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Multiple daily amphetamine administration decreases both [^{3}H]agonist and [^{3}H]antagonist dopamine receptor binding[1]

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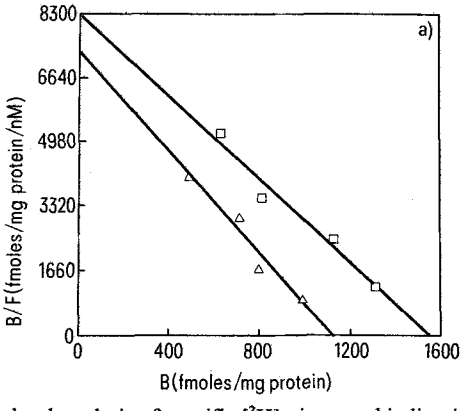
Summary. Multiple daily amphetamine injections in rats decreased both [^{3}H]agonist as well as [^{3}H]antagonist striatal dopamine receptor binding. Concurrently, these animals exhibited a decrease in striatal dopamine concentration and, paradoxically, an enhancement of behavioral responsivity.

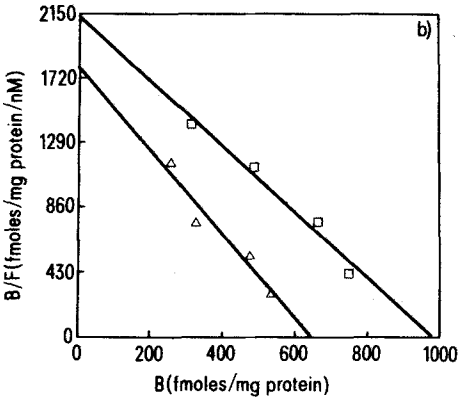
It has previously been shown that multiple injections of d-amphetamine in rats results in an enhanced responsivity to this drug[3-6]. Similar observations have been made in other species[7,8] and in man[9]. Chronic treatment of rats with dopamine receptor antagonists also leads to an augmentation in the behavioral response to dopamine agonists[10] which is accompanied by an increase in striatal dopamine receptor binding of both [^{3}H]agonists and [^{3}H]antagonists[11]. The paradoxical observation of increased behavioral sensitivity to agonists following either chronic agonist or antagonist treatment led us to investigate the effect of multiple daily doses of amphetamine on the dopamine receptor binding of both [^{3}H]agonist and [^{3}H]antagonist ligands.

Material and methods. Male Wistar rats (325-375 g) were treated with 30 successive, s.c. injections of either saline or d-amphetamine sulfate (2.5 mg/kg) at 4-h intervals for 5 days. The animals were sacrificed 4 h after the last injection by decapitation. The brains were quickly removed into ice-cold saline, the striata dissected out and frozen at −70 °C. The binding of the radiolabeled antagonist [^{3}H]spiperone (25.6 Ci/mmole, NEN) and the radiolabeled agonist [^{3}H]N-n-propylnorapomorphine ([^{3}H]NPA, 75 Ci/mmole, NEN) were assayed as previously described in detail[12-14]). Nonspecific binding was determined with 10^{-6}M (+)butaclamol and represented 10-20% of the total [^{3}H]spiperone binding and 30-40% of the total [^{3}H]NPA binding. All experiments were performed in duplicate. Protein was determined by the method of Bradford[15].

Results and discussion. The specific dopamine receptor binding of both [^{3}H]spiperone and [^{3}H]NPA was reduced following the chronic amphetamine treatment (figs a and b; table). The maximum binding capacity (B_{max}) for [^{3}H]spiperone was reduced by about 20% while the B_{max} of the agonist ligand, [^{3}H]NPA, was reduced by about 27%. Although the affinity of [^{3}H]spiperone for its binding sites was unaltered by the treatment the dissociation constant (K_d) for [^{3}H]NPA was slightly reduced from 0.51 to 0.40 nM ($p < 0.05$). Behavioral observations were made on a similar



a Scatchard analysis of specific [^{3}H]spiperone binding in striata of amphetamine (△) and saline (□) treated rats. The left and right striata from each individual animal were pooled and assayed for [^{3}H]spiperone and [^{3}H]NPA binding as described. The results for 2 individual animals assayed in parallel are shown. [^{3}H]spiperone concentrations were varied between 100 pM and 1 nM. The lines drawn represent the best fit to the data as determined by linear regression analysis.



b Scatchard analysis of specific [^{3}H]NPA binding in striata of amphetamine (△) and saline (□) treated rats. The saturation experiments were performed as in figure (a) varying the [^{3}H]NPA concentrations between 200 pM and 2 nM. Data from 2 individual animals assayed in parallel are shown.

group of amphetamine treated rats and have been reported previously[16]. Briefly, there was a progressive augmentation in response characterized by a more rapid onset and an increased magnitude of stereotypy with a contrasting shortening of both the stereotypy and the poststereotypy hyperactivity periods. Similarly treated rats demonstrated a 31% decrease in striatal dopamine concentration[16].

The major finding of the present study is the 'down regulation' of [^{3}H]agonist binding as well as [^{3}H]spiperone binding following chronic amphetamine administration. Similar findings using [^{3}H]spiperone have recently been reported[17,18] and are confirmed by the present results. Because [^{3}H]agonists label a population of dopaminergic binding sites in the striatum that differs, in part, from those labeled by [^{3}H]antagonists[19,20] it was important to determine if amphetamine treatment modulated [^{3}H]agonist binding sites and [^{3}H]antagonist binding sites in a similar fashion.

It is clear from these data that the enhanced behavioral sensitivity following multiple daily injections with amphetamine is not the result of an enhanced number of striatal dopamine receptor binding sites for either [^{3}H]agonists or [^{3}H]antagonists, as is the case following chronic antagonist treatment. These findings are consistent with previous observations that the amphetamine response pattern following antagonist pretreatment is markedly different from that after multiple amphetamine injections[5]. Such chronic amphetamine treatment would be expected to result in the continuous stimulation of dopamine receptors by increased synaptic levels of dopamine[21]. This hypothesis is reinforced by the finding of a marked dopamine depletion following the cessation of such chronic amphetamine treatments[16]. In the present situation it would appear that the chronic stimulation of striatal dopamine receptors by released dopamine is probably responsible for the significant decrease in both [^{3}H]agonist and [^{3}H]antagonist receptor binding. Such findings have been observed in other neurotransmitter receptor systems[22]. How this neurochemical finding relates to the enhanced behavioral sensitivity to amphetamine under these circumstances is still unclear. However, such a decrease in dopamine receptors may underlie the apparent tolerance that develops to oral stereotypies induced by apomorphine following such chronic amphetamine administration[6].

Amphetamine-induced changes in dopamine receptor binding

Ligand	Saline (n = 5)		Amphetamine (n = 5)	
	K_d(nM)	B_{max} (fmoles/mg protein)	K_d(nM)	B_{max} (fmoles/mg protein)
^{3}H-spiperone	0.15 ± 0.02	1449 ± 35	0.13 ± 0.01	1157 ± 108
^{3}H-NPA	0.51 ± 0.02	1092 ± 55	0.40 ± 0.03	802 ± 95

Striata from individual rats were subjected to saturation analyses using ^{3}H-spiperone and ^{3}H-NPA as described in figures (a) and (b). Using Student's t-test for paired observations (2-tailed) there was a statistically significant ($p < 0.05$) difference in the B_{max}-values between the amphetamine- and saline-treated groups for both 3H-spiperone (20% decrease) and ^{3}H-NPA (27% decrease). There was also a significant ($p < 0.05$) difference in the K_d-value for ^{3}H-NPA between the 2 treatment groups. The number of animals in each group is indicated in parentheses (n).

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Occurrence of an anti-Thomsen-Friedenreich-like lectin in jackfruit seeds reacting with a receptor in ant egg glycoprotein

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Summary. The occurrence of an anti-Thomsen-Friedenreich-like lectin in the seeds of jackfruit and of its receptor-dominant disaccharide in an ant egg glycoprotein is described by agar-gel precipitin reactions.

It has been reported in several earlier papers[2-4] that peanut *(Arachis hypogaea)* lectin recognizes the carbohydrate part of the Thomsen-Friedenreich (TF) receptor, which occurs as a cryptantigen in various glycosubstances from different sources and represents an interesting marker in medicine and oncology[5,6]. The finding of another anti-TF-like lectin