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Role of Dopamine and GABA in the Control of Motor Activity Elicited From the Rat Nucleus Accumbens

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WONG, L. S., G. ESHEL, J. DREHER, J. ONG AND D. M. JACKSON. *Role of dopamine and GABA in the control of motor activity elicited from the rat nucleus accumbens.* PHARMACOL BIOCHEM BEHAV **38**(4) 829–835, 1991.—The application of 1.2 and 12.0 μg/side of the $GABA_A$ receptor agonist 3-aminopropane sulphonic acid bilaterally into the nucleus accumbens (Acb) of rats nonsignificantly depressed locomotor activity as assessed in automated Animex® activity cages, while the highest dose (60 μg/side) significantly stimulated activity. The $GABA_A$ receptor antagonists picrotoxinin (0.0625 and 0.125 μg/side) and bicuculline (0.895 μg/side) produced forward locomotion around the cage accompanied by a number of other behaviours. The $GABA_B$ agonist baclofen (0.023 and 0.092 μg/side) induced a short-lasting (18 min) locomotor depression. None of the $GABA_B$ antagonists tested (2-hydroxysaclofen 2.6 μg/side, two novel beta-(benzo[b]furan) analogues of baclofen 9G or 9H each 6.8 μg/side, 4-aminobutylphosphonic acid 1.32 μg/side and phaclofen 0.535 and 2 μg/side) significantly affected locomotor activity. In rats pretreated with reserpine and α-methyl-p-tyrosine, picrotoxinin (0.0625 and 0.125 μg/side) did not significantly alter locomotor activity. Furthermore, when picrotoxinin (0.0625 μg/side) was combined with either the selective dopamine (DA) D1 agonist SKF38393 or the selective D2 agonist quinpirole, no significant alteration in locomotor function occurred. When SKF38393 and quinpirole were coadministered, significant stimulation occurred which was further enhanced by the addition of picrotoxinin. It is concluded that $GABA_A$ receptors, together with D1 and D2 receptors, play a major role in modulating the control of motor function by the Acb of rats.

Dopamine receptors GABA receptors Locomotor activity Nucleus accumbens Receptor interactions

THE nucleus accumbens (Acb) plays a role in mediating locomotion in rodents, perhaps as an interface between the limbic and motor systems (24,28). Many neurotransmitters (and their receptors) are found within the Acb, including high concentrations of dopamine (DA) (12) and γ-aminobutyric acid [GABA, (5)]. Manipulation of either of these neurotransmitter systems alters motor function.

Thus the direct injection into the Acb of d-amphetamine (which releases DA), the mixed D1/D2 agonist apomorphine, DA itself and a variety of other DA agonists such as ergometrine and ADTN (2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene) produces an increase in locomotion, which is characterised by coordinated forward locomotion, rearing and sniffing (2, 11, 12, 30). This activation requires the stimulation of both D1 and D2 receptor subtypes since neither D1 (such as SKF38393) nor D2 (such as quinpirole) agonists are active after local injection in catecholamine-depleted rats, whereas the application of both together produce marked excitation [(10,14); also see (41)]. In many instances, sufficient D1 or D2 stimulation can be obtained with endogenous DA (in rats not depleted of DA) when the complementary receptor subtype is stimulated with an exogenous agonist (33).

Local application into the Acb of low doses of GABA tends to increase, while high doses tend to decrease, activity (17,38) and the action of GABA is potentiated by pretreatment of the animals with a GABA transaminase inhibitor (38). Muscimol, a selective $GABA_A$ agonist, induced a marked hypoactivity (1). In contrast, local application of the noncompetitive $GABA_A$ antagonist picrotoxin into the Acb induced a marked, dose-dependent and long-lasting stimulation characterized by continuous, well coordinated and forward directed movements (17, 27, 38).

It is clear from such studies that there is a close relationship in the Acb between DA and GABA, with hyperactivity induced by the application of DA or apomorphine into the Acb being suppressed by intra-accumbal injections of GABA, the selective $GABA_B$ agonist baclofen, the selective $GABA_A$ agonist 3-aminopropane sulphonic acid [3-APS, (22,31)] and by muscimol (34,35). There is quite an extensive literature about the detailed anatomical basis for the DA-GABA interaction in modulating locomotor activity within the limbic areas and this is summarized in a variety of papers [for some pertinent references, discussions and fur-

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ther references, see (9, 16, 18, 25, 28, 36, 43, 44)].

In the current study, we have taken advantage of the availability of a number of selective agonists and antagonists and present data on the effects of manipulating $GABA_A$ and $GABA_B$ receptors within the Acb. We have utilised readily available compounds such as bicuculline (a competitive $GABA_A$ antagonist), picrotoxinin (PTXNN, the active constituent of picrotoxin), 3-APS and baclofen, together with a number of newly available $GABA_B$ antagonists including phaclofen (21), 2-hydroxysaclofen (19), and two novel beta-(benzo[b]furan) analogues of baclofen [4-amino-3-benzo[b]furan-2-ylbutanoic acid (9G) and 4-amino-3-(5-methoxybenzo[b]furan-2-yl] butanoic acid (9H) (6,20). Furthermore, because it is clear that the stimulation of both D1 and D2 DA receptors is required for the optimal expression of various motor activities, we examined the interaction between the $GABA_A$ receptor antagonist PTXNN and the DA agonists, quinpirole and SKF38393, in rats depleted of their DA (and noradrenaline and serotonin) stores.

METHOD

Animals

Male Sprague-Dawley strain rats (University of Sydney Animal House) weighing 250–350 g at the time of surgery were used. They were kept at a constant temperature (21 ± 2°C), artificially illuminated on a 12-h light/dark cycle (0700–1900 light) and allowed food and water ad lib except during experimentation.

Stereotaxic Implantation of Guide Cannulae and Drug Administration Into the Acb

Rats were anaesthetized with pentobarbitone sodium (Nembutal®, Abbott Laboratories) or a mixture of ketamine (Ketalar®, Troy Laboratories, Australia) and xylazine (Rompun®, Bayer, Australia) and, to reduce mucosal secretions, coadministered atropine sulphate (1 mg/ml, about 1 mg/kg). Using a stereotaxic apparatus, holes were drilled in the skull 2.2 mm anterior and 1.6 mm lateral from the bregmoid reference point (29). Stainless steel guide cannulae (length 10.0 mm, external diameter 0.9 mm, internal diameter 0.6 mm) were placed vertically into these holes with their tips resting on the dura mater. Small brass screws were inserted into two additional holes in the skull. Dental acrylic (Formatray®, Kerr, USA) cement was poured around the screws and cannulae and left to harden. A broad-spectrum antibiotic spray (Neotracin®) was applied topically to the wound and animals allowed to recover between 72 h and 144 h before use in behavioural studies. For drug injection, a cannula (external diameter 0.45 mm, length 16.4 mm) was inserted into the guide cannula and was linked to a 10 μl syringe filled with the appropriate drug solution. One μl of the drug solution was injected over a period of 60 s and the injection cannula was left in place for a further 30 s. After another 30-s delay the injection cannula was inserted into the contralateral guide cannula and the above procedure was repeated. All injections into the Acb were bilateral and the injection volume was always 1 μl/side. Thus a dose of 5 μg means that 5 μg was injected to each side, i.e., a total of 10 μg. Control animals received the same volume (1 μl) of vehicle. Each rat was used only once.

Measurement of Locomotor Activity

Immediately after the injection procedure, the rats were placed individually into clear acrylic boxes (length 45 cm × width 33 cm × height 18 cm) and each box was placed on a separate external sensor interfaced with an Animex® Activity meter, type DS (A.B. Farad, Hagersten, Sweden) as described previously (37). The sensitivity of the meter was adjusted to 30 μA so that only gross movements such as locomotion or rearing were recorded. There were 3 external sensor units, and the activity of each cage was sampled separately and in sequence for 58 s of each 3 min. Furthermore, each animal was visually (but not quantitatively) assessed to gauge the extent to which other behaviours such as rearing, jumping or grooming were contributing to the overall activity counts. To minimize the effect of changes in the surrounding environment, each acrylic box was enclosed in a wooden housing (length 49 cm × width 41 cm × height 28 cm) which was ventilated with a fan to provide background noise and to help maintain a constant temperature (21 ± 2°C) inside the housing.

Histological Confirmation of Injection Site

Between 6 and 18 h after completion of locomotor activity recording, each rat was sacrificed and its brain removed and fixed in a solution of 10% formalin in normal saline for 2–4 days. The tracks left in the brain by the injection cannula were exposed by manual dissection (in coronal plane) under an operating microscope and the appropriate section stained with 2% toluidine blue. Optimal staining contrast was achieved by alternate rinsing of the section with 95% ethanol and distilled water as necessary and the injection tracks located. Only the recordings made from rats with confirmed intra-accumbal injection sites were included in subsequent analysis.

Statistical Analysis

All experiments were of factorial design (42) and data were analyzed using ANOVA, with post hoc Newman-Keuls tests being used for systematic comparison of the means.

Drugs

RS-SKF38393 hydrochloride (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine HCl, Research Biochemicals Incorporated, USA) was dissolved in 0.01% ascorbic acid. Quinpirole hydrochloride [trans-(−)-4aR-4a,5,6,7,8,8a,9-octahydro-5-propyl-1H (or 2H)-pyrazolo [3,4-g] quinoline, LY171555, Eli Lilly, USA and Research Biochemicals Inc., USA] and α-methyl-dl-para-tyrosine methyl ester hydrochloride (αMPT, Sigma, USA), were dissolved in water. 3-APS (Sigma), baclofen (Ciba-Geigy, Australia), 2-hydroxysaclofen (kindly synthesized by Dr. Prager, Adelaide), bicuculline methoiodide (kindly synthesized in the Department of Pharmacology by Ms. Christine Apostopoulos), phaclofen (kindly synthesized in the Department of Pharmacology by Dr. Ken Mewitt), 9G and 9H [synthesized by Dr. Berthelot and colleagues (6,20)], 4 amino butyl phosphonic acid (4-ABPA) and PTXNN (Sigma, USA) were dissolved in 0.09% saline solution. Reserpine base (Sigma, USA) was dissolved in a few drops of 25% acetic acid and diluted with water.

RESULTS

Injection of $GABA_A$ Agonists and Antagonists

Low doses of 3-APS (0.12 to 12.0 μg/side) produced locomotor depression immediately after injection and this lasted for about 24 min (see Fig. 1). The highest dose (60.0 μg/side) produced an initial depression followed by a moderate stimulation. The stimulation was characterized by a general increase in activity. The accumulated 60-min totals are also shown in the figure and analysis indicated that only the stimulation produced by

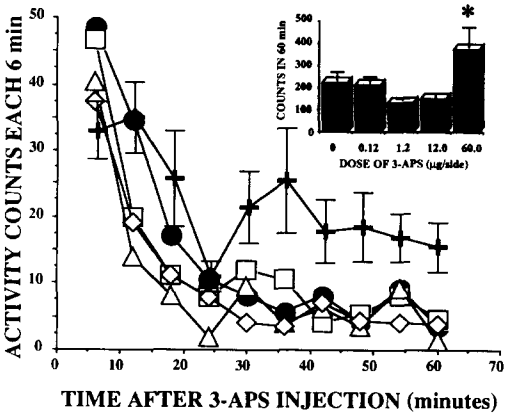

FIG. 1. Rats were challenged with 3-APS. The data represent the mean (±SEM) activity counts (of 8 to 12 replicates) each 6 min. The inset contains the data accumulated over 60 min and post hoc Newman-Keuls tests indicated that the highest dose of 3-APS significantly increased activity (indicated with an asterisk). The code is ●: vehicle, □: 0.12 μg/side, △: 1.2 μg/side, ◇: 12 μg/side, +: 60 μg/side.

60.0 μg/side (and not the depression produced by the lower doses) was significant.

In contrast, the $GABA_A$ antagonists PTXNN (Fig. 2) and bicuculline (Fig. 3) caused only motor excitation.

The stimulation produced by PTXNN (0.0625 and 0.125 μg/side) was of immediate onset and dose dependent; with the highest dose the activity peaked 12 to 24 min after injection and had returned to baseline by 54 min. The rats ran from one side of the cage to the other, and frequently and rapidly changed their direction of movement. Their gait was coordinated but they salivated heavily and some mouth chewing movements were observed.

The highest dose of bicuculline (0.895 μg/side, but not lower doses, 0.179 and 0.270 μg/side) produced an increased activity which was evident immediately after injection and greatest at onset, declining gradually to control values by 48 min. The animals

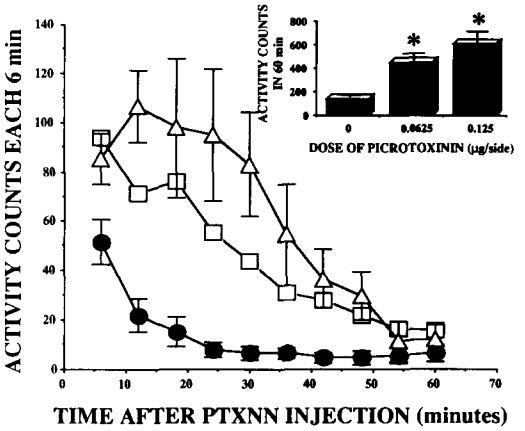

FIG. 2. Rats were challenged with various doses of PTXNN (●: vehicle, □: 0.0625 μg/side, △: 0.125 μg/side). The data represent the mean (±SEM) activity counts each 6 min and the inset shows the data accumulated over 60 min of 5 to 6 replicates. PTXNN exerted a significant effect, $F(2,14)=6.866$, $p=0.008$, and post hoc Newman-Keuls tests indicated that both doses of PTXNN significantly increased activity (marked with an asterisk).

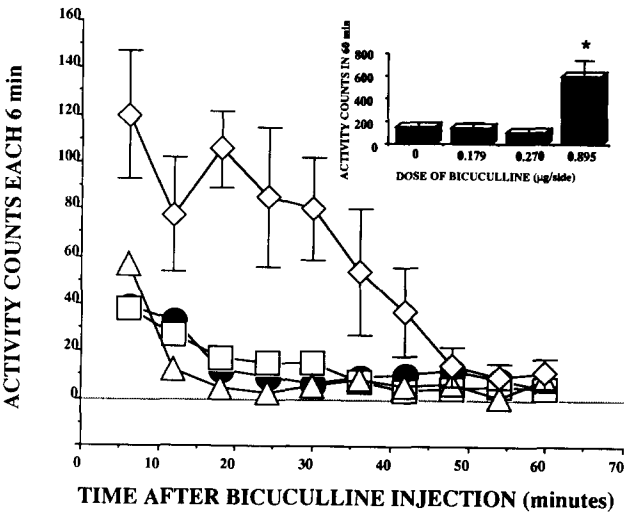

FIG. 3. Rats were challenged with various doses of bicuculline (●: vehicle, □: 0.179 μg/side, △: 0.270 μg/side, ◇: 0.895 μg/side). The data represent the mean (±SEM) activity counts each 6 min and the inset shows the data accumulated over 60 min of 3 to 8 replicates. Bicuculline exerted a significant effect, $F(3,17)=12.277$, $p=0.0002$, and post hoc Newman-Keuls tests indicated that the highest dose of bicuculine significantly increased activity (marked with an asterisk).

ran, apparently uncontrollably, around the cage. They ran on the tips of their paws, sniffing constantly, vocalizing and rearing or clawing up the walls of the cage. In some cases, they leapt off the floor of the cage and exhibited explosive jumping behaviour. All animals administered the highest dose appeared to be on the verge of convulsing.

Injection of $GABA_B$ agonists and antagonists

Both doses (0.023 and 0.092 μg/side) of the $GABA_B$ agonist baclofen produced an immediate and significant motor depression

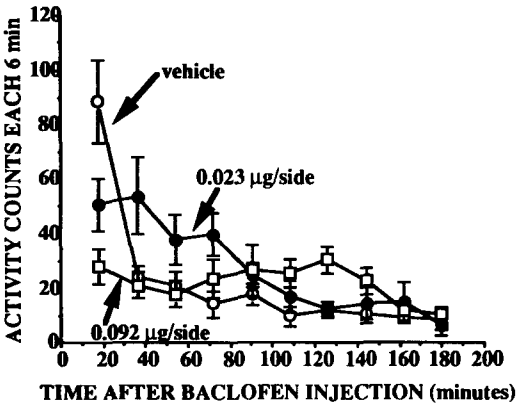

FIG. 4. Rats were challenged with various doses of baclofen. The data represent the mean activity counts each 18 min of 7 to 9 replicates. The SEM are shown by the vertical bars. ANOVAR indicated that baclofen exerted a significant effect on activity, $F(18,198)=5.884$, $p=0.001$, and subsequent analysis indicated that the difference was mainly due to a significant depression at 18 min in animals challenged with either dose of baclofen, compared to animals challenged with the vehicle.

TABLE 1

THE EFFECT OF VARIOUS $GABA_B$ ANTAGONISTS ON LOCOMOTOR ACTIVITY IN RATS[a]

Antagonist	Dose (μg/side)	Activity	n
Vehicle	1 μl	262 ± 53	10
2-Hydroxysaclofen	2.6 μg*	293 ± 37	6
9G	6.8 μg†	333 ± 103	4
9H	6.8 μg†	196 ± 18	4
4-ABPA	1.32 μg*	270 ± 155	4
Vehicle	1 μl	124 ± 13	4
Phaclofen	0.535 μg	108 ± 23	4
	2.0 μg*	117 ± 8	4

[a]The drugs were injected bilaterally into the Acb of rats and activity measured for 60 min. The data represent the total mean activity ± SEM of (n) replicates.

*Equimolar doses.

†Twice the molar concentration of 2 μg phaclofen.

in the first 18 minutes after injection (Fig. 4). During the depressant phase, rats administered baclofen appeared sedated and had their eyes shut. Some twitching, gnawing movements and yawning were seen.

None of the $GABA_B$ antagonists tested exerted any significant effect on locomotor function nor any observable effect on gross behaviour (Table 1).

Interaction of PTXNN With DA D1 and D2 Agonists in DA-Depleted Rats

Rats were pretreated with reserpine (5 mg/kg SC 24 h before intra-accumbal injection) and αMPT (200 mg/kg SC 1 h before) to deplete DA, noradrenaline and serotonin storage granules and to stop DA and noradrenaline synthesis. After intracerebral injection of various combinations of PTXNN (0.0625 μg/side), SKF38393 (1 μg/side) or quinpirole (1 μg/side), activity was monitored each 15 min for 300 min. The doses of the DA agonists were chosen in this experiment to be threshold for inducing activity [see (10)] so that any enhancement by PTXNN would be readily seen. The data are given in Fig. 5, both as the time-course curves and as the total accumulated activity over the 300 min. PTXNN, SKF38393 and quinpirole alone did not significantly alter locomotor activity when compared to the response of animals challenged the vehicle. Note, however, that quinpirole induced a short-lasting moderate stimulation immediately after injection, an effect reported by us previously (10). The combinations of PTXNN with SKF38393 or quinpirole were also without significant effect on activity. However, SKF38393 plus quinpirole produced a significant increase in activity compared to animals challenged with vehicle. The activity was evident 30 min after injection, peaked between 90 and 120 min after injection and had returned to control levels by 255 min. The excitation was characterized by coordinated locomotion around the cage. Rats would occasionally jump and hit the roof of the cage and after such jumps there would be short periods of inactivity. When PTXNN was added to this combination, a more marked stimulation was produced, characterized by an almost immediate increase in activity with a peak occurring 135–150 min after injection and

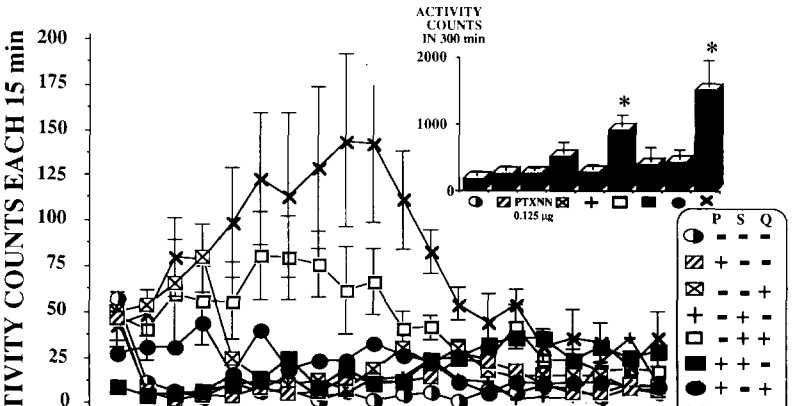

FIG. 5. Rats were pretreated with reserpine and αMPT as described and then challenged with PTXNN, SKF38393 or quinpirole, alone or in combination. The time course curves represent the mean activity each 15 min (SEM shown for the two most active groups) of 3 to 9 replicates. The inset contains the accumulated 300-min total activity. In addition, the inset includes one additional group of rats challenged with 0.125 μg/side of PTXNN. The code given in the small box corresponds to the code used in the time-course curves and indicates whether an animal received PTXNN (P), SKF38393 (S) or quinpirole (Q). ANOVAR of the accumulated data indicated that the challenges had exerted a significant effect, $F(8,35)=3.467$, $p=0.005$, and post hoc tests indicated that the combinations which included both DA agonists produced significantly more activity than vehicle-challenged animals (marked with an asterisk). When the time-course curves between 135 and 225 min were analyzed by ANOVAR (with repeated measures on time), the group challenged with SKF38393 plus quinpirole plus PTXNN was significantly greater than that challenged with SKF38393 plus quinpirole, $F(1,15)=5.44$, $p<0.05$, and from all the other groups.

returning to control levels at about 255 min after injection. The activity produced by this triple combination was more marked and "violent" than that produced by the combination of the two DA agonists. Although there was extensive forward locomotion, interspersed in some cases by rears up the sides of the cage, most rats also exhibited seemingly uncontrolled violent and convulsive movements, characterized by upward jumps to the roof of the cage and jumps from one side of the cage to the other. The total 300-min activity of the rats challenged with the three drugs was, however, not significantly different to the response of the rats challenged with just the DA agonists, because of the large errors associated with this type of behavioural paradigm and partly because of the conservative nature of the Newman-Keul's post hoc test employed. The activity produced by the DA agonists plus PTXNN was, however, significantly greater than that produced by the DA agonists alone (see legend to Fig. 5) when analyzed between 135 and 225 min.

DISCUSSION

In agreement with previous reports which used picrotoxin, the direct application of the noncompetitive $GABA_A$ receptor agonist PTXNN into the Acb of rats with intact stores of catecholamines produced marked locomotor stimulation (17, 27, 38). Furthermore, the application of the competitive $GABA_A$ antagonist bicuculline produced a similar excitation after direct application. The nature of the excitations produced by PTXNN and especially by bicuculline were qualitatively different from those produced by a variety of DA agonists such as DA and SKF38393 plus quinpirole. While the activity produced by the latter agents is coordinated, dose-dependent and accompanied by various amounts of sniffing and rearing, it is devoid of any major overt convulsive element. In our experience, even very high doses of DA itself will not produce convulsions, but rather cause an animal to run to exhaustion and death (12,13). In contrast, both PTXNN and bicuculline produced an excitation which seemed visually to incorporate an "explosive" character. Furthermore, marked salivation was seen after PTXNN application, an effect not seen in our experience after DA agonist administration. The qualitatively different nature of these excitations would suggest that at least some of the pathways involved are different, with DA being one of the neurotransmitters in common.

The PTXNN-induced excitation was dependent upon catecholaminergic mechanisms. Thus it was completely absent in rats pretreated with reserpine plus αMPT, implying that catecholamines and probably in the present case, specifically DA, are required for PTXNN-induced excitation. This is in agreement with a previous observation that the excitation produced by either picrotoxin or gammahydroxybutyrate injection into the Acb is blocked by a systemic injection of the selective D2 antagonist haloperidol and that gammahydroxybutyrate-induced excitation is blocked by αMPT (Jackson and Andén, unpublished data). Since locomotion in rodents requires the stimulation of both D1 and D2 receptors (15, 23, 32, 40), and involves a close interaction between the two receptor subtypes in the Acb (10,14), we were interested to see whether PTXNN-induced activity was also dependent upon D1 and/or D2 receptors located within the Acb, especially since it has previously been suggested that catecholamine depletion from brain areas other than the Acb is responsible for blocking picrotoxin-induced excitation (27). In DA-depleted animals PTXNN did not increase locomotor activity. Furthermore, when PTXNN was combined with either SKF38393 or quinpirole in DA-depleted rats, no significant stimulation occurred. However, although SKF38393 plus quinpirole produced an increase in locomotion, the addition of PTXNN to the combination produced even more activity. Furthermore, the addition of the $GABA_A$ antagonist qualitatively changed the pattern of stimulation to one that seemed to include convulsive aspects. This finding indicates that the ability of DA depletion to block PTXNN-induced excitation is due to a deprivation of DA at both D1 and D2 receptors, both of which appear to be located within the Acb. Interestingly, no stimulation was seen in the present study after quinpirole or SKF38393 injection into reserpine + αMPT-pretreated rats. This is in contrast to the stimulation produced by either of these agonists after injection into the Acb of rats within intact stores of neurotransmitters (10). In this case, endogenous DA probably provides the required stimulation for the complementary receptor subtype (33). Although systemic injection of either D1 or D2 agonists produce rotation in 6-hydroxydopamine-lesioned rats (Ungerstedt rats) (3), this activation probably reflects the presence of receptor supersensitivity, when the D1 and D2 receptors may become uncoupled (3), together with the presence of residual but functionally significant amounts of endogenous DA.

In contrast to the activating effects of the $GABA_A$ antagonists, the $GABA_A$ agonist 3-APS depressed activity in low doses but stimulated after a high dose. Similarly, the local application of another $GABA_A$ agonist muscimol (1) depressed the rats' activity at most doses. The stimulation seen after the highest dose may be nonspecific since 60 μg/side as a local injection into the brain must be considered a very large dose and extensive diffusion and toxicity cannot be ruled out.

Although $GABA_B$ receptors apparently play a role in mammalian physiology (7) and are found in the Acb (8), none of the $GABA_B$ antagonists tested in the present study exerted any significant effect on locomotor activity. This may be due to several causes. Firstly, the doses of antagonists may have been too low. While this can never be ruled out in these types of studies, we used, where possible, almost saturated concentrations of the various agents. Secondly, the model (increased locomotion or decreased locomotion) may be inappropriate. For example, $GABA_B$ receptor function may only become evident under conditions of elevated locomotor activity or alternatively, $GABA_B$ receptors may play no major role in this type of behaviour in the Acb. Thirdly, drugs that reduce activity are far more difficult to study than drugs that increase activity, as the baseline activity of control rats is only a little above zero readings, especially after adaptation to the cage.

The ability of GABA agonists and antagonists to alter locomotion after intracerebral injections is not restricted to injections into the Acb. For example, the application of the $GABA_A$ agonists muscimol and 4,5,6,7-tetrahydroisoxazole [5,4,-c]pyridin-3-ol (THIP) and GABA itself into the VTA, which sends a DA projection to the Acb induced a "compulsive hypermotility" (4), whereas picrotoxin induced either mild sedation (4) or excitation (26), while bicuculline caused convulsions (4). As there is evidence of GABA input into VTA neurons (39,45), these effects may be due to inhibition in the VTA by a GABAergic projection from the Acb or from short interneurons within the VTA itself. There is also substantial evidence for a GABA pathway from the Acb to the globus pallidus (9,16). Thus the direct application of the GABAergic drugs muscimol and baclofen into the globus pallidus can attenuate the stimulant effects of the DA agonist ADTN applied into the Acb (36), while the excitation induced by the administration of picrotoxin into the VTA is attenuated by the application of GABA into the globus pallidus (25). These data, together with many others, indicate a very complex relationship between DA and GABA in regulating aspects of motor function.

The ability of DA depletion to block the stimulant effect of PTXNN, and the efficacy of D1 plus D2 agonists to reinstate this activity, does not mean that the stimulant effect of PTXNN

is mediated directly through the VTA-Acb DA pathway. It suggests, rather, that an intact DA pathway is required for the PTXNN effect to be seen. Its primary locus of action may involve, for example, an interaction with elements of the Acb-Pallidal pathway which cannot, however, be expressed in the absence of a functioning VTA-Acb DA pathway.

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