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Comparison of the Density and Distribution of Brain D-1 and D-2 Dopamine Receptors in Buffalo vs. Fischer 344 Rats

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KERR, L. M., A. S. UNIS AND J. K. WAMSLEY. *Comparison of the density and distribution of brain D-1 and D-2 dopamine receptors in Buffalo vs. Fischer 344 rats.* PHARMACOL BIOCHEM BEHAV 30(2) 325–330, 1988.—In vitro autoradiography was used to compare the D-1 and D-2 receptor densities in brains from Buffalo (BUFF) and Fischer 344 (F344) rats. The latter strain has been proposed as a model for human attention deficit disorder with hyperactivity (ADDH). The radioligands [^{3}H]-SCH 23390 and [^{3}H]-sulpiride were used to selectively identify dopamine D-1 and D-2 receptors, respectively. Certain forebrain structures from F344 rats have a higher density of D-2 receptors, but similar numbers of D-1 receptors compared to BUFF rats. Scatchard analysis of D-2 binding (in caudate-putamen) revealed a B_{max} of 10.52±1.62 fmol/mg tissue and K_d of 12.72±0.93 nM in F344 rats and 3.00±0.57 and 3.87±0.58, respectively in BUFF rats (n=3). These results support the hypothesis that high D-2 levels are correlated with certain behavioral traits, e.g., high levels of spontaneous activity. A similar increase in D-2 receptors may be responsible for some of the behavioral manifestations of ADDH in children.

Dopamine D-1 D-2 Autoradiography Buffalo rats F344 rats Receptors

BUFFALO (BUFF) and Fischer 344 (F344) rats display different behavioral traits. For example, BUFF rats display more repetitive jaw movements than F344 rats [20]. On the other hand, F344 compared to BUFF rats display more spontaneous activity, slower habituation, higher stereotypy scores, higher avoidance behavior, greater percentage decreases in locomotion after apomorphine administration and a hypoactive response to moderate doses of stimulants [9, 10, 20, 24].

BUFF and F344 rats also differ in several parameters of biogenic amine metabolism. For example, F344 compared to BUFF rat brains have increased epinephrine content and phenylethanolamine-N-methyl transferase activity, as well as decreased alpha-adrenergic receptor density [18,23]. F344 rat brains also have increased dopamine D-2 receptor binding compared to BUFF rats; no differences are observed in dopamine D-1 receptor number [10,20].

The higher dopamine D-2 receptor density, as well as increased biogenic amine synthesis in F344 rats, appears to be correlated with this strain's behavior. These results suggest that the brain dopamine system might be important in modulating activity level and the hypoactive response to stimulant medication. Due to similarities in behavior and the response to stimulant administration, Helmeste and Seeman [11] have suggested that the F344 rat with its high D-2 receptor density may serve as a model for childhood attention deficit disorder with hyperactivity (ADDH).

Previous studies comparing D-1 and D-2 receptor densities in rats of the Buffalo and F344 strains have employed rather nonspecific ligands and binding techniques using membrane preparations from whole brain. In the present study, we used the specific dopamine D-1 and D-2 ligands SCH 23390 and sulpiride, respectively, to examine D-1 and D-2 receptors in microscopic areas of the brains of rats from these two strains using the technique of in vitro receptor autoradiography [16].

METHOD

Rats of the F344 and Buffalo strains (Charles River, Wilmington, MA) were sacrificed, while under deep chloroform anesthesia, by intracardial perfusion with cold isotonic saline. Their brains were quickly removed and placed in isopentane (−80°C) for freezing and then stored at −70°C until use. Brains were then allowed to equilibrate 1–2

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TABLE 1

COMPARISON OF [^{3}H]-SCH 23390 DISTRIBUTION IN BRAINS FROM RATS OF BUFF AND F344 STRAINS

Structure	F344	BUFF
Caudate-putamen	58.25 ± 8.50	57.00 ± 9.68
Globus pallidus	4.42 ± 0.13	3.58 ± 1.34
Cortex		
Layers I–III	0.45 ± 0.23	0.16 ± 0.31
Layers V–VI	0.52 ± 0.26	0.37 ± 0.19
Nucleus accumbens	46.05 ± 6.84	40.93 ± 5.05
Substantia nigra		
Zona reticulata	55.03 ± 25.19	49.70 ± 19.54
Hippocampus		
Stratum lacunosum moleculare	3.48 ± 1.15	2.65 ± 0.59

Distribution of [^{3}H]-SCH 23390 binding sites in brains from BUFF and F344 rat strains as determined by autoradiography. Ten micron thick sections were labeled with 1 nM [^{3}H]-SCH 23390 as described in the text and apposed to tritium-sensitive film to generate autoradiograms. Readings of the grain densities were converted to fmoles ligand bound/mg tissue using tritium brain paste standards. Non-specific binding, defined by incubating in the additional presence of 10^{-6} M SCH 23390, was uniform and subtracted from each value. Data is displayed as mean ± S.E.M. from six sections representing three animals. No significant differences between groups were observed.

hours in a −20°C cryostat microtome (Harris, North Billerica, MA) before being frozen onto brass cryostat chucks coated with OCT Compound (Miles Laboratories, Naperville, IL) plastic embedding media. Sections (10 μm in thickness) were then cut and thaw-mounted (two sections/slide) onto cold chrome-alum/gelatin coated microscope slides. These were then stored in a frost-free refrigerator at −20°C prior to being used for labeling experiments.

D-1 receptor autoradiography was performed according to the method of Wamsley and colleagues [5,6]. Specifically, slide-mounted tissue sections were incubated at room temperature for 30 min in a 50 mM Tris-HCl buffer (pH 7.4) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$ and 1 nM [^{3}H]-SCH 23390 (72.0 Ci/mmol, Dupont NEN; Boston, MA) and rinsed in cold buffer of the same solution (without added SCH 23390). Serial sections were treated in the same manner except for the addition of 3×10^{-6} M unlabeled SCH 23390 (an equal amount of displacement has been obtained in previous studies employing similar concentrations of fluphenazine or piflutixol) to the incubation media to represent nonspecific binding. Radiolabeled ligand concentrations in the solutions were examined before and after experimental procedures. For some experiments, sections were wiped with Whatman GF/B microfiber glass filter discs and placed in vials containing 5 ml of scintillation fluid and counted in a Beckman scintillation counter. For other experiments, the slide-mounted tissue sections were dried and then affixed to photographic mounting board and apposed to LKB Ultrofilm (Rockville, MD) in X-ray cassettes along with 10 μm thick tritium brain paste standards [22]. Films were removed and developed after 2–3 weeks. The resulting images from the labeled tissue sections were examined and results quantitated using a Stahl Research (Rochester, NY) DADS-560 computer-assisted microdensitometry system.

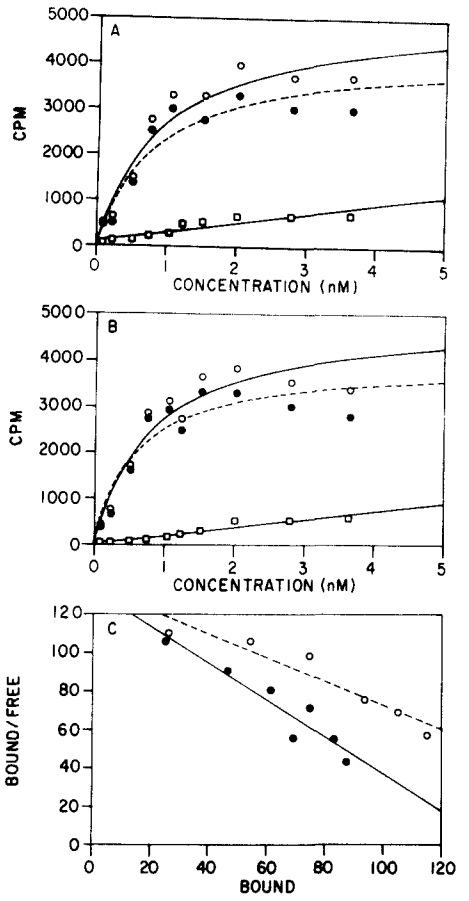

FIG. 1. Saturation and Scatchard analysis of [^{3}H]-SCH 23390 binding to slide-mounted tissue sections. BUFF (A) and F344 (B) rat tissue sections (caudate-putamen) were incubated in the presence of various concentrations of [^{3}H]-SCH 23390. Nonspecific binding was determined by adding an excess of unlabeled SCH 23390 to the incubation media. (○) total binding; (□) nonspecific binding; (●) specific binding. (C) Scatchard analysis of the data. (●) F344 rats; (○) BUFF rats. Linear approximation of the slope yielded a K_d of 1.63±0.15 nM and a B_{max} of 218.12±19.75 fmol/mg for BUFF rats and a K_d of 1.56±0.10 nM and a B_{max} of 188.5±18.41 fmol/mg for F344 rats (n=3 for each group).

Grain densities were determined, using a Leitz (F.R.G.) Orthoplan microscope, by focusing a 250 μm^2 photometer beam (MPV Compact) on an appropriate area of the autoradiogram. The percent transmission of this incident light was converted to femtomoles of [^{3}H]-SCH 23390 bound/mg tissue by comparison to the autoradiograph grain densities produced by the standards. Photography was performed on the Orthoplan microscope equipped with an Orthomat camera system using a 1× or 2.5× objective. Saturation plots and Scatchard plots were generated using a Hewlett-Packard computer and using data taken from the caudate-putamen area. Statistical comparison of the data was accomplished using a two-tailed Student's *t*-test.

The methods of Gehlert and Wamsley [8] were used to perform D-2 autoradiography. Specifically, treatment of tissue sections was as above except for the following: the buffer contained 0.17 M Tris-HCl (pH 7.4), 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.01% ascorbic acid with

TABLE 2

COMPARISON OF DISTRIBUTION OF [^{3}H]-SULPIRIDE BINDING SITES IN BRAINS FROM RATS OF THE BUFF AND F344 STRAINS

Structure	F344	BUFF
Caudate-putamen	29.61 ± 2.10	22.95 ± 1.37*
Nucleus accumbens	4.42 ± 0.13	3.58 ± 1.34
Olfactory tubercle	10.40 ± 0.60	7.07 ± 0.42*
Globus pallidus	1.67 ± 0.05	0.77 ± 0.19*
Hippocampus		
Stratum lacunosum moleculare	1.37 ± 0.27	0.50 ± 0.25
Substantia nigra	3.23 ± 0.46	2.25 ± 0.25
Cortex		
Layers I–III	1.11 ± 0.18	1.29 ± 0.16
Layers V–VI	0.72 ± 0.13	0.55 ± 0.32

Distribution of [^{3}H]-sulpiride binding sites in brains from rats of the BUFF and F344 strains as determined by autoradiography. Ten micron thick sections were labeled with 20 nM [^{3}H]-sulpiride as described in the text and apposed to tritium sensitive film to generate autoradiograms. Readings of the grain densities were converted to fmoles ligand bound/mg tissue using tritium brain paste standards. Non-specific binding, defined by incubating in the additional presence of 1 μM haloperidol, was uniform and subtracted from each value. Data is displayed as mean ± S.E.M. from twelve sections representing six animals.

*Significance $p<0.01$ and †$p<0.05$ by Student's t-test.

20 nM [^{3}H]-sulpiride (sp.act. 64–82 Ci/mmol, Dupont NEN; Boston, MA) for mapping studies and 0 to 25 nM of the radioligand for saturation experiments. Serial sections were incubated in the presence of 10^{-6} M unlabeled haloperidol to represent nonspecific binding. Sections were incubated for 20 min at room temperature and then rinsed four times in the same buffer, without added sulpiride, for five minutes at a time. Slides were then dried using a cool, dry stream of air. The exposure period for [^{3}H]-sulpiride films was 6 to 8 weeks.

RESULTS

Using the binding conditions described above for [^{3}H]-SCH 23390, a ligand which binds selectively to dopamine D-1 receptors [5,6], the saturation curves and Scatchard plots shown in Fig. 1 were obtained. Saturation studies were performed by varying concentrations of [^{3}H]-SCH 23390 from 0 to 4 nM. Specific [^{3}H]-SCH 23390 binding saturated at approximately 3 nM in both BUFF (Fig. 1A) and F344 (Fig. 1B) rat brains; and at the concentration used for autoradiography, specific binding accounted for 85% of the total binding. These data are consistent with mass action behavior as indicated by their fit to a least-squares regression line assuming a single [^{3}H]-SCH 23390 binding site. Data from several different experiments were included in the saturation plot. A representative Scatchard plot from one of these experiments is shown in Fig. 1C. Scatchard analysis using the caudate-putamen brain area (Fig. 1C) also showed that the data are in agreement with mass action behavior as a single straight line was obtained ($r=0.95$ for BUFF and 0.99 for F344 rat brains). BUFF and F344 rat brains had a B_{max} (fmol/mg tissue) of 218.12±19.75 and 188.50±18.41 and a K_d (nM) of 1.63±0.15 and 1.56±0.10, respectively ($n=3$). For mapping experiments, a concentration of 1 nM [^{3}H]-SCH 23390 was used to label slide-mounted tissue sections for autoradiography. Results of mapping experiments in the brains from the two rat strains are shown in Table 1. Binding was quantitated as femtomoles of ligand bound/mg of tissue. There were no statistically significant differences in D-1 receptor distribution between brains from Buffalo and F344 rats.

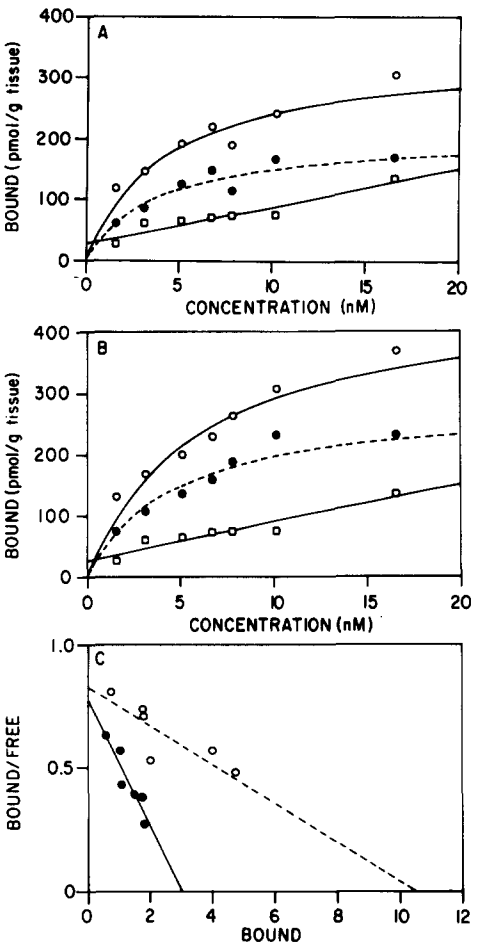

FIG. 2. Saturation and Scatchard analysis of [^{3}H]-sulpiride binding to slide-mounted tissue sections. BUFF (A) and F344 (B) rat tissue sections (same areas as in Fig. 1) were incubated in the presence of various concentrations of [^{3}H]-sulpiride. Nonspecific binding was determined by adding an excess of unlabeled haloperidol to the incubation media. (○) total binding; (□) nonspecific binding; (●) specific binding. (C) Scatchard analysis of the data. (●) BUFF rats; (○) F344 rats. Linear approximation of the slope yielded a K_d of 3.87±0.58 nM and a B_{max} of 3.0±0.57 fmol/mg for BUFF rats and a K_d of 12.72±0.93 nM and a B_{max} of 10.52±1.62 fmol/mg for F344 rats ($n=3$ for each group).

Similar experiments were performed using the ligand [^{3}H]-sulpiride which selectively labels the dopamine D-2 receptor [8]. Saturation curves and a Scatchard plot which also represent data from the caudate-putamen brain area are shown in Fig. 2. Saturation data were obtained by varying concentrations of [^{3}H]-sulpiride from 0 to 20 nM. At the concentration used for autoradiography, specific binding was approximately 66% of total binding. [^{3}H]-Sulpiride saturated its binding site at approximately 10 nM for BUFF rat brains and 15 nM for F344 rat brains (Fig. 2A and B, re-

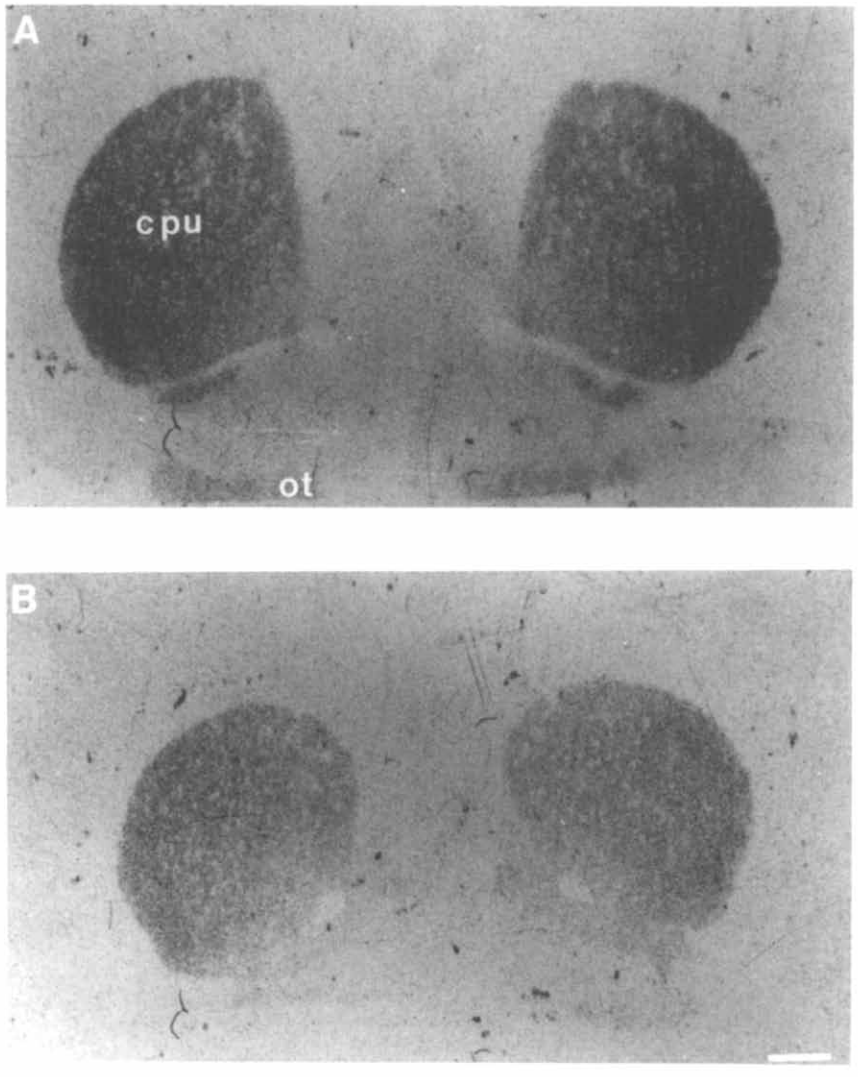

FIG. 3. Localization of [^{3}H]-sulpiride binding sites in F344 (A) and BUFF (B) rat brains. These photomicrographs show the grain distribution of autoradiograms representing total [^{3}H]-sulpiride binding. Note the higher density of autoradiographic grains corresponding to the caudate-putamen (CPu) and olfactory tubercle (OT) in the F344 (A) compared to the BUFF (B) rat brain. Autoradiograms produced by labeling in the presence of 1 μM haloperidol had a uniform grain distribution slightly above background. The level of nonspecific binding was similar in autoradiograms of BUFF and F344 rat brains. Bar=2 mm.

spectively). Data points at concentrations beyond saturation are not included in the Scatchard plot. Both saturation curves (Fig. 2A and B) and Scatchard analysis (Fig. 2C) showed that the data are consistent with mass action behavior for a single [^{3}H]-sulpiride binding site ($r=.93$ for BUFF and .93 for F344 rats). The Scatchard analysis yielded a B_{max} of 3.0±0.57 fmol/mg tissue for BUFF rat brains and 10.52±1.62 fmol/mg tissue for F344 rat brains. This difference was statistically significant, $t(3,3)=5.42$, $p<0.01$. The difference in K_d between brains from the two rat strains (BUFF, 3.87±0.58 nM; F344, 12.72±0.93 nM) was also statistically significant, $t(3,3)=4.97$, $p<0.01$.

Mapping data, obtained by labeling sections with 20 nM sulpiride, are shown in Table 2. There are several areas including the caudate-putamen, olfactory tubercle, and globus pallidus where there are statistically significant differences between BUFF and F344 rat brains. There were no differences between brains from the two rat strains in the cortex, hippocampus or substantia nigra (zona reticulata). An example of [^{3}H]-sulpiride binding sites in BUFF and F344 rat brains is shown in Fig. 3. Consistent with the data in Table 2, there is a higher density of grains representing total [^{3}H]-sulpiride binding in the caudate-putamen and olfactory tubercle of the F344 (A) compared to the BUFF (B) brain section.

DISCUSSION

In the present study, an in vitro autoradiographic technique was used to compare the characteristics of dopamine

D-1 and D-2 receptors in two behaviorally distinct rat strains using the specific ligands [^{3}H]-SCH 23390 and [^{3}H]-sulpiride, respectively. Both ligands obeyed mass action kinetics as has been previously reported [5, 6, 8]. Although no differences between the two groups were observed in [^{3}H]-SCH 23390 labeling of D-1 receptors, the F344 rats displayed higher total [^{3}H]-sulpiride labeling in several forebrain areas including striatum and olfactory tubercle. No differences in [^{3}H]-sulpiride binding were noted in frontal cortex or substantia nigra.

Scatchard analysis revealed that the denser labeling in the striatum was due to an increased B_{max} or density of receptors. In addition, the K_d, which is inversely proportional to the affinity of the ligand for the receptor, is increased in the F344 rat brains. This suggests that although there is an increase in D-2 receptors in the F344 rat brain, those receptors actually have a lower affinity for the D-2 antagonist [^{3}H]-sulpiride. This decrease in affinity is more than compensated for by an increase in the number of receptors and results in an increase in total binding per mg of tissue in F344 compared to BUFF rat brains. In this context, it is interesting that before the increase of D-2 receptors that occurs after the chronic neuroleptic administration, an increase in K_d is observed (Clow *et al.* [1]).

The results of the present study confirm and extend those of Helmeste and colleagues [10] and Rosengarten and colleagues [20]. Helmeste and colleagues [10] used brain homogenate binding assays with the ligand [^{3}H]-spiperone for labeling of the D-2 receptor. They found a significantly higher B_{max} in F344 compared to BUFF rat brains. The K_d was not significantly different in brains from the two groups of animals although it was higher in F344 than in BUFF brains. The increase in D-2 receptor density was correlated with increased behavioral sensitivity to apomorphine, a rather nonselective dopamine agonist. In the present study, a similar increase in D-2 receptor density has been noted and this increase was localized in the caudate-putamen, but not in the substantia nigra. Dopamine D-2 receptors are both pre- and postsynaptic in the caudate putamen, whereas they exist only presynaptically on catecholamine containing neurons (autoreceptors) in the substantia nigra [7].

Rosengarten and colleagues [20], using binding techniques, also reported higher D-2 binding in F344 compared to BUFF rats with no differences in D-1 binding. High D-2 binding was correlated with stereotypy, whereas low D-2 binding was correlated with repetitive jaw movements. They suggest that D-1 receptor dominance produced either pathologically or by drug administration is associated with oral dyskinesias in rats, as is the case in aged animals for example, and postulate that it may play a role in tardive dyskinesia. This hypothesis is supported by the data of Dawbarn and Pycock [4] which suggest that D-1 receptors increase in number following chronic neuroleptic administration and that this increase leads to enhanced oral stereotypy. In addition, D-1 agonists increase oral movements and D-2 agonists decrease oral movements and facilitate hyperactivity [12]. One conclusion from these data would be that an increase in D-2 relative to D-1 receptors leads to hyperactivity, whereas a decrease in D-2 compared to D-1 receptors leads to oral stereotypy [20].

However, results of other studies [1,17] suggest that chronic neuroleptic treatment preferentially increases D-2 receptors [21]. This increase is correlated with gnawing and biting behavior which is thought to be due to activation of striatal rather than mesolimbic dopamine receptors [2]. Although these results seem to be in disagreement with the conclusion suggested above, chronic neuroleptic blockade of dopamine D-2 receptors may conceivably lead to an increase in D-1 receptors relative to D-2 receptors and, therefore, to oral stereotypy. Alternatively, a blockade of D-2 receptors may lead to overstimulation of D-1 receptors and, hence, a relative decrease in the D-2 to D-1 receptor ratio [12].

It is feasible that the quantitative nature of these results could be hampered by tritium quenching due to potential differences in brain white matter content between the two strains [15]. Thus, the D-2 results are more appropriately defined as semiquantitative rather than quantitative. However, the lack of differences in D-1 receptor binding also ascertained using a tritiated ligand in the same areas would indicate that differential quenching of the signal is not occurring in these animals, at least in the areas examined.

To complicate matters, several of the experimental rat behaviors discussed above seem to be localized to different brain areas, for example, locomotor hyperactivity to the mesolimbic area and stereotypy to the nigrostriatal pathway [3, 13, 19]. Also, differential behavioral effects result depending on whether dorsal or ventral striatum is experimentally manipulated [14]. If a change in the ratio of dopamine receptor subtypes is involved, precise quantitative data will be important as different brain regions have different baseline D-2/D-1 ratios. The application of in vitro receptor autoradiography and of behavioral techniques to the study of BUFF and F344 rat strains in combination with administration of stimulants and neuroleptics may provide insight into the neural mechanisms involved in hyperactivity in the experimental setting and in the pathogenesis of childhood ADDH.

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