The Pharmacology of Mesocortical Dopamine Neurons: A Dual-Probe Microdialysis Study in the Ventral Tegmental Area and Prefrontal Cortex of the Rat Brain

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ABSTRACT
Receptor-specific compounds were applied by retrograde microdialysis to the ventral tegmental area (VTA) of the rat brain. The effects of intrategmental infusions on extracellular dopamine in the ipsilateral prefrontal cortex (PFC) were recorded with a second microdialysis probe. Intrategmental infusion of tetradotoxin (1 μM), muscimol (20 μM) or baclofen (50 μM) decreased extracellular dopamine in the PFC. Infusion of N-methyl-D-aspartate (NMDA) (300 μM; 1 mM, 15 min) or kainate (50 μM, 15 min) increased extracellular dopamine in the PFC. The effects of the excitatory amino acids were suppressed by co-infusion with (−)-3(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (300 μM), with (−)-2-amino-5-phosphonopentanoic acid (500 μM), with dizocilpine maleate (500 μM) and kainate (50 μM, 15 min) increased extracellular dopamine in the PFC. The antipsychotic effects of dopamine blockers are believed to exert their effects on prefrontal cortical dopamine release. This study demonstrates the release of dopamine in the PFC. For this purpose a comparison with other dopaminergic forebrain structures, such as nucleus accumbens and striatum, is crucial.

Because less than 10% of the VTA dopamine neurons project to the PFC, these neurons are difficult to discern by electrophysiologic means from A10 neurons that project to the nucleus accumbens. Therefore, compared with what we know about the mesolimbic and striatal dopamine neurons, our knowledge of the pharmacology of mesocortical dopamine neurons is still limited. An alternative way to study the mesocortical A10 neurons is to use dual-probe microdialysis.

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ABBREVIATIONS: VTA, ventral tegmental area; PFC, prefrontal cortex; TTX, tetradotoxin; (+)-HA966, (+)-3-amino-1-hydroxy-2-pyridolone; AP-5, (±)-2-amino-5-phosphonopentanoic acid; CPP, (±)-3(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid; (+)-MK-801, dizocilpine maleate; CGP 52432, 3-[[3,4-dichlorophenyl]methyl]propyl[diethoxymethyl] phosphonic acid.
PFC. Receptor-specific compounds were infused into the VTA, whereas extracellular dopamine was recorded in the ipsilateral PFC.

Three issues were investigated:
1. Identification of receptors that modify the activity of mesocortical dopamine neurons at the somatodendritic level.
2. The participation of afferents in the tonic regulation of the mesocortical dopamine neurons.
3. A comparison among the mesocortical, mesolimbic and nigrostriatal dopaminergic systems.

On the basis of earlier studies (for review see Kalivas, 1993), we investigated three different neuronal pathways that are well known to send efferents to the VTA. These pathways consists of GABAAergic, glutamatergic and cholinergic neurons. Six different types of receptor interactions were studied: GABA<sub>A</sub>, GABA<sub>B</sub>, NMDA, non-NMDA, D<sub>2</sub> and cholinergic.

**Materials and Methods**

**Animals, drug treatment and doses.** Male albino rats of a Wistar-derived strain (275–320 g) (Harlan, Zeist, The Netherlands) were used for the experiments. The rats were housed at most eight to a cage (40 × 25 × 55 cm) with light from 7 a.m. until 7 p.m. and food and water ad libitum.

The following drugs and chemicals were kindly provided by or obtained from the sources indicated: atropine, AP-5, (±)-baclofen, (−)-bicuculline methochloride, carbachol, CPP, (+)-HA966, kainate, CNQX, mecamylamine, HCl; NMDA, (+)-MK-801, muscimol (Research Biochemicals International, Natick, MA), TTX (Sigma, St. Louis, MO) and (−)-sulpiride (Ravizzi, Milano, Italy) and CGP 52432 (Ciba Geigy, Basel, Switzerland). All drugs were dissolved in the perfusion fluid and infused via retrograde microdialysis into the VTA.

Infused doses were based on earlier studies on related experiments (Santiago and Westerink, 1991, 1992; Westerink et al., 1992, 1996).

The experiments were approved by the Animal Care Committee of the Faculty of Mathematics and Natural Science of the University of Groningen.

**Surgery and brain dialysis.** Microdialysis was performed with two I-shaped cannulas. Polyacrylonitrile/sodium methalyl sulfonate copolymer (I.D. 0.22 mm, O.D. 0.31 mm; AN 69, Hospal, Bologna, Italy) was used as the dialysis membrane. One probe (exposed length 4 mm) was implanted into the ipsilateral PFC. Drugs were infused into the brain via the microdialysis probe into the VTA in concentrations of 50 μmol/l. The infusions caused a decrease in extracellular dopamine in the ipsilateral PFC to about 20% of controls (fig. 2). This effect can be used as a functional test of proper implantation of the probe. The TTX effect demonstrates that the two probes are properly implanted with respect to the mesocortical dopaminergic pathway. Occasionally some turning behavior was noticed during TTX infusion.

**Effect of infusion of muscimol and bicuculline into the VTA on the dialysate content of dopamine in the ipsilateral PFC.** The GABA<sub>A</sub> agonist muscimol was infused via the microdialysis probe into the VTA in concentrations of 20 μmol/l. The infusions caused a decrease in extracellular dopamine in the PFC to about 60% of controls (fig. 2). This decrease was statistically significant (χ<sup>2</sup><sub>.05</sub>, P < .0001; n = 5). The decrease in extracellular dopamine reached statistical significance 30 min after the start of the infusion.

**Effect of infusion of baclofen and CGP 52432 into the VTA on the dialysate content of dopamine in the ipsilateral PFC.** The GABA<sub>B</sub> agonist baclofen was infused into the brain via the microdialysis probe into the VTA in concentrations of 50 μmol/l. The infusions caused a decrease in extracellular dopamine in the PFC to about 50% of controls (fig. 3). This increase was statistically significant (χ<sup>2</sup><sub>.05</sub>, P < .0001; n = 5). The rise in extracellular dopamine reached statistical significance 30 min after the start of the infusion. Bicuculline infusion occasionally caused some behavioral activation.

**Effect of infusion of baclofen and CGP 52432 into the VTA on the dialysate content of dopamine in the ipsilateral PFC.** The GABA<sub>B</sub> agonist d,l-baclofen was infused...
into the VTA in a concentration of 50 μmol/l. The GABA<sub>B</sub> agonist caused a decrease of extracellular dopamine in the ipsilateral PFC to about 60% of controls (fig. 4). This decrease was statistically significant ($\chi^2 = 107.9; P < .0001; n = 20$) and was used as functional test for proper implantation of the probes. The decrease was statistically significant 30 min after the start of the infusion.

Intrategmental infusion of the GABA<sub>B</sub> antagonist CGP 52432, infused in a dose (100 μmol/l; n = 4) that maximally blocks GABA<sub>B</sub> receptors (Westerink et al., 1996), did not modify extracellular dopamine in the PFC (results not shown).

**Effect of infusion of NMDA, CPP, AP-5, MK-801 and (+)-HA-966 into the VTA on the dialysate content of dopamine in the ipsilateral PFC.** NMDA was infused into the VTA in a concentration of 1 mmol/l. Because NMDA caused strong behavioral activation, the infusion period was restricted to 15 min. The extracellular dopamine in the ipsilateral PFC increased to about 210% of controls (fig. 5). This increase was statistically significant ($\chi^2 = 50.9; P < .0001; n = 8$). The rise in dopamine reached statistical significance 15 min after the start of the infusion.

The intrategmental infusion of 1 mmol/l NMDA induced hyperlocomotion, turning behavior, rearing and grooming that lasted for about 20 min, after which the animals returned to their usual resting state. Infusion of 300 μmol/l of NMDA induced mild behavioral activation. Infusion of NMDA (300 μmol/l) was combined with various NMDA antagonists. The results of these experiments are shown in figures 6–9.

During infusion of the competitive NMDA antagonist CPP in a concentration of 300 μmol/l, extracellular dopamine in the ipsilateral PFC decreased to about 75% of controls (fig. 6). This decrease was statistically significant ($\chi^2_{13} = 32.6; P = .002; n = 4$). During infusion of CPP, the effects of NMDA on extracellular dopamine in the PFC, as well as its effects on behavior, were fully blocked.

During infusion of the competitive NMDA antagonist AP-5
in a concentration of 500 μmol/l, extracellular dopamine in the ipsilateral PFC decreased to about 75% of controls (fig. 7). This decrease was statistically significant ($\chi^2_{13} = 36.5; P = .0005; n = 4$). During infusion of AP-5, the effects of NMDA on extracellular dopamine in the PFC, as well as its effects on behavior, were fully blocked.

During infusion of 1 mmol/l (+)-MK-801, extracellular dopamine in the ipsilateral decreased to about 85% of controls (fig. 8). This decrease did not reach statistical significance ($\chi^2_6 = 21.9; P = .057; n = 4$). The NMDA-induced increase seen after $t = 90$ min was statistically significant ($\chi^2_7 = 25.5; P = .001; n = 4$). Co-infusion of 1 mmol/l (+)-MK-801 and NMDA (300 μmol/l) partly blocked the increase in extracellular dopamine in the PFC. During infusion of (+)-MK-801, the effects of NMDA on behavior were not blocked.

During infusion of 1 mmol/l (+)-HA-966, extracellular dopamine in the ipsilateral decreased to about 79% of controls (fig. 9). This decrease was statistically significant ($\chi^2_6 = 13.6; P = .035; n = 4$). Infusion of NMDA (300 μmol/l) in the presence of 1 mmol/l (+)-HA-966 increased extracellular dopamine in the PFC to 157% of controls. However, when this effect was corrected for the decrease in basal values (to 79% of controls), the suppression by (+)-HA-966 of the stimulation by NMDA did not reach statistical significance. (+)-HA-966 also did not modify the behavioral effects of NMDA infusion. We conclude that although intrategmentally infused (+)-HA-966 decreased basal values of extracellular dopamine in the PFC, the compound was unable to block the NMDA-induced stimulation of dopamine.

**Effect of intrategmental infusion of NMDA during halothane anesthesia on extracellular dopamine in the ipsilateral PFC.** Because NMDA infusion caused strong behavioral activation, we investigated whether indirect stress effects were implicated in the stimulation of dopamine release in the PFC. When NMDA (1 mmol) was infused into the VTA during halothane anesthesia, extracel-
lular dopamine in the PFC increased to about 210% of controls (fig. 10). This effect was statistically significant ($\chi^2 = 24.8; P = .0017; n = 4$) and comparable to the effects seen in nonanesthetised animals. Halothane itself did not affect extracellular dopamine (results not shown).

**Effect of infusion of kainate and CNQX into the VTA on extracellular levels of dopamine in the ipsilateral PFC.** Kainate was infused into the VTA in a concentration of 30 $\mu$mol/l. Because kainate caused behavioral activation, the infusion period was restricted to 15 min. The extracellular dopamine in the ipsilateral PFC increased to about 195% of controls (fig. 11). This increase was statistically significant ($\chi^2 = 64.3; P < .0001; n = 10$). The rise in dopamine reached statistical significance 15 min after the start of the infusion.

Intrategmental infusion of 30 $\mu$mol/l kainate induced hyperlocomotion, rearing and grooming that lasted for about 20 min, after which the animals returned to their usual resting state. Intrategmental kainate was co-infused with the non-NMDA antagonist CNQX. The result of this experiment is shown in figure 12. During infusion of CNQX in a concentration of 500 $\mu$mol/l, extracellular dopamine in the ipsilateral PFC decreased to about 79% of controls. This decrease was statistically significant ($\chi^2 = 19.3; P = .037; n = 4$). When kainate was co-infused with CNQX, the rise in extracellular dopamine in the PFC was suppressed. The suppression was statistically evaluated after the dopamine values at 90 min were reset as 100%. The suppression by kainate reached statistical significance at $t = 120$ min. We conclude that the effects of kainate on extracellular dopamine in the PFC are partly blocked by CNQX.

The behavioral effect of kainate was fully blocked by co-infusion with CNQX.

**Effect of intrategmental infusion of kainate during halothane anesthesia on extracellular dopamine in**
the ipsilateral PFC. Because intrategmental infusion of kainate caused a behavioral activation, we investigated whether indirect stress effects were implicated in the stimulation of dopamine release in the PFC. When kainate (30 μmol) was infused into the VTA during halothane anesthesia, extracellular dopamine in the PFC increased to about 200% of controls (fig. 13). This increase was statistically significant ($\chi^2 = 26.3; P < .001; n = 4$) and comparable to the effect of kainate infusion seen in control rats. Halothane itself did not modify extracellular dopamine in the PFC (data not shown).

Effect of infusion of carbachol, atropine and mecamylamine into the VTA on the dialysate content of dopamine in the ipsilateral PFC. The cholinomimetic compound carbachol was continuously infused into the VTA in a concentration of 50 μmol/l. Carbachol caused an increase of extracellular dopamine in the ipsilateral PFC to about 150% of controls (fig. 14) ($\chi^2 = 23.6; P = .003; n = 4$). The increase in dopamine reached statistical significance 45 min after start of the infusion of carbachol. The muscarinic antagonist atropine and the nicotinic antagonist mecamylamine, both infused in a relatively high concentration of 100 μmol/l, were without effect on the ipsilateral concentration of dopamine in the PFC (data not shown).

Effect of infusion of (−)-sulpiride into the VTA on the dialysate content of dopamine in the ipsilateral PFC. The specific D₂ antagonist (−)-sulpiride, infused into the VTA in a concentration of 50 μmol/l, induced an increase in extracellular dopamine in the ipsilateral PFC to about 150% of controls. This increase was statistically significant ($\chi^2 = 32.1; P < .0001; n = 5$). The increase in extracellular dopamine reached statistical significance 30 min after the start of the sulpiride infusion (fig. 15).

Comparison of mesocortical, mesolimbic and nigrostriatal neurons. For comparison of the present data with those generated in other studies, we have indicated the results from mesolimbic and nigrostriatal experiments in the various figures. Data were taken from earlier dual-probe
Similar to results with mesolimbic neurons (fig. 2), muscimol (20 μmol/l) infusions into the VTA decreased extracellular dopamine in the PFC to about 60% of controls. In contrast, muscimol (10 μmol/l) clearly increased extracellular dopamine in the striatum. Infusion of bicuculline into the VTA or substantia nigra induced comparable increases in the PFC, nucleus accumbens and striatum (fig. 3).

Intrategmental or intranigral infusion of baclofen (50 μmol/l) induced a clear decrease in all three types of dopamine neurons (fig. 4). However, the decrease that we observed in the PFC was somewhat less pronounced than the changes seen in the nucleus accumbens and striatum. This difference reached the level of statistical significance (indicated in fig. 4).

The increase in extracellular dopamine seen after infusion of 1 mmol/l NMDA was in the same range as reported earlier for the mesolimbic dopamine neurons but was more pronounced than that reported for nigrostriatal neurons. The latter effect was statistically significant (indicated in fig. 5). Note that the NMDA infusion lasted 15 min in the VTA but 60 min in the substantia nigra.

The increase in extracellular dopamine seen after infusion of 30 μmol/l kainate was in the same range as reported earlier for mesolimbic dopamine neurons but was more pronounced than that reported for nigrostriatal neurons. The latter effect was statistically significant (indicated in fig. 11).
Note that the kainate infusion lasted 15 min in the VTA but 60 min in the substantia nigra.

Infusion of carbachol into the VTA induced an increase in the PFC that was more pronounced than the increases seen in the mesolimbic and nigrostriatal dopamine neurons. The differences between the mesocortical and nigrostriatal dopamine systems reached the level of statistical significance (indicated in fig. 14).

Infusion of (-)-sulpiride into the substantia nigra or VTA induced a rise in extracellular dopamine in the PFC that was somewhat more pronounced than the increases seen in the mesolimbic and nigrostriatal dopamine neurons. This difference reached statistical significant difference 75 min after the start of the infusion (indicated in fig. 15).

Discussion

GABA, glutamate and ACh receptors in the VTA.

Infusion of the GABA_A agonist muscimol and the GABA_B agonist baclofen into the VTA clearly decreased extracellular dopamine in the ipsilateral PFC. These findings indicate the presence of GABA_A as well as GABA_B receptors on somatodendritic sites of mesocortical dopamine neurons. The localization of both types of GABA receptors on dopamine cell bodies in the VTA is supported by anatomical data (Bayer and Pickel, 1991) and by electrophysiologic studies based on brain slices (Johnson and North, 1992; Jiang et al., 1993; Seutin et al., 1994).

When the present results are compared with previously published data from dual-probe experiments on nigrostriatal and mesolimbic neurons (Santiago and Westerink, 1991; 1992; Westerink et al., 1992; 1996), a significant difference emerges with respect to the participation of GABA_A receptors. Although the stimulatory effect of bicuculline was very similar for the three dopamine systems studied, muscimol stimulated the A9 neurons but inhibited the A10 neurons. Although there are some differences in methodology in terms of probe length and perfusion time when VTA and substantia nigra
nigra probes are compared, it is unlikely that they could contribute to the observed qualitative differences between the A9 and A10 neurons. Stimulation of nigrostriatal neurons after intranigral administration of GABA receptor agonists has been described by various authors, and some speculate that a second inhibitory interneuron located in the A9 participates in the GABAergic striatonigral pathway (Leviel et al., 1979; Grace and Bunney, 1979). Apparently it is not necessary to postulate such an interneuron in the GABAergic regulation of both types of A10 dopamine neurons. The finding that muscimol interacts in opposite ways with the two dopamine systems is of theoretical interest, because it opens the possibility of discriminating pharmacologically between mesolimbic-mesocortical and striatal dopamine neurons. Mesocortical neurons seem to be somewhat less sensitive to GABA<sub>x</sub> stimulation than are mesolimbic and nigrostriatal neurons.

Infusion of the glutamate receptor agonists NMDA and kainate into the VTA induced a pronounced increase in extracellular dopamine in the PFC. The stimulation by NMDA was fully suppressed during co-infusion of the competitive antagonist CPP or AP-5. However, the noncompetitive antagonist MK-801 was less effective, and (+)-HA-966, a potent inhibitor of the glycine site of the NMDA receptor, even infused in high concentrations (1 mmol/l) did not inhibit the effect of NMDA stimulation. The finding that MK-801 did not affect the NMDA-induced behavior could be explained if the compound by itself induced behavioral activation. The enhancement of extracellular dopamine in the PFC after kainate infusion in the VTA was partly blocked by CNQX. This could be explained by the limited potency of CNQX as a non-NMDA receptor antagonist. Interestingly all glutamate receptor antagonists, including CNQX, decreased basal values of extracellular dopamine in the PFC. A similar tendency, but much less pronounced, was observed during dual-probe experiments on mesolimbic dopamine neurons.

**Fig. 13.** Effect of infusion of kainate (30 µM, 15 min, black bar) on extracellular dopamine in the ipsilateral PFC (expressed as percent of basal values ± S.E.M.) in the presence (○) or absence (●) of halothane anesthesia. * and # P < .05 vs. t = 30 min.

**Fig. 14.** Effect of infusion of carbachol (50 µM, black bar) into the VTA on the extracellular concentration of dopamine (expressed as percent of basal values ± S.E.M.) in the ipsilateral PFC (●). Data on a similar experiment carried out in the mesolimbic pathway (Westerink et al., 1996) and the nigrostriatal pathway (Santiago and Westerink, 1992) are included. * P < .05 vs. t = 30 min; # P < .05 vs. mesocortical neurons.
(Karreman et al., 1996; Westerink et al., 1996). The finding that MK-801 and HA-966, at the high doses used, either did not block or hardly blocked the effect of NMDA infusion was unexpected. The fact that the two antagonists clearly modified the basal values in the PFC argues against a poor penetration efficiency of the drugs from the dialysis probe. Apparently it is easier to antagonize the basal activity of the tonic glutamatergic excitation than to block the pharmacologically enhanced activity (with the competitive antagonists an exception).

During intrategmental infusion of NMDA and kainate, we noted behavioral activation such as grooming and turning. Numerous studies have shown that stress stimulates dopamine release in the PFC. The reported stress-induced increase in extracellular dopamine in the PFC is in the same range as seen after intrategmental NMDA or kainate infusion (Abercrombie et al., 1989). We therefore investigated whether induction of stress during infusion of the glutamate agonists might have indirectly induced an increase in extracellular dopamine in the PFC. We did this by repeating the NMDA and kainate infusions in anesthetised animals. Because the anesthetised animals showed similar responses to the conscious rats, we concluded that stress effects probably did not contribute to the observed effects.

Taken together, the present data clearly indicate that NMDA as well as non-NMDA receptors are present on somatodendritic sites of mesocortical dopamine neurons. This conclusion is consistent with electrophysiologic studies that have provided evidence for the presence of NMDA and non-NMDA on dopamine cell bodies in the VTA (Seutin et al., 1990; Johnson and North, 1992; Johnson et al., 1992; Wang and French 1993; Zhang et al., 1994). It should be noted that the latter studies could not discriminate between mesolimbic and mesocortical A10 neurons.

On the basis of local injection and post-mortem tissue analysis, it has been speculated that the NMDA receptor subtype modulates mesocortical dopamine neurons, whereas the non-NMDA subtype regulates mesolimbic neurons (Kalivas et al., 1989). The latter conclusion is not supported by the present data, because NMDA infusions and kainate infusions induced comparable increases in extracellular dopamine in the PFC; moreover, NMDA antagonists and the non-NMDA antagonist decreased extracellular dopamine in the PFC to a similar degree (80%–75% of controls). However, the present data clearly indicate that A10 dopamine neurons are more responsive than A9 neurons to NMDA as well as non-NMDA receptor stimulation.

The marked increase in extracellular dopamine in the PFC during infusion of carbachol into the VTA illustrates the ability of cholinergic afferents to stimulate mesocortical dopamine cells at the level of the VTA. This result is consistent with a recent electrophysiologic study showing that dopamine neurons in the VTA were excited by carbachol (Seutin et al., 1990). Electrophysiologic studies on brain slices indicated the presence of muscarinic as well as nicotinic receptors on dopamine cell bodies in the VTA (Calabresi et al., 1989; Lacey et al., 1990). Because carbachol is a nonspecific agonist, additional experiments are needed to interpret this effect in terms of muscarinic or nicotinic receptors.

Although the various experiments clearly indicated the presence of GABAergic, glutamatergic, cholinergic and dopamine receptors on mesocortical neurons in the VTA, we cannot, by the present methodology, rule out the possibility that certain indirect effects participated in the observed changes in extracellular dopamine in the PFC.

**Tonic regulation of the activity of mesocortical dopamine neurons.** Regarding the tonic regulation of mesocortical dopamine neurons, the results of the infusion of a series of receptor-specific antagonists are meaningful. Indeed, both NMDA antagonists and non-NMDA antagonists decreased the extracellular dopamine in the ipsilateral PFC to about 80% to 75% of controls. These results indicate that glutamatergic projections to the VTA play a significant role in the tonic excitation of mesocortical dopamine neurons. It has been suggested that glutamatergic pathways projecting to the midbrain dopamine neurons induce burst firing in A10 neurons. However, results of studies on the administration of competitive glutamate antagonists are controversial. Some authors report an inhibition of the burst firing of A10 neurons by glutamate antagonists (Charlety et al., 1991; Overton

![Fig. 15. Effect of infusion of (−)-sulpiride (50 μM, black bar) into the VTA on the extracellular concentration of dopamine (expressed as percent of basal values ± S.E.M.) in the ipsilateral PFC (●). Data on a similar experiment carried out in the mesolimbic pathway (Westerink et al., 1996) and the nigrostriatal pathway (Santiago and Westerkink, 1991) are included. * P < .05 vs. t = 30 min; # and + P < .05 vs. mesocortical neurons.](image)
and Clark, 1992; Chergui et al., 1993), but French et al. (1993) found no effect of the systemic administration of competitive glutamate antagonists on the firing rate or firing pattern of the A10 neurons. The present data indicate that mesocortical neurons display a greater sensitivity than mesolimbic neurons to glutamate antagonists (Karreman et al., 1996; Westerink et al., 1986); this finding could account, in part, for the discrepant reports on this matter.

The stimulatory effect of the GABA_A antagonist bicuculline demonstrates that mesocortical dopamine neurons are tonically inhibited by GABA_A receptors in conscious rats. The ineffectiveness of the GABAB antagonist CGP 52432 demonstrates that GABA_B receptors are not activated under normal conditions. The finding that the intrategmentally infused GABA agonists muscimol and baclofen decreased extracellular dopamine in the ipsilateral PFC suggests that the capacity of GABAergic neurons to inhibit mesocortical dopamine neurons is much larger than is expressed under control conditions. A recent electrophysiologic study provided evidence that GABAergic projection neurons mediate burst firing of midbrain dopamine neurons through disinhibition by GABA_A and GABA_B receptors (Tepper et al., 1995). The present data suggest that any such mechanism is restricted to GABA_B receptors.

Intrategmental infusion of high concentrations of the muscarinic agonist atropine and that of the nicotinic antagonist mecamylamine were without effect on extracellular dopamine in the PFC. These findings support the notion that the mesolimbic dopamine system is phasically rather than tonically regulated by cholinergic receptor activation within the VTA. Infusions of carbachol revealed that the three types of dopamine neurons all receive a cholinergic input. Mesocortical dopamine neurons displayed a higher sensitivity for ACh receptor stimulation than did mesolimbic and nigrostriatal neurons.

Finally, we infused (−)-sulpiride in a dose that is effective in maximally blocking D_2 receptors (Santiago and Westerink, 1991). From the observed increase in extracellular dopamine in the ipsilateral PFC, we conclude that D_2 autoreceptors at somatodendritic sites of mesocortical neurons participate in tonic autoinhibition under control conditions. Infusions of sulpiride revealed that the three types of dopamine neurons all contain D_2 autoreceptors. Mesocortical dopamine neurons displayed a higher sensitivity for D_2 receptor stimulation than did mesolimbic and nigrostriatal neurons.

In conclusion. The results of the present study support the following conclusions:

1. The dual-probe microdialysis approach is a sensitive and unique method of studying the pharmacology of mesocortical dopamine neurons.
2. GABA_A, GABA_B, NMDA, non-NMDA, cholinergic receptors and D_2 autoreceptors are functionally present at somatodendritic sites of mesocortical dopamine neurons.
3. Mesocortical dopamine neurons are tonically excited by glutamatergic neurons via NMDA receptors as well as non-NMDA receptors.
4. Mesocortical dopamine neurons are tonically inhibited by GABAergic neurons acting via GABA_A receptors and D_2 autoreceptors.
5. No tonic stimulation by cholinergic neurons or inhibition by GABAergic neurons acting via GABA_B receptors could be demonstrated on the mesocortical neurons.
6. Mesocortical neurons are less sensitive to GABA_B stimulation than are mesolimbic or nigrostriatal dopamine neurons.
7. Compared with nigrostriatal and mesolimbic dopamine neurons, mesocortical dopamine neurons are more responsive to stimulation of cholinergic receptors and inhibition of D_2 autoreceptors.

References


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