence of 5-HT upon frontocortical dopaminergic and noradrenergic pathways. While there is substantial evidence for an inhibitory role of 5-HT_2 receptors (Done and Sharp, 1994; Prisco *et al.*, 1994; Kelland and Chiodo, 1996), only more recently, with the availability of selective ligands, has it become possible to distinguish the potential roles of closely related 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors (Boess and Martin, 1994; Baxter, 1996). Indeed, the mixed 5-$HT_{2B/2C}$ antagonist, SB206,553 (Kennett *et al.*, 1996), dose-dependently increased extracellular levels of dopamine and NAD in the FCX (Lejeune *et al.*, 1997a; Millan *et al.*, 1998b; Gobert *et al.*, in press b). That this action of SB206,553 reflected blockade of 5-HT_{2C} rather than 5-HT_{2B} sites was indicated by the similar, facilitatory action of the selective 5-HT_{2C} antagonist, SB242,084 (Kennett *et al.*, 1997b), whereas the selective 5-HT_{2B} antagonist, SB204,741 (Forbes *et al.*, 1996), was inactive (Lejeune *et al.*, 1997a; Millan *et al.*, 1998b; Gobert *et al.*, in press b). In line with these observations, the preferential 5-HT_{2C} receptor agonist, Ro60–0175 (Bös *et al.*, 1997), dose-dependently suppressed dialysate levels of dopamine and NAD in FCX, whereas the preferential 5-HT_{2B} agonist, BW723, C86 (Kennett *et al.*, 1997a), was ineffective (Millan *et al.*, 1998b; Gobert *et al.*, in press b). The population of 5-HT_{2C} receptors inhibitory to frontocortical dopaminergic neurons is likely localized in the VTA itself – presumably upon GABAergic interneurons (Pompeiano *et al.*, 1994) – inasmuch as the electrical activity of dopaminergic cell bodies therein was enhanced and attenuated by SB206 553 and Ro60–0175, respectively (Lejeune *et al.*, 1997a; Gobert *et al.*, in press b; see also Pessia *et al.*, 1994; Prisco *et al.*, 1994). Similarly, 5-HT_{2C} receptors appear to tonically inhibit noradrenergic cell bodies in the LC via GABAergic interneurons (Clement *et al.*, 1992; Chiang and Aston-Jones, 1993; Morilak *et al.*, 1993; Done and Sharp, 1994; Gobert *et al.*, in press b). In analogy to the marked inhibitory influence of 5-HT_{2C} receptors upon frontocortical dopaminergic projections, recent data suggest that 5-HT_{2C} receptors, localized in the VTA and substantia nigra, may similarly exert a tonic (though less pronounced) inhibitory control of mesolimbic and nigrostriatal dopaminergic pathways, respectively (Rick *et al.*, 1995; Stanford and Lacey, 1996; Lejeune *et al.*, 1997a; Di Matteo *et al.*, 1998; Willins and Meltzer, 1998; De Deurwaerdere and Spampinato, 1999; Gobert *et al.*, in press b).

The above, novel observations concerning 5-HT_{2C} receptors bear comparison to an older study in which the selective 5-HT_{2A} antagonist, MDL100,907 (Sorensen *et al.*, 1993), increased FCX levels of dopamine (Schmidt and Fadayel, 1995). However, this effect was documented at a dose of 1.0 mg/kg s.c, which is excessively high relative to the approximately 50-fold lower doses which exert full blockade of cerebral 5-HT_{2A} receptors as determined by biochemical, endocrinological and behavioural parameters. Thus, MDL100,907 blocks head-twitches, corticosterone secretion and discriminative stimuli elicited by the hallucinogen and 5-HT_{2A} agonist, DOI, with Inhibitory $Dose_{50}$ s of 0.005–0.01 mg/kg s.c, values close to its potency in blocking locomotion elicited by phencyclidine (0.005 mg/kg s.c.), a further response effected via 5-HT_{2A} receptors (Schreiber *et al.*, 1994; Maurel-Remy *et al.*, 1995; Schreiber *et al.*, 1995; Rivet *et al.*, 1996). The ability of MDL100,907 to elevate FCX levels of dopamine at high doses may, then, simply reflect its weak antagonist properties at 5-HT_{2C} receptors, for which its affinity is 40-fold lower (Palfreyman *et al.*, 1993; Gobert *et al.*, in press b). Pehek and Crish (1998) have also reported that direct infusion of MDL100,907 into FCX does not elevate levels of dopamine. Intriguingly, we have found that the mixed 5-$HT_{2A/2C}$ agonist, DOI, increases FCX levels of dopamine, an action reversed by a low dose of MDL100,907 (0.04 mg/kg s.c.) selective for 5-HT_{2A} receptors (Gobert and Millan, 1999a; Pessia *et al.*, 1994). These data suggest that 5-HT_{2A} receptors may actually potentiate frontocortical dopaminergic and noradrenergic transmission. The underlying mechanisms remain unclear since, at least in anaesthetized rats, DOI inhibits the firing rate of noradrenergic cell bodies in the LC (Done and Sharp, 1992). Moreover, both facilitatory and inhibitory effects have been seen with DOI at dopaminergic perikarya in the VTA, while its local infusion into the FCX did not elevate dopamine levels therein (Pessia *et al.*, 1994; Iyer and Bradberry, 1996; see also Ichikawa and Meltzer, 1995; Wurtman and Balcioglu, 1998). Presumably, the excitation by 5-HT_{2A} receptors of NAD release is exerted at the level of noradrenergic terminals in the FCX.

In conclusion, there is evidence for an opposite control of frontocortical dopaminergic and noradrenergic transmission by 5-HT_{2C} receptors (tonic, inhibitory and indirect, at the cell body level) versus 5-HT_{2A} receptors (phasic, excitatory and of unknown localization, at the terminal level). The relevance of this dual control for the actions of antidepressants and other classes of psychoactive agents will be of interest to elucidate.

Finally, it has been suggested that excitatory 5-HT_3 receptors on the terminals of dopaminergic neurons in the FCX enhance

release of dopamine, but equivalent actions of 5-HT_3 receptors have been more convincingly documented for subcortical dopaminergic projections (Chen *et al.*, 1992; Tanda *et al.*, 1995; Iyer and Bradberry, 1996; De Deurwaerdere *et al.*, 1998) (see below). Similarly, it is unlikely that FCX-localized 5-HT_3 receptors enhance NAD release in FCX (Mongeau *et al.*, 1994b) (see below).

Lack of pronounced dopaminergic modulation of serotonergic (and noradrenergic) transmission (Table 2)

As discussed above, serotonergic networks exert a modulatory influence upon dopaminergic input to the FCX. Messenger RNA encoding D_3 receptors were recently identified in the DRN (Suzuki *et al.*, 1998) and a few studies (e.g. Chen HY *et al.*, 1992; Ferré *et al.*, 1994; Adell and Artigas, 1999; Mendlin *et al.*, 1999) have suggested that, possibly via actions in the DRN, dopaminergic mechanisms may reciprocally modify serotonergic transmission. However, such data remain fragmentary and, in our studies, we have acquired no indication of a specific influence of D_3/D_2 receptor agonists or antagonists upon levels of 5-HT in FCX (Gobert *et al.*, 1998; Millan *et al.*, in press a). Indeed, although high doses of the 'selective' D_3 agonists, 7-OH-DPAT and PD128,907, inhibit DRN serotonergic neuron firing and decreases FCX levels of 5-HT, these effects reflect their modest affinity for 5-HT_{1A} receptors inasmuch as they are prevented by the 5-HT_{1A} antagonist, WAY100,635, but not by dopaminergic antagonists (Lejeune *et al.*, 1997b). Further, the novel and highly selective D_3/D_2 agonist, S32504, fails to modify either the firing rate of serotonergic neurons in the DRN or the release of 5-HT in the FCX (Millan *et al.*, 1999a). Similarly, the highly selective D_2/D_3 antagonist, raclopride, does not significantly modify DRN firing or FCX levels of 5-HT (Gobert *et al.*, 1998).

The visualization of mRNA encoding D_3 receptors in the LC provides a potential neuroanatomical substrate for an influence of dopamine upon noradrenergic transmission (Herroelen *et al.*, 1994; Suzuki *et al.*, 1998). Indeed, Rossetti *et al.* (1989) claimed that D_2 receptors modulate NAD release in FCX, based on the stimulatory and inhibitory influence of sulpiride and quinpirole, respectively. However, doses were high and Ohmori *et al.* (1990) did not obtain such effects. Similarly, we have observed little or no influence of selective agonists at D_2/D_3 receptors upon extracellular levels of NAD in FCX (Table 2) (Gobert *et al.*, 1998). Furthermore, although raclopride slightly increases FCX levels of NAD at high doses, selective D_3 and D_2 antagonists are completely ineffective (Table 2) (Millan *et al.*, in press a). Any specific influence of D_3 or D_2 receptors upon frontocortical noradrenergic transmission remains, thus, to be established.

Noradrenergic modulation of serotonergic transmission (Table 2)

In-vitro studies have shown that frontocortical release of 5-HT is subject to an inhibitory influence of α_2-ARs, likely localized on serotonergic terminals themselves (Starke *et al.*, 1989; Trendelenburg *et al.*, 1994b). This approach has generated contradictory data as concerns the question of whether the subtype of α_2-AR controlling 5-HT release differs to that controlling NAD release (Maura *et al.*, 1992; Gobbi *et al.*, 1993). However, in line with studies of transgenic mice (Sallinen *et al.*, 1997), our pharmacological analysis of the modulation of FCX levels of 5-HT as compared to those of NAD by α_2-AR subtype-selective ligands suggests that α_{2A}-ARs are, in each case, implicated (Gobert *et al.*, 1998). Interestingly, the inhibition of FCX release of 5-HT by α_{2A}-ARs may, nevertheless, be distinguished from the control of NAD release therein inasmuch as it is not expressed tonically. That is α_{2A}-AR antagonists do not elevate levels of 5-HT in FCX (Gobert *et al.*, 1998), although it remains controversial as to whether α_2-ARs tonically inhibit 5-HT levels in other cerebral structures (Tao and Hjorth, 1992; Mongeau *et al.*, 1993; Hertel *et al.*, 1998). This finding parallels the lack of tonic control of serotonergic transmission by 5-$HT_{1A/1B}$ autoreceptors as compared to the tonic modulation of noradrenergic transmission by α_{2A}-ARs (*vide supra*). In addition to this role of α_{2A}-ARs in the FCX itself, it has been suggested that activation of α_{2A}-AR autoreceptors in the LC may contribute to the inhibitory control of cerebral (hippocampal) serotonergic output by suppressing a facilitatory noradrenergic input to the DRN (De Boer *et al.*, 1996). Although this mechanism has not been shown to operate in the FCX to date, there does appear to be a tonic, excitatory influence of α_1-ARs upon serotonergic cell bodies of the DRN. Correspondingly, although the α_1-AR agonist, cirazoline, did not increase frontocortical levels of 5-HT, blockade of α_1-ARs by prazosin suppresses DRN firing and markedly reduced dialysate levels of 5-HT in FCX and elsewhere (Lejeune *et al.*, 1994; Rouquier *et al.*, 1994; Hjorth *et al.*, 1995) (Table 2). The high concentration of α_{1D}-ARs in the DRN suggests that this subtype may be involved, but this remains to be demonstrated (Cahir *et al.*, 1998).

Noradrenergic modulation of dopaminergic transmission (Table 2)

In-vitro studies of the FCX and other tissues have demonstrated that α_2-AR agonists exert a suppressive influence upon extracellular levels of dopamine. In contrast, α_2-AR antagonists enhance levels of dopamine, suggesting that this inhibitory modulation is expressed in a tonic fashion. Recent studies of the subtype of α_2-heteroreceptor controlling dopamine release have suggested that the α_{2A}-AR subtype is involved, in analogy to the control of NAD release (Trendelenburg *et al.*, 1994a; Gobert *et al.*, 1997a; Millan *et al.*, 2000). Correspondingly, we found that the influence of ligands interacting selectively with α_{2A}-ARs compared to $\alpha_{2B/C}$-AR subtypes upon FCX levels of dopamine was indistinguishable from their influence upon NAD levels quantified in the same dialysate samples (Gobert *et al.*, 1998). The contention that α_{2A}-AR receptors tonically inhibit FCX levels of dopamine is supported by studies in transgenic mice lacking α_{2A}-ARs (Lakhlani *et al.*, 1997; Sallinen *et al.*, 1997), as well as neuroanatomical data indicating the presence of (mRNA encoding) α_{2A}-ARs in the VTA (Lee *et al.*, 1998a). Nevertheless, a possible, minor modulatory role of α_{2C}-ARs cannot be discounted (Sallinen *et al.*, 1997; Lee *et al.*, 1998b). Dopamine in FCX is cleared not only by dopamine uptake sites on dopaminergic terminals, but also by NAD uptake sites on noradrenergic neurons. Under certain circumstances, an increase in extracellular levels of dopamine in the FCX may thus be a consequence of an increase in NAD levels,

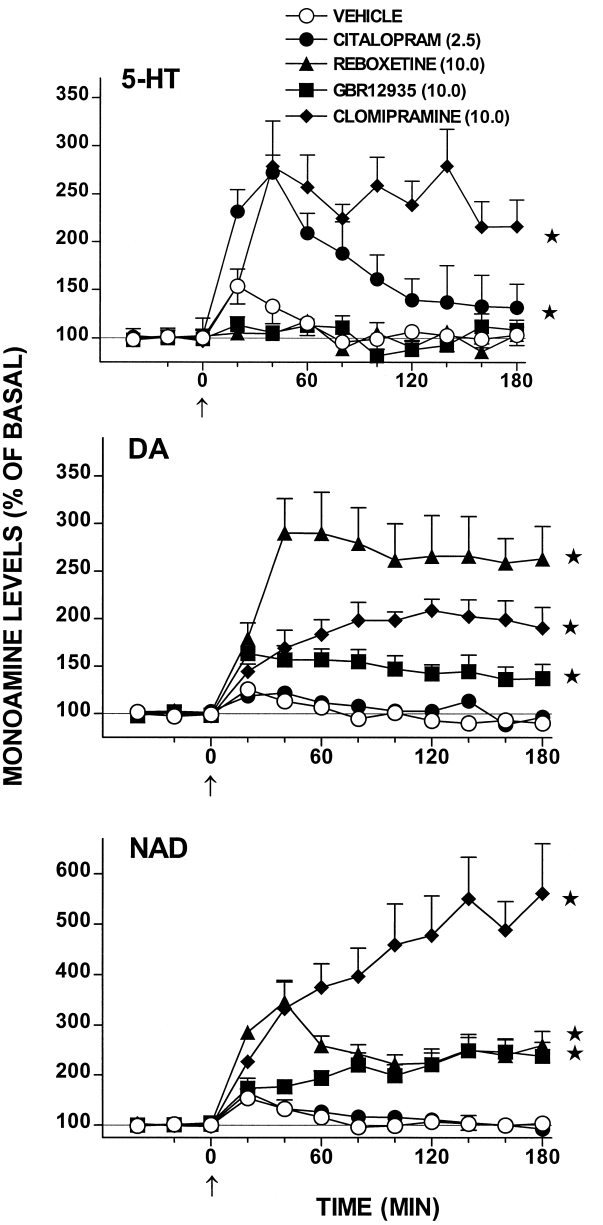

Figure 3 Influence of citalopram, reboxetine, GBR12935 and clomipramine upon levels of 5-HT, dopamine and NAD simultaneously quantified in single dialysate samples of the FCX in freely moving rats. Citalopram was evaluated at a low dose (2.5 mg/kg i.p.) which selectively influences 5-HT levels (Table 3). Doses of reboxetine, GBR12935 and clomipramine were 10.0 mg/kg s.c. in each case. Data are means ± SEM values of 5-HT, dopamine and NAD levels expressed as a percentage change from baseline (100%). Absolute (basal) levels of 5-HT, dopamine and NAD were 0.68 ± 0.06, 1.22 ± 0.08 and 1.11 ± 0.14 pg/20 µl dialysate, respectively. $n \geq 5$ per value. The asterisks indicate significance of drug versus vehicle values

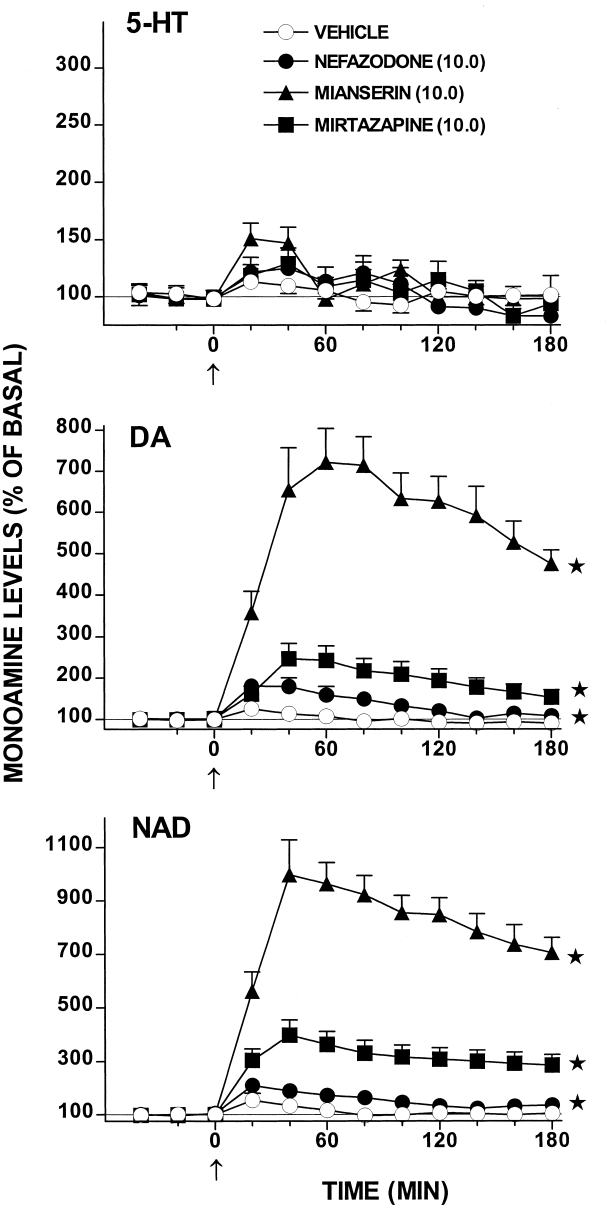

Figure 4 Influence of nefazodone, mianserin and mirtazapine upon levels of 5-HT, dopamine and NAD simultaneously quantified in single dialysate samples of the FCX in freely moving rats. Doses were 10.0 mg/kg s.c. in each case. Data are means ± SEM values of 5-HT, dopamine and NAD levels expressed as a percentage change from baseline (100%). For basal levels, see Fig. 3. $n \geq 5$ per value. The asterisks indicate significance of drug versus vehicle values

which competes with dopamine at the NAD reuptake site. Consequently, a component of the elevation in dialysate levels of dopamine elicited by α_{2A}-AR antagonists in the FCX may reflect a primary, facilitatory influence on NAD release (Pozzi *et al.*, 1994; Gresch *et al.*, 1995). It should also be pointed out that postsynaptic α_1-ARs in the VTA control the firing pattern of dopaminergic cell bodies (Andersson *et al.*, 1994; Svensson *et al.*, 1995). This stabilizing influence is expressed primarily in interaction with dopaminergic and serotonergic mechanisms: for example, α_1-AR antagonists moderate the activation of mesocortical dopaminergic neurons elicited by D_2/D_3 autoreceptor blockade (Andersson *et al.*, 1994; Svensson *et al.*, 1995). Consequently, the blockade or stimulation or α_1-ARs by prazosin or cirazoline, respectively, does not itself modify FCX levels of dopamine (Gobert *et al.*, 1998).

While β-ARs have been shown to enhance dopamine release in the striatum, accumbens and hypothalamus (Saigusa *et al.*, 1999;

see Misu and Kubo, 1986), there is no equivalent information for the FCX. Furthermore, β-AR ligands do not modify the electrical activity of dopaminergic cell bodies in the VTA (Grenhoff *et al.*, 1993). Nevertheless, mRNA encoding β_1-ARs has been detected in the VTA, and β_1-ARs may, in principle, be transported to their terminals. This would provide a (direct) substrate for our observations of a facilitatory influence of β_1-AR stimulation upon FCX levels of dopamine – although the localization of β_2-ARs excitatory to the FCX release of dopamine remains unclear (Gobert and Millan, 1999b). In this light, the above-mentioned possibility that increases in FCX levels of dopamine mimic those of NAD, due to a common uptake site on noradrenergic terminals, should be reiterated.

Influence of diverse classes of antidepressant agent upon frontocortical versus subcortical levels of 5-HT, dopamine and NAD (Table 3)

The above observations, summarized in Tables 1 and 2, yield a receptorial and neuronal framework (Fig. 2) for an interpretation of the influence of various classes of antidepressant agent upon FCX levels of 5-HT, dopamine and NAD (summarized in Table 3). Our comparative studies were encouraged by the intriguing suggestion that an increase in FCX levels of dopamine may be a trait common to diverse classes of antidepressant agents (Tanda *et al.*, 1994). The examination of an extensive and diverse series of antidepressants – in comparison to anxiolytic and antipsychotic agents – upon frontocortical levels of 5-HT and NAD as well as dopamine levels permits a reasonable assessment of this proposition (Table 3). The following general points may be made.

First, in parallel to their greater degree of tonic control by auto- and heteroreceptor mechanisms (*vide supra*), FCX levels of dopamine and NAD are more labile than those of 5-HT. Indeed, the only drug classes which increased dialysate levels of 5-HT in FCX (Table 3 and Figs 3 and 4) were those either (1) interacting directly with 5-HT uptake site (SSRIs, 5-HT/NAD reuptake inhibitors (SNRIs), SSRIs/5-HT_{2C} antagonists and tricyclics) or (2), preventing the degradation of 5-HT (the monoamine oxidase A/B inhibitor, tranylcypromine). Indeed, selective NAD reuptake inhibitors (NARIs), such as reboxetine (Fig. 3), and mixed 5-HT_2/α_2-AR antagonists, such as mirtazapine (Fig. 4) did not elevate levels of 5-HT in FCX, although they are effective antidepressant agents (Riva *et al.*, 1989; Pinder and Wieringa, 1993; He and Richardson, 1997; Sperling and Demling, 1997; Carpenter *et al.*, 1999; Millan *et al.*, in press b). An elevation in FCX levels of

Table 3 Influence of antidepressant agents, as compared to anxiolytic (BZP) and antipsychotic agents, upon dialysate levels of 5-HT, DA and NAD in FCX

Class	Drug	Dose	5-HT	DA	NAD
	Vehicle	–	0	0	0
SSRI	Fluoxetine	10.0	↑↑	↑	↑
SSRI	Citalopram	2.5	↑↑	0	0
SSRI	Paroxetine	10.0	↑↑	↑	↑
SSRI	Sertraline	10.0	↑↑	↑	↑
SNRI	Duloxetine	5.0	↑	↑	↑↑
SNRI	Venlafaxine	10.0	↑↑	↑↑	↑↑
Tricyclic	Clomipramine	10.0	↑↑	↑↑	↑↑↑
Tricyclic	Imipramine	10.0	↑	↑↑	↑↑
NARI	Maprotiline	10.0	0	↑↑	↑↑↑
NARI	Reboxetine	10.0	0	↑↑	↑↑↑
NARI	DMI	10.0	0	↑↑	↑↑
DARI	GBR12935	10.0	0	↑	↑
DARI	Bupropion	10.0	0	↑	↑↑
RIMA	Moclobemide	10.0	0	↑↑	↑↑
MAOI	Tranylcipromine	20.0	↑↑↑	↑↑↑	↑↑↑
β-ago	Clenbuterol	2.5	0	↑	↑
α_2/5-HT_2 ant	Mianserin	10.0	0	↑↑↑	↑↑↑
α_2/5-HT_2 ant	Mirtazapine	10.0	0	↑↑	↑↑
α_2 ant	Fluparoxan	0.63	0	↑	↑↑
α_2 ant	Idazoxan	2.5	0	↑↑	↑↑
5-HT_{1A} ago/α_2 ant	Sunepitron	10.0	↓	↑	↑↑
5-HT_{1A} ago	Buspirone	2.5	↓	↑	↑
5-HT_{1A} ago	Flexinoxan	10.0	↓	↑	↑
SSRI/5-HT_{2C} ant	Trazodone	10.0	↑↑	↑	↑↑
SSRI/5-HT_{2C} ant	Nefazodone	10.0	0	↑	↑
Triazolo-BZP	Alprazolam[a]	0.63	↓	0	0
Triazolo-BZP	Triazolam	0.63	↓	0	0
BZP	Diazepam[a]	10.0	↓	↓	↓
BZP	Clorazepate	10.0	↓	↓	↓
Antipsychotic	Haloperidol	0.08	0	↑	0
Antipsychotic	Clozapine	2.5	0	↑	↑↑

Doses are expressed in mg/kg, base, s.c. or [a]i.p. 0 = no effect; ↑, increase significantly different (in ANOVA) to vehicle, or increase from 150 to 250% relative to basal values (defined as 100%); ↑↑, increase from 250 to 400% relative to basal values; ↑↑↑, increase > 400% relative to basal values; ↓, decrease. Ago, agonist; ant, antagonist; SSRI, selective 5-HT reuptake inhibitor; SNRI, mixed 5-HT and NAD reuptake inhibitor; NARI, selective NAD reuptake inhibitor; DARI, selective dopamine (DA) uptake inhibitor; RIMA, reversible inhibitor of monoamine oxidase A; MAOI, irreversible inhibitor of monoamine oxidases A/B; BZP, benzodiazepine. Data are derived exclusively from data acquired by the present authors under identical test conditions for all drugs (Gobert *et al.*, 1997b; Lejeune *et al.*, 1998; Millan *et al.*, 1998c,1999d; Rivet *et al.*, 1998; Millan *et al.*, 2000).

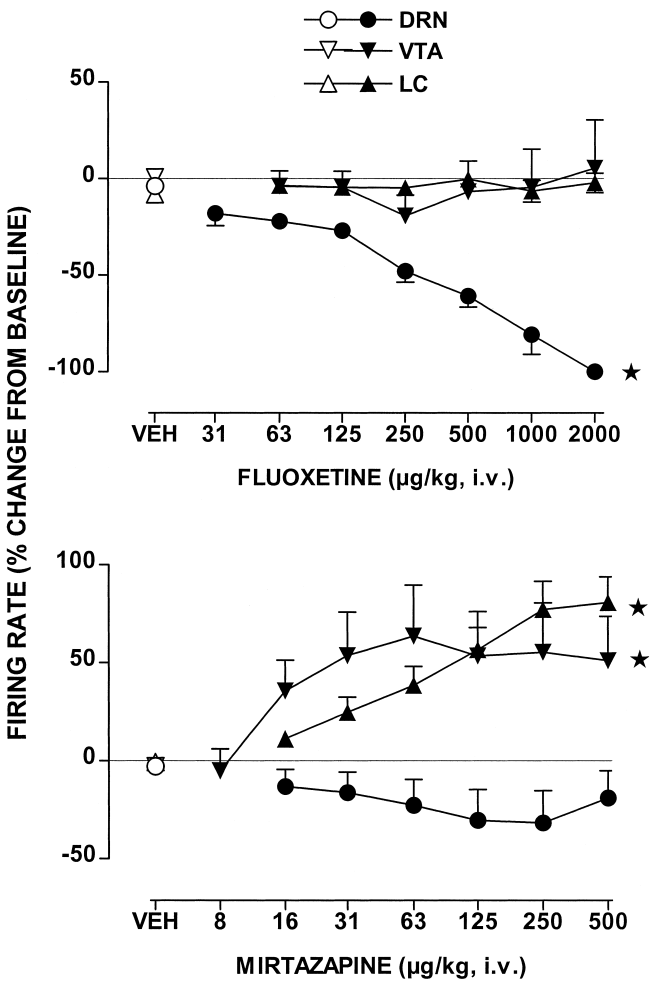

Figure 5 Influence of fluoxetine as compared to mirtazapine upon the firing rate of dopaminergic (VTA, ventrotegmental area), serotonergic (DRN, dorsal raphe nucleus) and noradrenergic (LC, locus coeruleus) neurons in anaesthetized rats. Data are expressed as percentage firing rate relative to basal values (defined as 0%). The inhibitory influence of fluoxetine upon the firing rate of serotonergic neurons was abolished by the 5-HT_{1A} antagonist, WAY100,635 (0.016 mg/kg i.v.) (not shown). Data are means ± SEM. $n \geq 5$ per value. The asterisks indicate significance of drug versus vehicle values

5-HT is not, thus, invariably an effect of the acute administration of antidepressant agents. Mirtazapine has, in fact, been claimed to enhance serotonergic transmission (De Boer *et al.*, 1996; Haddjeri *et al.*, 1996). However, employing a broad dose-range, acute and chronic administration, dialysis studies of the FCX and numerous subcortical regions, as well as recordings of the electrical activity of the DRN, neither we (Rivet *et al.*, 1998; Gobert *et al.*, 1999a; Millan *et al.*, in press b; Figs 4 and 5), nor others (Bengtsson *et al.*, 1999), have confirmed this contention. Interestingly, the 5-HT_{1A} agonists, buspirone, flesinoxan and sunepitron, decreased 5-HT levels in FCX, although such actions of 5-HT_{1A} autoreceptor agonists may desensitize, and their clinical antidepressant actions still require consolidation (see Artigas *et al.*, 1996; Millan *et al.*, 1997b; Silvestre *et al.*, 1998; Apter and Allen, 1999).

Second, in contrast to 5-HT, all classes of antidepressant did, indeed, elevate FCX levels of dopamine. Of these, only the dopamine reuptake inhibitors (DARIs), GR12935 and, probably, bupropion act via the dopamine uptake site (Cooper *et al.*, 1980; Reith *et al.*, 1994). Agonist actions at 5-HT_{1A} receptors, and blockade of 5-HT_{2C} and/or α_2-ARs underlie increases in dopamine levels for several other classes of antidepressant (*vide supra*) while, as likewise mentioned above, this action of clenbuterol likely reflects activation of excitatory β_1 and/or β_2-ARs on dopaminergic neurons (O'Donnell, 1993; Lejeune *et al.*, 1998; see Gobert and Millan, 1999b). The inhibitory influence of moclobemide and tranylcipromine upon dopamine degradation is presumably involved in their ability to increase extracellular levels of dopamine (Broekkamp *et al.*, 1995; Frazer, 1997). The facilitatory influence of SSRIs and SNRIs upon dopamine levels is less easy to decipher. However, their ability to elevate dopamine levels may be secondary to an increase in NAD levels elicited via their inhibition of NAD uptake (see below).

Third, all drugs which elevated dopamine levels also, and more markedly, increased FCX levels of NAD. Thus, while a 'common trait' of antidepressant agents is, indeed, an enhancement in extracellular levels of dopamine in FCX (Tanda *et al.*, 1994), an increase in NAD levels is even more robust. This observation is in line with the hypothesis evoked above that the elevations of dopamine levels seen in FCX with SSRIs, SNRIs and, possibly, other drug classes may follow rises in dopamine levels inasmuch as extracellular dopamine is also cleared by NAD uptake sites. Note, however, that this argument does not provide a satisfactory explanation for the surprising increase in NAD levels provoked by GR12935. In any event, 5-HT_{1A} agonist and 5-HT_{2C}/α_2-AR antagonist properties offer an alternative mechanism for an enhancement in FCX levels of NAD (*vide supra*).

Fourth, if alterations in extracellular concentrations of dopamine in the FCX are to be interpreted as indicative (or causative) of antidepressant properties, it is reasonable to ask whether such changes are detected with other classes of psychoactive agent. In this regard, the two obvious drug classes of comparison are anxiolytics and antipsychotics – although anxious (Kuikka *et al.*, 1995; Morgan and LeDoux, 1995; Espejo, 1997; Coplan and Lydiard, 1998) and psychotic (Kotrla and Weinberger, 1995: Millan *et al.*, 1998c) states also implicate monoaminergic mechanisms in the FCX, and this comparison is not as simple as it may seem.

Comparative influence of anxiolytic and antipsychotic agents upon FCX levels of dopamine, NAD and 5-HT

The prototypical anxiolytic agents and benzodiazepines (BZPs), diazepam and clorazepate, at doses corresponding to those expressing their anxiolytic properties (Millan *et al.*, 1997a), markedly suppressed FCX levels of 5-HT, dopamine and NAD (Table 3). These findings are analogous to those obtained in the hippocampus and other subcortical tissues and reflect the facilitation of $GABA_A$ receptor-mediated mechanisms inhibitory to monoaminergic pathways (Pan and Williams, 1989; Miczek *et al.*, 1995; Broderick, 1997; Millan *et al.*, 1997a; Broderick *et al.*, 1998; Gonzalez *et al.*, 1998; Millan *et al.*, 1999b). In fact, it has been suggested that a reinforcement in GABAergic transmission might counteract depressive states (Lloyd *et al.*, 1989; Petty *et al.*, 1995). This theory is, however, contentious and classic BZPs, such as

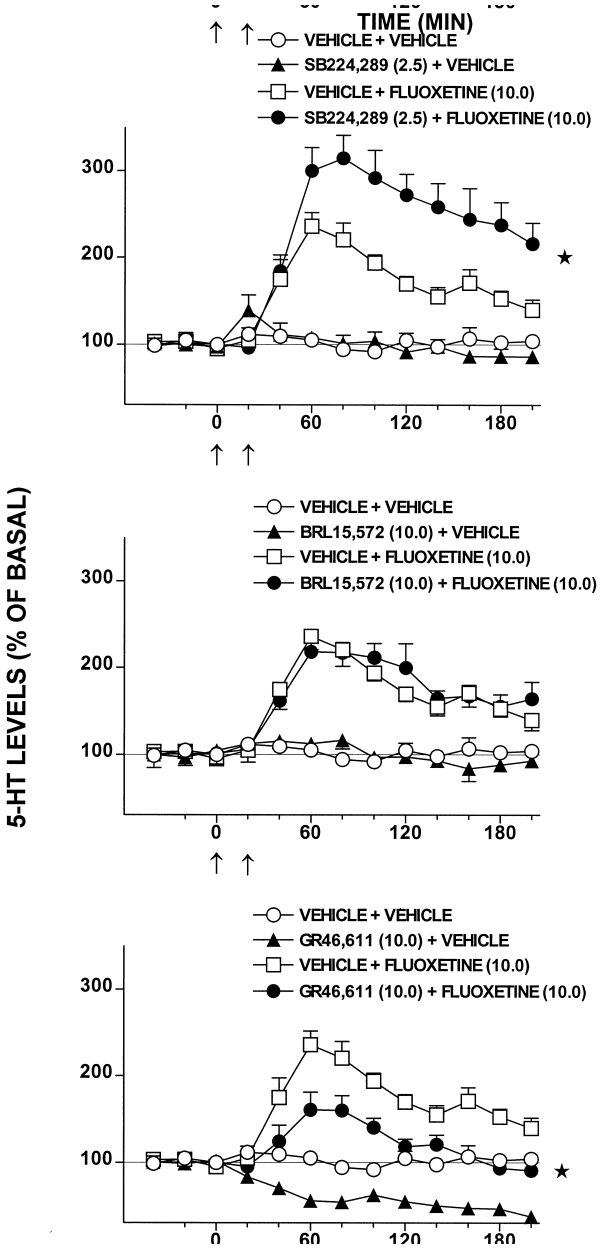

Figure 6 Influence of the 5-HT_{1B} antagonist, SB224,289 and the 5-HT_{1D} antagonist, BRL15,572, compared to the 5-$HT_{1B/1D}$ agonist, GR46,611, upon modulation of FCX levels of 5-HT by fluoxetine. Dose (mg/kg) were as follows: SB224,289 (2.5 s.c.), BRL15,572 (10.0 i.p.), GR46,611 (10.0 s.c.) and fluoxetine (10.0 s.c.). Data are means ± SEM values of 5-HT levels expressed as a percentage change from baseline (100%). For basal levels, see Fig. 3. $n \geq 5$ per value. The asterisk indicates significance of SB224,289/fluoxetine or GR46,611/fluoxetine versus vehicle/fluoxetine values

diazepam or clorazepate, exert little or no positive effect upon 'pure' depressive states independent of anxiety disorders (Birkenhäger *et al.*, 1995). On the other hand, alprazolam and other, high potency triazolo-BZPs are effective, at least in mild to moderate depression, and they may also accelerate the actions of SSRIs (Jonas and Cohon, 1993; Petty *et al.*, 1995; Srisurapanont and Boonyanaruthee, 1997; Smith *et al.*, 1998). In this light, it is of interest that alprazolam and triazolam could be distinguished from diazepam and clorazapate in that, at doses exhibiting anxiolytic activity, they did not suppress FCX levels of dopamine or NAD (Table 3). Interestingly, although 5-HT levels were decreased in FCX, observations in the hippocampus of anaesthetized rats likewise differentiated alprazolam from diazepam in showing that they, respectively, elevate and diminish dialysate levels of 5-HT (Broderick, 1997; Broderick *et al.*, 1998). Clearly, it would be of interest to extend such findings in order to determine the mechanistic basis of such differences between triazolo-BZPs and BZPs with regard to their contrasting utility in the management of depressive states.

With respect to antipsychotic agents, comparisons to antidepressants are complicated by the above-mentioned implication of frontocortical hypofrontality in the negative symptoms of schizophrenia, which respond to clozapine. This atypical antipsychotic is known to facilitate frontocortical – but not subcortical – levels of dopamine and NAD (Kotrla and Weinberger, 1995; Meltzer, 1995; Goodwin, 1997; Millan *et al.*, 1998c; Westerink *et al.*, 1998). Thus, a more appropriate reference compound may be the prototypical neuroleptic, haloperidol, which is not effective in controlling negative symptoms and which may, itself, induce hypofrontality (Bartlett *et al.*, 1994; Meltzer, 1995). In fact, even at a high dose, haloperidol, only slightly increased dopamine levels in FCX (Table 2) and this effect was less pronounced than in subcortical structures (Millan *et al.*, 1998c). Haloperidol also only slightly elevated FCX levels of NAD. Nevertheless, it must be pointed out that numerous antipsychotic agents – albeit of uncertain efficacy against negative symptoms – increase FCX levels of dopamine and/or NAD (Millan *et al.*, 1998c; Westerink *et al.*, 1998; Kuroki *et al.*, 1999). There are, thus, similarities between several antipsychotic and antidepressant drugs as concerns their common ability to reinforce release of dopamine and NAD in FCX (see further below).

Influence of antidepressant agents upon frontocortical levels of dopamine: summary

To summarize, the contention that an elevation in FCX levels of dopamine is characteristic of antidepressant agents (Tanda *et al.*, 1994), while valid, is an oversimplification. While all clinically effective classes of antidepressant increase FCX levels of dopamine, they also more markedly elevate levels of NAD in parallel. Furthermore, despite their pronounced influence upon FCX levels of NAD and dopamine, the antidepressant properties of 5-HT_{1A} agonists and α_2-AR antagonists in man remain to be concretely demonstrated (Dickinson, 1991; Broekkamp *et al.*, 1995; Apter and Allen, 1999). Furthermore, clozapine and several other antipsychotic agents likewise elevate levels of dopamine and NAD in FCX (Westerink *et al.*, 1998). Therefore, notwithstanding the importance of frontocortical monoaminergic transmission in depressive states and their treatment, an elevation in FCX levels of dopamine and/or NAD is not sufficient as a criterion for the attribution of antidepressant properties *per se*. Furthermore, the absence of an increase in 5-HT levels upon acute administration is obviously not contraindicative of antidepressant activity – for example, for reboxetine and other NARIs. Not surprisingly, in addition to the demonstration of an elevation in monoamine levels

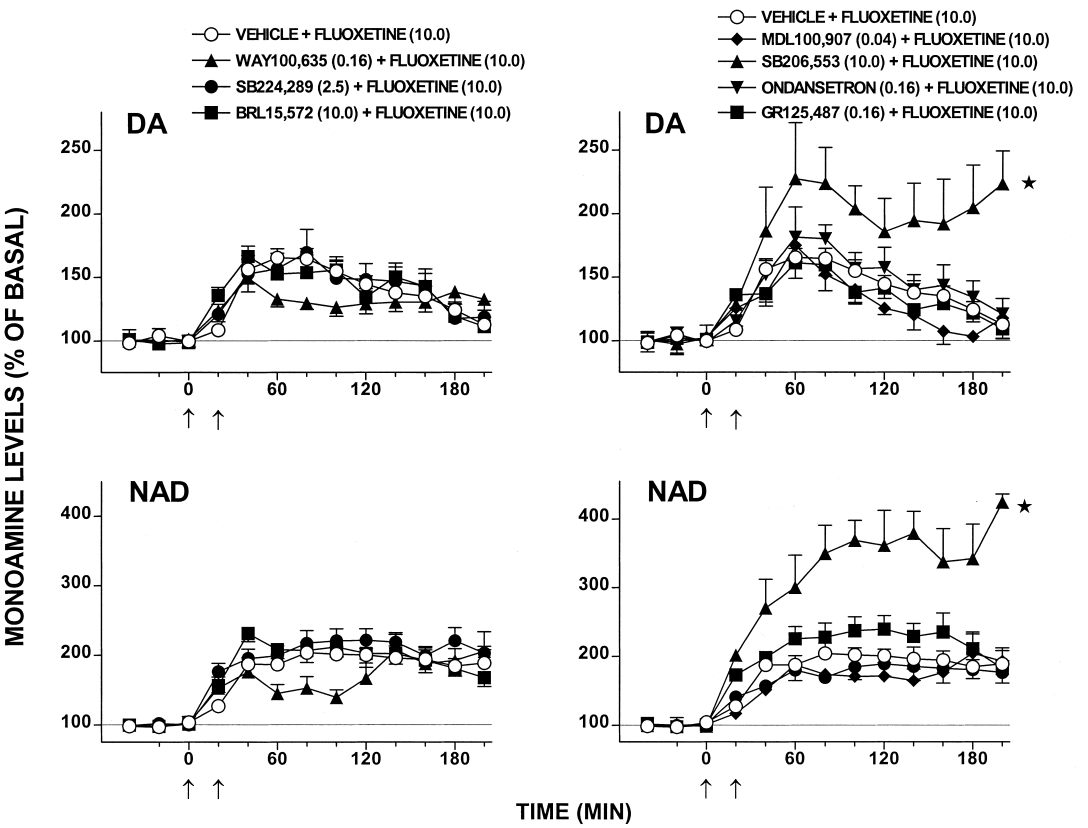

Figure 7 Influence of the 5-HT_{1A} antagonist, WAY100,635, the 5-HT_{1B} antagonist, SB224,289, the 5-HT_{1D} antagonist, BRL15,572, the 5-$HT_{2B/2C}$ antagonist, SB206,553, the 5-HT_{2A} antagonist, MDL100,907, the 5-HT_3 antagonist, ondansetron and the 5-HT_4 antagonist, GR125,487 upon modulation of FCX levels of dopamine and NAD by fluoxetine. Doses (mg/kg) were as follows: WAY100,635 (0.16 s.c.), SB224,289 (2.5 s.c.), BRL15,572 (10.0 i.p.), SB206,553 (10.0 s.c.), MDL100,907 (0.04 s.c.), ondansetron (0.16 s.c.), GR125,487 (0.16 i.p.) and fluoxetine (10.0 s.c.). Data are means ± SEM values of dopamine and NAD levels expressed as a percentage change from baseline (100%). For basal levels, see Fig. 3. $n \geq 5$ per value. The asterisks indicate significance of SB206,553/fluoxetine vs. vehicle/fluoxetine values. Note that SB206,553 itself elevates FCX levels of dopamine and NAD (Table 1), so this is an additive effect with fluoxetine

in the FCX – or any other structure – complementary mechanistic and behavioural studies are requisite for the compelling delineation of antidepressant properties for any specific drug.

Modulation of the influence of fluoxetine by ligands at 5-HT_{1A} and 5-$HT_{1B/1D}$ autoreceptor

It has been suggested that a progressive desensitization of 5-HT_{1A} and/or 5-HT_{1B} autoreceptors may be associated with the delay to onset of action of SSRIs (Blier and de Montigny, 1994; Artigas *et al.*, 1996). This intriguing possibility has triggered numerous clinical trials with the 5-HT_{1A} receptor ligand, pindolol, and the balance of evidence suggests that the actions of antidepressant agents are, indeed, accelerated (Blier and Bergeron, 1995; Tome *et al.*, 1997; Zanardi *et al.*, 1997; Bordet *et al.*, 1998; McAskill *et al.*, 1998; Mundo *et al.*, 1998), although non-serotonergic mechanisms may be involved in these clinical findings (see Gobert and Millan, 1999a; Millan and Gobert, 1999). In support of a role of 5-HT_{1A} and 5-HT_{1B} autoreceptors in braking SSRI-induced elevation in 5-HT levels, many studies have shown that their blockade facilitates the influence of fluoxetine and other SSRIs both upon extracellular levels of 5-HT and upon various behavioural responses (Hjorth and Sharp, 1993; Gartside *et al.*, 1995; Rollema *et al.*, 1996; Invernizzi *et al.*, 1997; Sharp *et al.*, 1997; Dawson and Nguyen, 1998; Grignaschi *et al.*, 1998; Hervàs and Artigas, 1998; Trillat *et al.*, 1998; Barton and Hutson, 1999). In line with these studies, the selective 5-HT_{1A} and 5-HT_{1B} receptor antagonists, WAY100,635 and SB224,289, respectively, synergistically enhanced the influence of fluoxetine upon FCX levels of 5-HT without modifying its influence upon levels of NAD or dopamine (Figs 6 and 7; Gobert *et al.*, 1997c): furthermore, the 5-$HT_{1B/1D}$ antagonist, GR127,935, acted similarly (Gobert *et al.*, 1997c; Millan and Perrin-Monneyron, 1997). The predominant, inhibitory role of 5-HT_{1B} versus 5-HT_{1D} autoreceptors is indicated by the lack of influence of the selective 5-HT_{1D} antagonist, BRL15,572, upon the action of fluoxetine (Figs 6 and 7).

Not surprisingly, the administration of 5-HT_{1A} or 5-HT_{1B} agonists which suppress 5-HT levels in FCX alone (*vide supra*), counteracts the elevation of 5-HT levels in FCX provoked by fluoxetine (Gobert *et al.*, 1997b, 1999b). While the influence of fluoxetine upon frontocortical levels of dopamine and NAD was not modified by 5-$HT_{1B/1D}$ agonists, there was an – at least additive – facilitatory effect of 5-HT_{1A} agonists and fluoxetine upon FCX levels of dopamine (Table 1; Gobert *et al.*, 1999b). Interestingly, low loses of buspirone also enhance the functional, antidepressant properties of SSRIs in rats (Redrobe and Bourin,

1998). As discussed elsewhere (De Battista *et al.*, 1998; Dimitriou and Dimitriou, 1998; Apter and Allen, 1999; see also Menkes, 1995; Gobert *et al.*, 1997b, 1999b), these findings are of interest in light of reports that buspirone may be a useful adjunctive agent with SSRIs for the improved treatment of depressive states. These observations also have implications for drugs possessing mixed 5-$HT_{1A/1B}$ agonist and SSRI properties (Matos *et al.*, 1994; Bartoszyk *et al.*, 1997). Chronic studies are, however, required to determine the long-term significance of combined 5-$HT_{1A/1B}$ autoreceptor agonist and SSRI properties

Modulation of the influence of SSRIs upon dopamine and NAD levels by antagonists at postsynaptic 5-HT receptors

Inasmuch as fluoxetine indirectly activates 5-HT_{1A} autoreceptors in the DRN, it might be argued that this mechanism may intervene in its ability to increase FCX levels of dopamine and NAD. However, this may be discounted inasmuch as WAY100,635 abolishes the inhibition by fluoxetine of DRN firing (Fig. 5), yet it does not significantly modify its induction of dopamine and NAD levels in FCX (Gobert *et al.*, 1997c; Fig. 7). Furthermore, this mechanism would act indirectly via disinhibition of VTA-localized dopaminergic cell bodies yet, in contrast to 5-HT_{1A} autoreceptor agonists, fluoxetine does not enhance the firing rate of dopaminergic neurons (Prisco and Esposito, 1995; Fig. 5). Although Iyer and Bradbury (1996) suggested that the increase in FCX levels of dopamine elicited by 5-HT itself may be mediated by activation of 5-HT_{1B} receptors in FCX, antagonists at 5-$HT_{1B/1D}$, 5-HT_{1B} or 5-HT_{1D} receptors do not modify induction of dopamine and NAD levels in FCX by fluoxetine, suggesting that such mechanisms are not implicated (Gobert *et al.*, 1997c; Table 1 and Fig. 7).

Although the indirect activation of 5-HT_{2A} receptors could, theoretically, be involved in the induction of dopamine and NAD release by fluoxetine (Schmidt *et al.*, 1994; Gobert and Millan, 1999a), its actions were little affected by MDL100,907 (Fig. 7). Interestingly, fluoxetine itself shows mild affinity for 5-HT_{2C} receptors, at which it behaves as an antagonist (Palvimaki *et al.*, 1996). However, 5-HT_{2C} receptor blockade is unlikely to be important for several reasons. First, it cannot explain increases in FCX levels of dopamine and NAD elicited by other SSRIs lacking affinity for 5-HT_{2C} sites. Second, at doses increasing FCX levels of dopamine and NAD, and in the presence of combined 5-$HT_{1A/1B}$ receptor blockade, fluoxetine activates 5-HT_{2C} receptors via a marked increase in synaptic levels of 5-HT (Prisco *et al.*, 1994; Millan and Perrin-Monneyron, 1997). Third, the 5-HT_{2C} antagonist, SB206,553, additively increased FCX levels of dopamine with NAD (Fig. 7). Fourth, in contrast to 5-HT_{2C} antagonists, fluoxetine fails to excite dopaminergic and noradrenergic cell bodies in the VTA and LC, respectively (Prisco *et al.*, 1994; Ichikawa and Meltzer, 1995; Esposito, 1996) (Fig. 5).

As discussed above, it has been suggested that excitatory 5-HT_3 receptors enhance release of dopamine in the FCX (Chen *et al.*, 1992). Furthermore, Tanda *et al.* (1995) reported that systemic administration of the 5-HT_3 (and 5-HT_4) antagonist, tropisetron, or its local infusion into the FCX, blocked the increase in extracellular levels of dopamine elicited by fluoxetine. However, conflicting data were acquired by Iyer and Bradberry (1996) as concerns the influence of 5-HT itself upon FCX levels of dopamine and, herein, a further 5-HT_3 antagonist, ondansetron, did not modify the influence of fluoxetine upon levels of dopamine, NAD or 5-HT (Fig. 7). Thus, 5-HT_3 receptors do not appear to play a major role in the elevation in FCX levels of dopamine or NAD by SSRIs. Furthermore, although 5-HT_4 receptors have been suggest to mediate an increase in dopamine levels in the striatum (Bonhomme *et al.*, 1995), the selective 5-HT_4 antagonist, GR125,487, did not modulate the influence of fluoxetine upon dopamine and NAD levels herein (Fig. 7).

These observations suggest that fluoxetine and other SSRIs probably do not elevate FCX levels of dopamine or NAD via the activation of specific 5-HT receptor types. This argument is supported by the observation that low doses of citalopram can elevate frontocortical levels of 5-HT without affecting those of dopamine or NAD (Table 3 and Fig. 3). In fact, fluoxetine displays modest affinity for the NAD uptake site. Thus, it is possible that the ability of fluoxetine and other SSRIs to elevate FCX levels of NAD simply reflects their occupation of NAD uptake sites in FCX – perhaps a subtype distinct from that at which desipramine and other NARIs exert their actions (Pacholczyk *et al.*, 1991; Hughes and Stanford, 1996, 1998). The relatively weak influence of citalopram upon NAD and dopamine levels relative to fluoxetine would reflect, then, its high selectivity for 5-HT versus NAD uptake sites (Hyttel, 1994; Millan *et al.*, 1999d). In contrast, although fluoxetine and other SSRIs have negligible affinity for dopamine uptake sites, inasmuch as extracellular levels of dopamine in FCX are controlled by 'NAD' uptake sites (Giros *et al.*, 1994; Gu *et al.*, 1994; Gresch *et al.*, 1995), dopamine levels may simply rise in parallel with those of NAD (*vide supra*).

To summarize, it is likely that the low selectivity of fluoxetine for 5-HT versus NAD uptake sites accounts for its relatively marked influence upon FCX levels of dopamine and NAD. Nevertheless, inasmuch as fluoxetine does not elevate levels of dopamine in the nucleus accumbens – despite its rich noradrenergic innervation (Prisco and Esposito, 1995; Millan *et al.*, 1997b), the generality of this NAD uptake hypothesis still remains to be validated further. Irrespective of the underlying mechanisms, it might be questioned whether fluoxetine is genuinely a 'SSRI' at all. This question is particular apposite in the light of increasing interest in drugs which (1) jointly block 5-HT and NAD uptake, such as venlafaxine, or (2) selectively act at NAD uptake sites, such as reboxetine (Bel and Artigas, 1996; Berzewski *et al.*, 1997; Brunello, 1997; Dubini *et al.*, 1997; Schweizer *et al.*, 1997; Beique *et al.*, 1998; Burrows *et al.*, 1998; Reneric and Lucki, 1998; Schatzberg, 1998; Szabadi *et al.*, 1998).

Modulation of the influence of SSRIs upon 5-HT, dopamine and NAD levels by antagonists at α_2-noradrenergic receptors (Tables 1 and 2)

As discussed in detail elsewhere (Gobert *et al.*, 1997a, 1999b; Millan *et al.*, 2000), α_2-AR antagonists markedly potentiate the influence of fluoxetine upon FCX levels of 5-HT, dopamine and NAD. Palij and Stanford (1996) have also reported that the α_2-AR antagonist, rauwolscine, potentiates increases in NAD levels evoked by the NARI, desipramine. The argument that the facilitatory influence of α_2-AR antagonists upon fluoxetine may reflect metabolic factors is unlikely inasmuch as similar effects are

seen with the SNRI, duloxetine: furthermore, four different chemical classes of α_2-AR antagonist potentiate the increase of dopamine and NAD levels in FCX elicited by fluoxetine. That is the imidazoline, atipamezole; the benzodioxane, fluparoxan, the arylpiperazine, 1-PP and the alkaloid, yohimbine (Gobert *et al.*, 1997a, 1999b; Millan *et al.* 2000). Furthermore, the latter may be distinguished from other α_2-AR antagonists inasmuch as it diminished the influence of fluoxetine upon 5-HT levels in the same samples as those in which dopamine and NAD levels were potentiated (Millan *et al.* 2000). This opposite pattern of modulation of 5-HT versus dopamine/NAD levels is clearly inconsistent with an implication of pharmacokinetic factors. This distinctive decrease in fluoxetine-induced levels of 5-HT with yohimbine reflects its agonist properties at 5-HT_{1A} autoreceptors (Millan *et al.* 2000). These findings with α_2-AR antagonists are of particular interest in the light of data suggesting that α_2-AR autoreceptors may desensitize upon chronic antidepressant treatment (Crews and Smith, 1978; Mongeau *et al.*,) 1994a; Yoshioka *et al.*, 1995; Mateo *et al.*, 1998). Indeed, coadministration of α_2-AR antagonists and tricyclic agents accelerates downregulation of β-ARs in FCX, an adaptive response to long-term treatment with several classes of antidepressant agent (Wiech and Ursillo, 1980; Crews *et al.*, 1983; Klysner and Geisler, 1991; Duncan *et al.*, 1994; Okada and Tokumitsu, 1994; Newman-Tancredi *et al.*, 1996). Moreover, experimental and clinical studies suggest that α_2-AR antagonists possess modest antidepressant properties (Osman *et al.*, 1989; Dickinson, 1991) and that they potentiate the therapeutic effects of other classes of antidepressant agent and electroconvulsive therapy (Sachs *et al.*, 1986; Pollack and Hammerness, 1993; Cappiello *et al.*, 1995; Nemeroff, 1997; see also Lauritzen *et al.*, 1992). However, such limited, clinical observations still require consolidation in rigorously controlled trials employing genuinely selective α_2-AR antagonists.

Modulation of the influence of SSRIs upon 5-HT, dopamine and NAD levels by the dopaminergic receptor antagonist and neuroleptic, haloperidol

Although the selective D_2/D_3 antagonist, raclopride, failed to modify the influence of fluoxetine upon FCX levels of 5-HT, dopamine and NAD, at a high dose, the neuroleptic, haloperidol, significantly enhanced its ability to increase levels of 5-HT, dopamine and NAD in each case (Fig. 8). This result was surprising, and it is unlikely to reflect the antagonist properties of haloperidol at D_2/D_3 receptors in light of the above-mentioned inactivity of raclopride. Clearly, the underlying mechanism requires clarification, and a pharmacokinetic interaction cannot be excluded (Gram and Fredricson-Overo, 1972; Ciraulo and Shader, 1990; Baumann, 1996; Avenoso *et al.*, 1997). Nevertheless, this observation is of considerable interest inasmuch as neuroleptics are employed in association with tricyclics – and SSRIs – for the treatment of delusional, post-psychotic depression, treatment-resistant depression and impulsive disorders (Nelson, 1987; Dassa *et al.*, 1993; Rothschild *et al.*, 1993; McDougle *et al.*, 1994; Wolfersdorf *et al.*, 1995; Thase and Rush, 1995; Agid and Lerer, 1999). Moreover, the relevance of this finding is underlined by the following: (1) SSRIs are coadministered with neuroleptics to

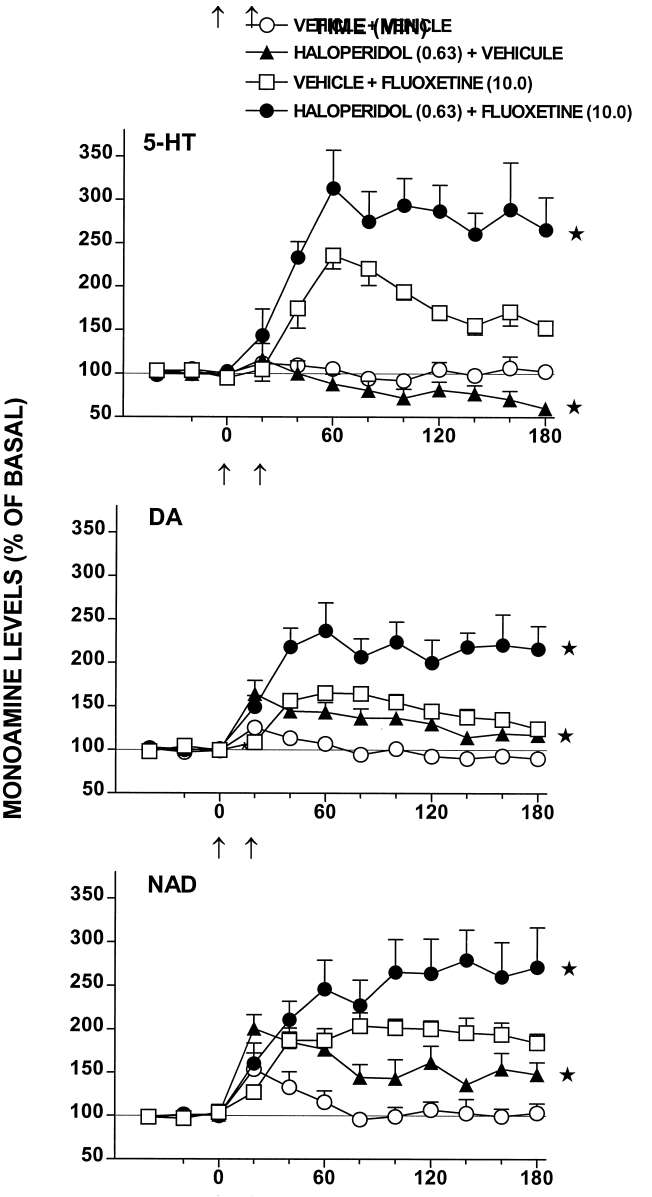

Figure 8 Influence of the neuroleptic, haloperidol, upon modulation of FCX levels of 5-HT, dopamine and NAD by fluoxetine. Doses (mg/kg s.c.) were as follows: haloperidol (0.63) and fluoxetine (10.0). Data are means ± SEM values of 5-HT, dopamine and NAD levels expressed as a percentage change from baseline (100%). For basal levels, see Fig. 3. $n \geq 5$ per value. The asterisks indicate significance of haloperidol/vehicle versus vehicle/vehicle and of haloperidol/fluoxetine versus vehicle/haloperidol values

psychotic patients in order to improve refractory, deficit and associated depressive symptoms (Silver and Nassar, 1992; Siris *et al.*, 1994; Goff *et al.*, 1995; Hogarty *et al.*, 1995; Evins and Goff, 1996); (2) hypofrontality is implicated in the pathogenesis of both the negative symptoms of schizophrenia (Kotrla and Weinberger, 1995) and depressive states (Goodwin, 1997; King *et al.*, 1998) – which show several commonalties (Newcomer *et al.*, 1990; Siris, 1991; Bermanzohn and Siris, 1992; Kibel *et al.*, 1993; McPhillips and Barnes, 1997); and (3) as mentioned above, clozapine and other potentially atypical antipsychotics mimic

antidepressants in preferentially enhancing frontocortical versus subcortical dopaminergic and noradrenergic transmission (Bartlett *et al.*, 1994; Rollema *et al.*, 1997; Millan *et al.*, 1998c; Westerink *et al.*, 1998; Kuroki *et al.*, 1999). Studies of interactions amongst antidepressant and antispsychotic agents would therefore be worthwhile pursuing.

Modulation of frontocortical monoaminergic transmission and the improved management of depression

The present data clarify several receptorial mechanisms underlying functional interrelationships amongst serotonergic, dopaminergic and noradrenergic projections to the FCX. Inasmuch as these pathways may be compromised in depressive states (Caldecott-Hazard *et al.*, 1991; Maes and Meltzer, 1995; Willner, 1995; Leonard, 1997), the observations discussed herein suggest several strategies whereby their activity might be restored and/or the actions of antidepressant agents improved. For example, the ability of 5-HT_{1A} agonists to reinforce frontocortical dopaminergic pathways may be involved in their potential antidepressant properties (Schreiber and De Vry, 1993; Lucki *et al.*, 1994; Millan *et al.*, 1997b) and similar actions might be anticipated for 5-HT_{2C} receptor antagonists inasmuch as they facilitate dopaminergic transmission in the FCX – and nucleus accumbens (Di Matteo *et al.*, 1998). On the other hand, the most effective approach for strengthening monoaminergic transmission in the FCX may be the association of α_2-AR antagonist with SSRI properties (Giardina *et al.*, 1995; Gobert *et al.*, 1997a; Meyer *et al.*, 1997).

The interaction studies with fluoxetine described above provide a potential foundation both for the use of drug combinations and for the development of multireceptorial ligands in the improved management of depressive states (Broekkamp *et al.*, 1995; Thase and Rush, 1995; Meyer *et al.*, 1997; Nemeroff, 1997; Samburanis *et al.*, 1997; Bottcher *et al.*, 1998; McAskill *et al.*, 1998). Two interrelated and crucial questions concern the impact upon, first, beneficial, antidepressant properties and, second, side-effect profiles. Indeed, the identity of 5-HT receptors underlying the therapeutic actions of SSRIs is still intensively debated (Cesana *et al.*, 1993; Redrobe *et al.*, 1996; Da-Rocha *et al.*, 1997; Redrobe and Bourin, 1997; Finn *et al.*, 1998; Greenberg *et al.*, 1998; Kent *et al.*, 1998; Mos *et al.*, 1999).

The hypothesis that blockade of 5-HT_{1A} and/or 5-HT_{1B} autoreceptors may enhance the rapidity and efficacy of action of SSRIs has justifiably attracted considerable interest (Artigas *et al.*, 1996; McAskill *et al.*, 1998) and is supported by neurochemical data in rodents *(vide supra)*. However, should postsynaptic 5-HT_{1A} and/or 5-HT_{1B} receptors be involved in the desirable, antidepressant actions of SSRIs (Luscombe *et al.*, 1993; Lucki *et al.*, 1994; O'Neill *et al.*, 1996; Moser and Sanger, 1996; Redrobe *et al.*, 1996; Finn *et al.*, 1998; Haddjeri *et al.*, 1998; Heisler *et al.*, 1998b; Ramboz *et al.*, 1998), it is difficult to imagine that the assimilation of 5-$HT_{1A/1B}$ antagonist actions into a SSRI would improve its clinical efficacy. In this line, the results of ongoing clinical studies with the 5-HT_{1A} ligand, pindolol, are of great interest. As mentioned above, the balance of evidence currently suggests that pindolol accelerates the onset of action of antidepressant in a significant population of patients (Tome *et al.*, 1997; Mundo *et al.*, 1998; Zanardi *et al.*, 1998; see also McAskill *et al.*, 1998). Nevertheless, pindolol is a partial agonist at human 5-HT_{1A} receptors (Meltzer and Maes, 1994; Newman-Tancredi *et al.*, 1998) and, at doses equivalent to those employed in clinical studies, only modest occupation is seen in PET imaging studies (Farde L., personal communication). In fact, pindolol also possesses partial agonist properties at $\beta_{1/2}$-ARs as well as rat – although not human – 5-HT_{1B} receptors (Millan and Gobert, 1999). As discussed in detail elsewhere (Millan and Gobert, 1999), actions at these non-5-HT_{1A} sites are implicated in the intrinsic ability of pindolol to enhance frontocortical levels of dopamine and NAD. Thus, the mechanism of action of pindolol in man is complex and definitive, clinical validation of the joint 5-HT_{1A} autoreceptor blockade/SSRI hypothesis is still awaited.

On other hand, if 5-HT_{2A} and/or 5-HT_{2C} receptor blockade (or downregulation) is involved in antidepressant actions (Rickels *et al.*, 1994; Biver *et al.*, 1997; He and Richardson, 1997; Newton and Elliot, 1997; Quested *et al.*, 1997; Sibille *et al.*, 1997; Sargent *et al.*, 1998), auxiliary 5-$HT_{2A/2C}$ antagonist properties might be profitable for a SSRI (but see Cesana *et al.*, 1993; Jenck *et al.*, 1993, 1994; Katz and Rosenthal, 1994; Greenberg *et al.*, 1998; Martin *et al.*, 1998).

This fundamental question of the identity of the receptorial mechanisms underlying the antidepressant actions of SSRIs and other classes of antidepressant in man requires urgent resolution for the successful implementation of such strategies.

With respect to side-effects, it might be argued that the potentiation of SSRI-induced increases in 5-HT levels is merely equivalent to a dose increase: side-effects will, thus, be exacerbated in parallel (Mir and Taylor, 1997; Glassman, 1998; Goldstein and Goodnick, 1998; Olivier *et al.*, 1998). That is, the therapeutic window will not be radically altered. However, it is also uncertain which receptors underlie the undesirable actions of antidepressants. Indeed, certain additional, receptorial actions may improve the security profile of antidepressant agents. For example, if disruption of sleep patterns can be attributed to activation of postsynaptic 5-HT_{1A} receptors (Driver *et al.*, 1995; Dorsey *et al.*, 1996), concomitant 5-HT_{1A} blockade would be advantageous. Furthermore, 5-HT_{2C} receptor blockade may reduce nervousness and anxiety (Griebel *et al.*, 1997; Kennett *et al.*, 1997a,b; Heisler *et al.*, 1998a; but see also Jenck *et al.*, 1998) and improve sexual dysfunction, and the latter effect might likewise be anticipated with α_2-AR blockade (Balon, 1993; Aizenberg *et al.*, 1997; Nemeroff, 1997; Olivier *et al.*, 1998; Rosen *et al.*, 1999).

Limitations and possible extensions of the present studies

Several limitations of the present studies and their interpretation should be noted. First, for reasons indicated in the Introduction, these studies were performed in the FCX. It should be emphasized that the intrinsic circuitry and interconnections of the FCX to other cortical and subcortical structures are highly complex. Furthermore, in this regard, the FCX of the rat is considerably less evolved than equivalent cortical structures in man.

Second, notwithstanding the central role of the FCX in the modulation of mood, cognition and motor behaviour, and implication in the actions of antidepressant agents, the findings summarized herein cannot be automatically extrapolated to other cerebral regions. Although certain effects observed, in particular

those reflecting actions at auto- and heteroreceptors localized at the cell body level, are likely apparent in other regions, it would be of interest to extend the present studies to additional structures implicated in depressive states. In this light, we are currently examining the hippocampus, nucleus accumbens and amygdala. For example, while SSRIs elevate dialysate levels of 5-HT in all cerebral regions, they increase dopamine levels only in FCX. On the other hand, the α_2-AR/5-HT$_2$ antagonist, mirtazapine, fails to affect 5-HT levels in any cerebral structure, and enhances dopamine levels only in FCX (Rivet *et al.*, 1998; Bengtsson *et al.*, 1999; Gobert *et al.*, 1999a; Millan *et al.*, in press b) (Fig. 4).

Third, the majority of the effects described herein were acquired upon acute drug administration. This approach is eminently suitable to the characterization of the functional roles of various auto- and heteroreceptor subtypes. However, inasmuch as antidepressant agents are administered chronically, and may trigger adaptive changes, it would be interesting to expand the present observations with studies of long-term drug administration. In this light, we have initiated analyses of the long-term effects of several key drugs. For example, the facilitatory influence of citalopram and mirtazapine upon FCX levels of 5-HT and dopamine/NAD, respectively, is maintained upon their long-term (2 weeks) administration (Gobert *et al.*, 1999a; Millan *et al.*, in press b). On the other hand, the induction of FCX levels of dopamine and NAD by fluoxetine shows tolerance upon chronic administration (Tanda *et al.*, 1994). This issue clearly requires further study.

Fourth, it would be desirable to complement neurochemical/electrophysiological parameters with functional measures. This is difficult to perform systematically inasmuch as simple behaviours mediated by well-defined receptorial mechanisms and integrated in the FCX are largely unknown. Nevertheless, 5-HT$_{2A}$ receptor-mediated head-twitches are expressed in the FCX (Willins and Meltzer, 1997) and the potentiation of FCX levels of 5-HT by SSRI administration following 5-HT$_{1A/1B}$ autoreceptor blockade elicits a pronounced, MDL100,907-reversible head-twitch response (Gobert *et al.*, in press a). Further, although the issue is still controversial, we have observed that an enhancement in SSRI-induced 5-HT release by 5-HT$_{1A}$ receptor blockade similarly enhances the antidepressant actions of the SNRI, duloxetine (Grignaschi *et al.*, 1998; Millan *et al.*, 1998a; Trillat *et al.*, 1998). Such functional studies require considerable development.

Fifth, in our interaction studies with SSRIs, only single doses were examined inasmuch as the performance of full dose–response curves for both SSRIs and auto- and heteroreceptor ligands in interaction would be prohibitively time-consuming. Nevertheless, such information would be necessary to formally define (e.g. by isobolographic analysis) whether drug interactions are genuinely additive or synergistic.

Sixth, as indicated above, intrinsic actions of antagonists were interpreted in terms of a blockade of the tonic actions of spontaneously released monoamines. It cannot be categorically excluded that certain drugs behave as inverse agonists at autoreceptors, an issue requiring further evaluation *in vivo* (see Millan *et al.*, 1999c). Furthermore, the degree of 'tone' at auto- and heteroreceptors controlling FCX release of monoamines may vary as a function of the physiological state or pathological conditions. For example, monoaminergic transmission in the FCX may be chronically suppressed in depressive states, whereas it may rapidly be enhanced in response to specific arousing, environmental stimuli (Cenci *et al.*, 1992; Frazer, 1997). Thus, the precise influence of drugs upon extracellular levels of monoamines in FCX may vary as a function of such variables.

Seventh, as discussed above, all classes of antidepressant agent examined herein enhance monoaminergic transmission in the FCX. However, these actions differ in this respect, with a reinforcement of noradrenergic and, to a lesser extent, dopaminergic pathways appearing to be a common factor. It remains to be established as to how such differential influence upon FCX levels of 5-HT, NAD and dopamine can be related to the therapeutic efficacy and other clinical properties of the antidepressants examined herein.

Eighth, for several reasons, this work employed the systemic route of drug administration, not least, since patients are treated by this route. Furthermore, this route permits the exploitation of other functional models for the precise definition of active dose-ranges of ligands selective for the specific auto- and/or heteroreceptors targeted. Although local perfusion methods are popular, the variable and, in general, unknown permeability of dialysis membranes to various drugs, the rapid diffusion of lipophilic agents from their sites of local application, as well as the need for high, micromolar drug concentrations renders interpretation of such data difficult. Furthermore, at the neuronal level, the parallel examination of drug actions upon the electrical activity of dopaminergic, serotonergic and noradrenergic cell bodies in the VTA, DRN and LC, respectively, permits the identification of mechanisms coordinated at the cell body level. Nevertheless, additional studies would be of interest to more precisely define sites and mechanisms of drug action.

Conclusions

In summary, the use of a complementary dialysis and electrophysiological approach, together with several highly selective ligands, has permitted important insights into the complex pattern of reciprocal interactions via which multiples classes of auto- and heteroreceptor control the activity of frontocortical monoaminergic pathways. These data facilitate interpretation of the influence upon FCX levels of 5-HT, dopamine and NAD of diverse classes of antidepressant agent, and suggest numerous possible receptorial strategies for modulation (potentiation) of their therapeutic actions. It remains to be seen whether such approaches, either employing judicious drug combinations or multireceptorial ligands displaying several, directed actions (such as SSRI plus 5-HT$_{1A}$ antagonist), can genuinely improve the management of depressive states.

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