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The Effect of Drugs Altering Striatal Dopamine Levels on Apomorphine Induced Stereotypy

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FEIGENBAUM, J. J., J. YANAI, R. B. BLASS, B. MOON AND H. KLAWANS. *The effect of drugs altering striatal dopamine levels on apomorphine induced stereotypy*. PHARMAC. BIOCHEM. BEHAV. **16**(2) 235–240, 1982.—Drugs that increase or decrease striatal dopamine levels appear to affect apomorphine induced stereotypy. This finding was unexpected, as it has previously been maintained that drugs which exert any action on striatal DA terminals exclusively would affect only indirect dopaminergic agonists, as opposed to apomorphine which induces stereotypy by acting directly on postsynaptic dopamine receptors. Specifically, inhibiting intrastriatal dopamine levels inhibits this behavior. This effect is explained in terms of apomorphine having a greater intrinsic activity and agonist affinity for striatal dopamine receptors than dopamine itself. Thus, dopamine and drugs which promote its release, may diminish the central behavioral effects induced by apomorphine relative to drugs which inhibit dopamine release centrally.

Apomorphine α-Methyl-p-tyrosine Amphetamine γ-Hydroxybutyrate Dopamine
Post-synaptic striatal dopamine receptor Stereotypy

PARKINSONISM is generally believed to be associated with a deficiency of striatal dopamine [1,2] and is consequently treated with drugs which exert an agonist effect on striatal dopaminergic neurons. The systemic injection of such agents (e.g. L-DOPA and apomorphine) reliably produces stereotyped behavior which has been demonstrated to primarily result from agonist induced arousal of striatal dopamine receptors [3, 4, 31]. Consequently, the stereotypy elicited by the directly acting dopamine agonist apomorphine, or by the indirect dopamine agonists amphetamine and L-DOPA [7,8], has been frequently used as a model to assess the efficacy of potential anti-Parkinsonian agents [9,10].

In accordance with this model, drugs which inhibit dopamine agonist induced stereotyped behavior would be expected to exacerbate Parkinsonism, while drugs exerting a converse effect would likely ameliorate this disorder [11]. However, contrary to this model and to the apparent nature of the drugs involved, the indirectly acting dopamine agonists L-DOPA and amantadine which have been shown to be effective in treating Parkinsonism and in eliciting stereotypy [12, 13, 25] reportedly also inhibit apomorphine induced stereotypy [11,14]. On the other hand, several studies have suggested that drugs which deplete central dopamine stores (reserpine and α-methyl-p-tyrosine, potentiate apomorphine induced stereotypy [15–18]. Since apomorphine has been demonstrated to induced stereotyped behavior by acting directly on post-synaptic dopamine receptors in the striatum, α-methyl-p-tyrosine and reserpine would not be expected to produce any effect on apomorphine induced stereotyped behavior, as suggested by several reports [19–21]. Furthermore, if indirect dopamine agonists did affect the stereotypy elicited by apomorphine, one would expect them to enhance this behavior in an additive if not synergistic manner, since most indirect dopaminergic agonists produce stereotypy on their own.

Because of the surprising nature of these reports, it was decided to evaluate them further by systematically observing the effect on apomorphine induced stereotypy of drugs either stimulating striatal dopamine release (e.g. d-amphetamine; [22]) or inhibiting it (α-methyl-p-tyrosine; [23], γ-hydroxybutyric acid; [24]). Moreover, a suggestion by Cox and Tha [12], and Cox [11] as to the means by which indirectly acting DA agonists might inhibit apomorphine elicited stereotyped behavior was also evaluated. This was done both with respect to the findings obtained in the present study, and also relative to the data of several studies of apomorphine and dopamine binding done in striatal tissue.

METHOD

Subjects

Male Sprague-Dawley rats (ARS Sprague-Dawley Farms, Madison, WI) 200–250 g were used throughout. The animals were group housed in transparent plastic cages 45×50 cm situated within a large colony room, and were maintained at

TABLE 1
DISTRIBUTION OF ANIMALS IN TREATMENT GROUPS

Group No.	No. of Animals	Pretreatment Drug (mg/kg)	Final Drug Treatment (mg/kg)
1	6	Saline	Apomorphine (0.5)
2	24	d-Am (0.5, 1, 3, 6)	Apomorphine (0.5)
3	24	Saline	d-Am (0.5, 1, 3, 6)
4	24	GHBA (50, 100, 150, 200)	Apomorphine (0.5)
5	24	Saline	GHBA (50, 100, 150, 200)
6	24	AMPT (250, 300, 350, 400)	Apomorphine (0.5)
7	24	Saline	AMPT (250, 300, 350, 400)
8	6	Saline	Saline

a constant room temperature of 23°±1°C with a relative humidity of 55% and a 12 hour light-dark cycle (0600–1800 hr on and 1800–0600 hr off). All animals were given water and Purina rat chow ad lib.

Drugs

Drugs used included apomorphine HCl (Merck); d-amphetamine sulphate (d-Am; Sigma); γ-hydroxybutyric acid (GHBA; Sigma); DL-α-methyl-para-tyrosine methyl ester HCl (AMPT; Regis).

Following a 60 minute habituation period for each animal, 156 rats were randomly divided into one of the groups shown in Table 1.

All drugs were dissolved in 0.9% saline in a volume of 1.0 ml/kg body weight, and administered subcutaneously. Drug doses are expressed in terms of the salt. Animals were pretreated with d-amphetamine 15 min prior to the first apomorphine injection and with GHBA 60 min before apomorphine. The first injection of AMPT (200 mg/kg) was administered 330 min prior to apomorphine, and was followed one hour later (270 min before apomorphine) by a second injection of AMPT of either 50, 100, 150, or 200 mg/kg.

Behavioral Observation

Following the administration of the final drug treatment, each animal was observed continuously by three independent observers in a 'blind' manner for 6 ten min periods, with the exception of animals injected with d-amphetamine, which were observed for 15 ten min intervals. To make it possible to precisely discriminate among the various levels of stereotyped behavior produced, an 11 point stereotypy rating scale was used. Modified from the 4 point scale of Costall and Naylor [18], the gradient contains mutually exclusive categories as shown in Table 2.

All three observers of the behavior assessed were extensively trained, at first separately and then together, on rating the stereotypy induced by a wide variety of dopaminergic agonists, including apomorphine. In the course of such training, inter-rate reliability was continuously measured in terms of the rating each gave of specific aspects of the stereotypy observed, as described in detail by the rating scale. This training continued, until there was verbal unanimity as to the rating to be assigned a given behavior relative to the behavioral description for that rating given in the stereotypy rating scale.

TABLE 2
STEREOTYPY RATING SCALE

Rating	Behavioral Description
0.0	Totally inert; asleep or catatonic
0.5	Extremely mild SB interrupted by prolonged activity
1.0	Occasional SB other than licking (L) or biting (B)
1.5	Constant SB other than licking or biting
2.0	Intense SB without licking or biting
2.5	Intense SB including occasional licking
3.0	Constant licking; no locomotor activity or biting
3.5	Intense licking without biting or with only very slight biting
4.0	Licking and biting fairly frequent but not constant
4.5	Constant L and B; animals distractable (e.g. by noise)
5.0	Constant licking and biting; animals not distractable

Quantitative terms appearing in the table are defined as follows: *Extremely mild:* SB is very weak in intensity, brief in duration (5–10 seconds) and infrequent (20 occurrences of SB per interval). *Occational:* SB is seen at least every 30 sec, with each occurrence lasting a minimum of 10–20 sec. *Constant:* SB is fairly vigorous in intensity with less than 10 sec intervening between stereotypies. The animals can be distracted by noise. *Intense:* SB is very vigorous with no more than a few sec intervening between stereotypies. Each episode of SB is at least a few min in duration. LA is not seen, and it is difficult or impossible to distract the animals from their SB for more than a few sec.

Statistical Treatment

Since stereotyped behavior is comprised of several components which may be independent of each other, the use of a parametric test such as the Student *t*-test did not seem justified in evaluating the statistical significance of the treatment administered, relative to their controls. For this reason, the Mann-Whitney U test was employed throughout.

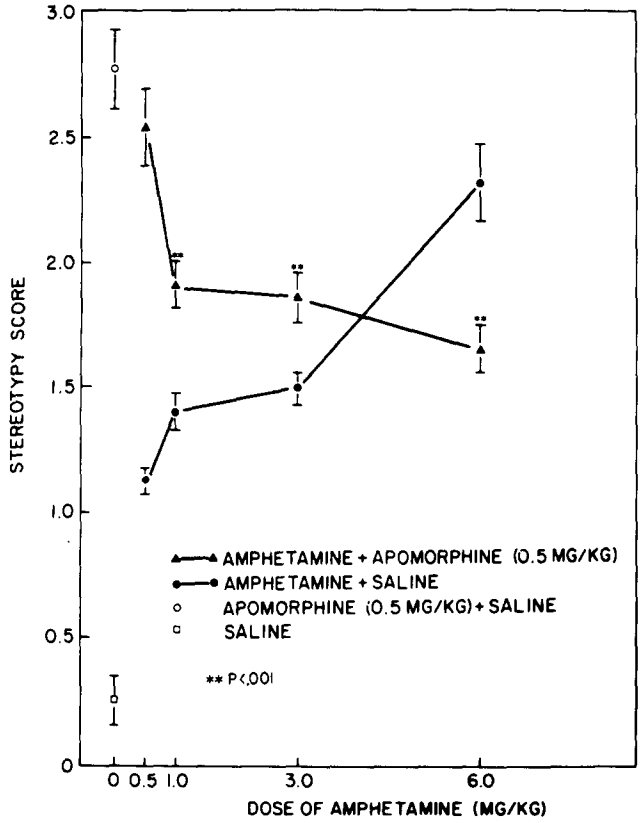

FIG. 1. The inhibition of the stereotypy induced by apomorphine (0.5 mg/kg) by sequentially doubling doses of d-amphetamine (0.5–6.0 mg/kg) administered 15 minutes prior to apomorphine (Amphetamine + Apomorphine values compared to Apomorphine alone).

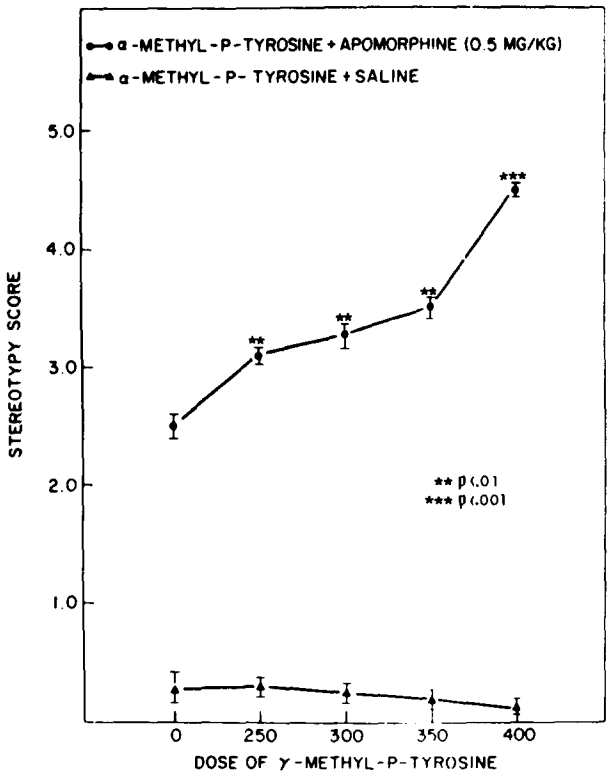

FIG. 2. Potentiation of Apomorphine Induced Stereotypy by α-methyl-p-tyrosine (250–400 mg/kg) (AMPT + Apomorphine values compared with Apomorphine alone).

RESULTS

Dose Related Inhibition of Apomorphine Induced Stereotypy by d-Amphetamine; and Inhibition of Amphetamine Induced Stereotyped Behavior by Apomorphine

Apomorphine (0.5 mg/kg) produced a relatively high level of stereotypy which was markedly inhibited by low doses of amphetamine (0.5-1.0 mg/kg). Increasing doses of d-amphetamine further reduced apomorphine stereotypy. However, this effect was not statistically significant. While the interaction of d-amphetamine and apomorphine inhibited apomorphine induced stereotypy, the relatively weak stereotyped behavior produced by the lower dose of d-amphetamine was enhanced by subsequent treatment with a low dose of apomorphine (0.5 mg/kg), relative to saline-amphetamine controls (Fig. 1). By contrast, the stereotypy induced by a higher dose of d-amphetamine (6 mg/kg) was markedly attenuated by the same low dose of apomorphine (0.5 mg/kg).

Potentiation of Apomorphine Induced Stereotyped Behavior by AMPT

AMPT potentiated the stereotypy induced by apomorphine (0.5 mg/kg) in a sigmoidal, dose-related manner, with the highest dose of AMPT (400 mg/kg) producing total inactivity in control animals and a nearly 2-fold enhancement of apomorphine induced stereotypy (Fig. 2). The stereotyped behavior observed in the animals injected with the highest dose of AMPT administered was also very close to the maximum sterotypy rating on the scale used (Table 2). Doses higher than 400 mg/kg were not used because of the considerable toxicity produced.

Potentiation of Apomorphine Induced Sterotypy by γ-Hydroxybutyric Acid

Increasing doses of γ-hydroxybutyric acid (50–200 mg/kg) also potentiated apomorphine induced stereotyped behavior in a sigmoidal manner. While the two lower doses of γ-hydroxybutyric acid (50 and 100 mg/kg) produced virtually the same insignificant effect on apomorphine elicited stereotypy, the two higher doses (150 and 200 mg/kg) elicited a very marked albeit nearly identical potentiation of AISB (Fig. 3). Quite unexpectedly, while control animals administered the two higher doses concomitantly with saline exhibited the same level of activity as saline-saline controls, the two lower doses of γ-hydroxybutyric acid induced increases in sterotypy levels that were somewhat greater than that seen in saline pre- and post-treated animals. The reasons for this are unclear.

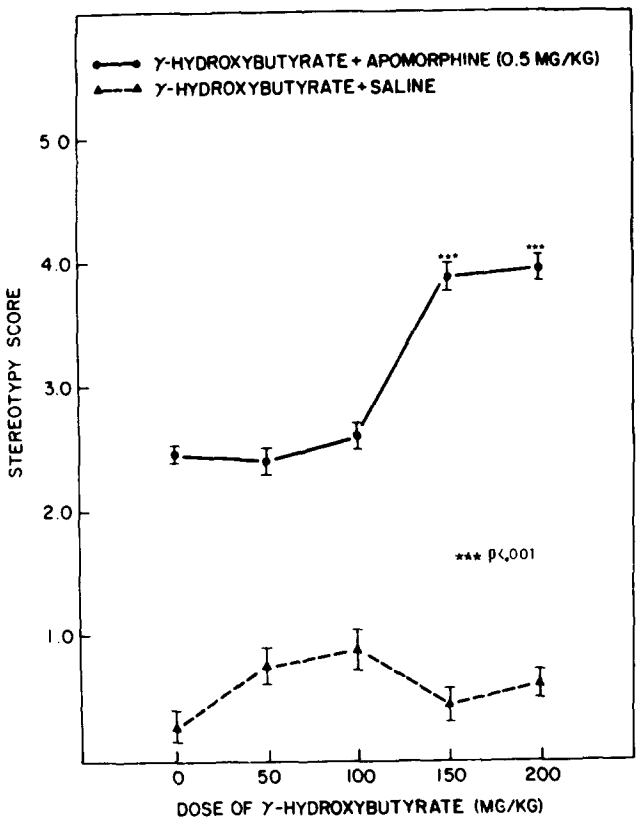

FIG. 3. Potentiation of Apomorphine Induced Stereotypy by γ-hydroxybutyric acid (γ-HB + Apomorphine compared with Apomorphine alone).

DISCUSSION

Dose Related Inhibition of Apomorphine Induced Stereotyped Behavior by Indirectly Acting Dopaminergic Agonists

To our knowledge, this is the first study assessing the interaction of amphetamine and apomorphine on the stereotyped behavior induced by either agonist. Apomorphine induced stereotypy was antagonized to an extent that increased with the dose of d-amphetamine administered. Furthermore, the greatest enhancement of amphetamine induced stereotypy produced by apomorphine occurred in animals injected with the lowest dose of amphetamine administered (0.5 mg/kg); one that had no significant effect on apomorphine induced stereotypy. Conversely, the dose of d-amphetamine producing the greatest antagonistic effect on apomorphine elicited stereotypy (6.0 mg/kg; the highest dose administered) induced, in combination with apomorphine, a level of stereotyped behavior far below that produced by amphetamine-saline control animals.

These results are analogous to those obtained by Cox [11] who used two other indirect dopaminergic agonists, amantadine [33] and L-DOPA [15]. In a preliminary study, we observed an inhibition of apomorphine induced stereotypy after the administration of a dose of L-DOPA and a decarboxylase inhibitor that could produce weak stereotypy by itself (400 mg/kg; Feigenbaum *et al.*, unpublished observations). Very similar results were also reported by Cox and Tha [12] who explained the antagonism of apomorphine elicited stereotypy by L-DOPA in terms of receptor occupation by the dopamine synthesized from L-DOPA, which would thereby compete with and prevent the access of apomorphine to striatal dopaminergic receptors. This suggestion is based on the premise that the apomorphine molecule has a greater efficacy or intrinsic activity than that of dopamine itself, at least with regard to the induction of stereotyped behavior. By extension of this argument, one might expect that any indirect dopamine agonist which acts by enhancing the intrasynaptic striatal levels of dopamine would inhibit apomorphine elicited stereotypy. While it is by no means certain that this premise is correct, there are a number of reports that appear to support it. It is widely accepted that apomorphine mediates its central effects by means of a direct action exerted on dopamine receptors generally [13,16], and elicits stereotypy through a direct action on postsynaptic striatal dopaminergic receptors specifically [14,22]. Earlier pharmacological findings [1,45] and recent pharmacological evidence [4, 42, 43] strongly suggest that apomorphine binds striatal dopamine receptors in a manner very similar or identical to that of dopamine itself [3, 42, 43]. Moreover, the ^{3}H-apomorphine binding site has been shown to be virtually identical to the ^{3}H-dopamine binding site by several procedures [3, 35, 36, 37]. Thus, dopamine and apomorphine appear to compete for the same receptor. However, the affinity of apomorphine for this receptor has been found to be consistently higher than that of dopamine in both calf and rat striatal tissue [3, 35, 36, 37]. Apomorphine not only possesses a somewhat greater affinity for the dopamine receptor, but also appears to have a greater efficacy (in terms of inducing such central behaviors as stereotyped behavior) than either dopamine or indirect dopamine agonists which induce stereotypy through their stimulation of dopamine release. In this regard, it has been found that twice as much dopamine must be injected intrastriatally in nialamide pretreated rats to produce the same level of stereotypy as that produced by 25–50 μg of apomorphine [9,26].

Apomorphine Possesses Greater Efficacy Than Amphetamine in Inducing Stereotyped Behavior

Apomorphine has been found to be more potent and efficacious thatn amphetamine relative to the induction of stereotypy [27]. The data of Costall and Naylor [7] indicate that apomorphine (0.25–2.0 mg/kg) is approximately five-fold more effective in inducing stereotypy than amphetamine (1.25–10.0 mg/kg) across all four doses administered. This, and similar reports only express dose equivalences however. Until recently, high intensity sterotyped behavior could only be rated and not quantified (e.g. in terms of the number of bites per minute; with biting the most intense form of stereotypy in rats; [8]). Recently however, a device has been described which can automatically record high intensity stereotypy (biting) in rats [27]. Using this apparatus, it was found that 10 mg/kg apomorphine elicited a plateau response which was four times greater than that produced by a maximally effective dose of amphetamine (15 mg/kg). Higher doses of amphetamine could not be administered as the highest dose injected produced non-specific toxic effects, resulting in the expiration of all animals so injected within a few hours [27].

Apparently then, d-amphetamine cannot induce the same intensity of stereotypy in any dose as can maximally effective doses of apomorphine. Since amphetamine, which acts

by releasing newly synthesized dopamine, has a lower efficacy than apomorphine, and antagonizes apomorphine induced stereotyped behavior only in concentrations 2–6× that of apomorphine; its inhibition of apomorphine elicited stereotypy is likely due to a competitive antagonism between amphetamine (or rather, the dopamine it releases) and apomorphine.

Potentiation of Apomorphine Induced Steroetyped Behavior by Drugs Depleting Striatal Dopamine Levels

α-Methyl-p-tyrosine (AMPT) is a potent inhibitor of tyrosine hydroxylase [24], the rate limiting enzyme involved in the biosynthesis of dopamine and norepinephrine [40]. Presumably, the inhibitory effect of AMPT on brain levels of dopamine and norepinephrine is secondary to an inhibition of catecholamine synthesis [30].

In a recent study, AMPT (200 mg/kg) was administered intraperitoneally in a single dose which was followed three hours later by apomorphine (1.0 mg/kg). These authors reported that AMPT had no effect on the apomorphine induced stereotypy produced [39]. In an earlier study, Ernst [13] used α-methyl-l-tyrosine (10 mg/kg) six and again three hours before the administration of apomorphine (1 mg/kg) and also observed no effect on apomorphine stereotypy. In yet another study, AMPT (100 mg/kg) injected the same time before apomorphine as in the Ernst study (i.e. six and three hours before 10 mg/kg apomorphine, was similarly without effect on apomorphine induced stereotypy [20]. All three studies reported findings that contradict those of the present study. However, these studies also used doses of apomorphine that were 2–20 times greater than the dose used in the present study; and challenged the apomorphine stereotypy produced with pretreatment doses of AMPT that were 1.25–12.5 times less than the lowest dose used in the present study. Finally, the interval between the last injection of AMPT and the subsequent administration of apomorphine was 1.5 hours longer in our study than in the three studies cited above. Though the use of a sufficient dose α-methyl-p-tyrosine is critical in ensuring an effective blockade of dopamine synthesis [30]; the interval between pretreatment with AMPT and apomorphine may be as critical as the dose of α-methyl-p-tyrosine used, for Costall and Naylor [8,10] have found that the potentiation of apomorphine induced stereotyped behavior by AMPT (using the same doses of both drugs that were used in the present study; 0.5 mg/kg and 250 mg/kg, respectively) is time dependent, with no enhancement seen after only 1 hour; a significant effect seen after 4 hours, and a maximal effect produced after 24 hours. This time course, moreover, closely follows the effect of AMPT on the inhibition of catecholamine synthesis over time [8,10].

In agreement with the present findings, α-methyl-p-tyrosine, and reserpine, which also depletes central dopamine levels, has been found by others to potentiate apomorphine induced stereotypy [10, 16, 18], though no explanation for this enhancement of apomorphine elicited stereotypy was advanced [8]. A probable explanation for this effect may be found in the greater efficacy of apomorphine in inducing stereotypy relative to dopamine. If apomorphine is more efficacious than dopamine, then events which inhibit the endogenous release of dopamine (i.e. as elicited by γ-hydroxybutyric acid; α-methyl-p-tyrosine and reserpine) would result in a greater striatal dopamine receptor occupancy by the more effective apomorphine molecules. This in turn would result in an enhancement of apomorphine induced stereotypy relative to saline pretreated controls.

At least one other explanation for the enhancement of apomorphine stereotypy by AMPT might be forewarded. Thus, α-methyl-p-tyrosine has been shown to produce striatal dopamine receptor supersensitivity after the acute administration of AMPT [5], that could account for the enhancement of apomorphine induced stereotypy observed. However, it is quite unlikely that this would apply to the potentiation seen in the present study, as supersensitivity induced by AMPT (and other drugs) is generally regarded as requiring far more time to develop (in terms of significant increases in B_{max}), than the relatively few hours involved in the present study. Furthermore, apomorphine stereotypy was also very markedly elevated by another agent inhibiting dopamine release more specifically than AMPT; i.e. by γ-hydroxybutyric acid. Pretreatment with this drug occurred only 1 hour before the administration of apomorphine, resulting in somewhat similar augmentations of apomorphine induced stereotypy, yet it would appear rather unlikely that this was the result of γ-hydroxybutyric acid induced receptor supersensitivity developing in 60 minutes.

γ-Hydroxybutyric acid produces an effect on striatal intra-synaptic dopamine levels that is quite similar to that elicited by reserpine and α-methyl-p-tyrosine. However, all three drugs induce the same effect on striatal dopamine by entirely different means. While AMPT diminishes striatal levels of dopamine through an inhibition of dopamine biosynthesis, and reserpine acts by depleting and preventing dopamine stores in striatal terminals, γ-hydroxybutyric acid inhibits striatal dopamine release by diminishing neuronal firing in dopaminergic neurons [2,17], and causes alterations in dopamine metabolism similar to those produced by axotomy [19,45]. Unlike AMPT and reserpine, γ-hydroxybutyric acid does not produce a very significant effect on brain acetylcholine, serotonin or norepinephrine levels [2, 17, 45], which is one of the primary reasons it was chosen for use in the present study. Thus, while it could be argued that α-methyl-p-tyrosine or reserpine-induced alterations of apomorphine induced stereotypy are secondary to an effect on non-dopaminergic mechanisms; this would be far less applicable to the effects on apomorphine stereotypy produced by γ-hydroxybutyric acid. It therefore appears likely that irrespective of the means, any drug that exerts an inhibitory effect on dopamine levels within striatal synapses will enhance apomorphine induced stereotypy.

In conclusion, drugs which enhance striatal dopamine levels apparently inhibit apomorphine induced stereotypy through competitive antagonism with apomorphine which has a greater efficacy and a somewhat greater affinity for striatal dopamine receptors than dopamine itself. Through the same mechanism, drugs which diminish striatal dopamine levels likely exert a reverse effect on apomorphine induced stereotypy, i.e. they enhance this behavior.

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