Pharmacology Biochemistry & Behavior, Vol. 35, pp. 937–942. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Chronic Thioridazine Treatment Differently Affects DA Receptors in Striatum and in Mesolimbo-Cortical Systems

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Received 9 February 1989

PIAZZA, P. V., L. CALZÀ, L. GIARDINO AND G. AMATO. *Chronic thioridazine treatment differently affects DA receptors in striatum and in mesolimbo-cortical systems.* PHARMACOL BIOCHEM BEHAV **35**(4) 937–942, 1990.—Chronic thioridazine administration (5 mg/kg for 22 days) caused both behavioral and dopamine (DA) receptor modifications in rats. After chronic thioridazine administration, a significant increase in both locomotion and stereotypies induced by apomorphine was observed. In particular, only sniffing increased significantly, whereas grooming behavior decreased and the number of rearings did not change. Autoradiographic data were consistent with the behavioral results. Chronic thioridazine caused an up-regulation of DA receptors both in the striatum and in the olfactory tubercle (O.T.). The striatal effect may account for the increase of stereotypies, whereas the effect in the olfactory tubercle may account for the increase in locomotion. An increase in DA receptors was also found in the medial (MCTX) and dorsal cortex (DCTX). However, a decrease in DA receptors appeared in the nucleus accumbens septi (NAS) and in the lateral cortex (LCTX). This decrease, selectively localized in the mesolimbic DA system, may represent the neurobiological substrate of the depolarization block observed in A10 neurons after chronic thioridazine treatment.

Thioridazine Dopamine Mesolimbic-mesocortical DA system Apomorphine Antipsychotic effect DA receptors

NEUROLEPTICS which are currently used as antipsychotic drugs, primarily act by blocking central dopamine (DA) receptors (13,14). These drugs have been divided into typical and atypical according to their clinical and experimental effects. The typical ones, which include haloperidol, chlorpromazine and fluphenazine, significantly decrease stereotyped behavior induced by DA agonists, elicit catelepsy (11, 28, 41) and produce extrapyramidal side effects (10,30). The atypical ones which include sulpiride, thioridazine and clozapine, inhibit locomotion induced by DA agonists (28,41), whereas they inhibit less the stereotypies, and do not produce extrapyramidal side effects (10, 20–22, 34) or catalepsy (11,41). These different effects indicate that typical neuroleptics could act predominantly on the DA neurons of area A9 and the atypical ones on mesolimbic-mesocortical structures. This is also supported by the functional studies of the mesencephalic A9 and A10 DA systems (5, 23, 25, 35, 37). However, both typical and atypical compounds show antipsychotic properties that have been attributed to their action on the mesolimbic-mesocortical DA system (9, 15, 31, 32, 39). Their interaction with the nigrostriatal system is suspected of inducing extrapyramidal side effects (1). Among the atypical neuroleptics thioridazine, a piperidine side-chain phenothiazine derivate, has been widely studied using both in vivo voltammetry (7, 27, 29) and electrophysiological (8, 9, 37, 40) techniques. Acute administration of this drug increases DA release in the nucleus accumbens septi (NAS) but not in the striatum (27), augmenting the neuronal firing only in A10 neurons (8,40). Chronic administration of thioridazine induces a decrease in DA release in the NAS but not in the striatum (7), and decreases the neuronal firing only in A10 DA neurons (8,40).

Data concerning the chronic action of neuroleptics are important because the therapeutic effects of these drugs appear only after a latency period of several weeks (4,12). Since the substrate of neuroleptic action is the DA receptor (13,14), it may be that DA receptor modifications could be responsible for the described electrophysiological, biochemical and therapeutic effects. Therefore, an experiment has been performed to study possible modifications of the DA-2 receptors in the projection areas of A9 and A10 neurons (6) after chronic treatment with thioridazine. Quantitative receptor autoradiography was used to determine the precise anatomical location of the drug effects. Hypersensitivity to apomorphine has been used as an index of thioridazine-induced DA receptor supersensitivity.

METHOD

Animals

Adult (225–250 g body weight), male, pathogen-free Sprague-

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Dawley (Charles River, Calco, Varese, Italy) rats were used (n = 36). The animals were maintained with a standard light/dark cycle (light on 8.00 a.m., off 8.00 p.m.), and fed ad lib with food pellets and water.

Behavioral Procedure

The test box (l 40 × w 40 × h 80 cm) in which the experiments were performed was in a sound-proof environment, maintained at constant illumination and temperature. All tests were performed in a 4-hr daily period (1 p.m. to 5 p.m.). Each animal was allowed 1 hr to habituate in the box the day before the pharmacological test and 10 min to habituate before drug administration. Locomotor and stereotyped behaviors were studied after inoculation with apomorphine (Sigma, 1 mg/kg in 1 ml saline IP) (n = 24) and saline (NaCl 0.9%, 1 ml IP). Behavior was recorded on video tape for 2 min every 5 min, starting 5 min after drug inoculation and continuing for 1 h. Tapes were analyzed during playback; time displayed on the monitor during recording permitted assessing duration of the studied behaviors. Quantification of the stereotypies was carried out determining the duration (sec) of chewing, sniffing, gnawing and licking and the number of rearings. Grooming duration was also analyzed, because grooming is considered a control behavior that decreases when stereotypies increase. Locomotor activity was calculated on the basis of the number of lines crossed. Two days after the apomorphine test, the animals were randomly divided into two groups and treated chronically with saline (n = 12) 0.9% NaCl (0.2 cc) or with thioridazine (n = 12) 5 mg/kg (in 0.2 cc saline) orally administered for 22 days. After a washout period of 5 days the effects of apomorphine administration on the two groups were tested by the procedure previously described.

The behavioral data collected following apomorphine injection and obtained from the 2 groups after chronic treatment were compared using the Mann-Whitney U-test, and with the data recorded before treatment, using the Wilcoxon matched-pairs signed-rank test.

Autoradiographic Procedure

A group of animals (n = 12) was chronically treated once daily for 22 days with either orally administered 5 mg/kg thioridazine dissolved in 0.2 cc saline (n = 6) or with 0.2 cc saline solution (n = 6). The treatment was carried out at 9.00 a.m. and the withdrawal period lasted for 5 days (14).

Preparation of the Tissue

Under ketamine (10 mg/kg) anaesthesia, the rats were killed by perfusion through the ascending aorta with 100 ml saline solution (50 ml at 37°C + 50 ml 4°C), followed by 100 ml 0.1% paraformaldehyde in PBS pH 7.4. During the perfusion the rats were kept in an ice-water bath. After 5 min of perfusion, the brains were quickly removed, frozen and sectioned in a cryostat (−25°C, 20 μm thickness). Alternating sections were kept for total and unspecific binding, at the rostro-caudal level A8620 according to the König and Klippel stereotaxic atlas (26).

Receptor Autoradiography

The sections were incubated with ^{3}H-spiperone (4 nM) (NEN, Boston, USA; spec.act. 23.2 Ci/mmol) in 170 mM Tris-HCl buffer, pH 7.4, containing 120 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$ for 60 min at room temperature. Binding of ^{3}H-spiperone to 5HT-2 receptors was prevented by adding 50 nM ketanserin to the assay buffer. The ^{3}H-spiperone binding to DA receptors was assessed in the presence of 1 μM cold (+) butaclamol. Both series of slides were rinsed with two washes in the buffer at 4°C for 10 min each, followed by one wash in bidistilled water, buffered with Tris-HCl, pH 7.5 (4°C, 1 min). After 6 weeks exposure, the films (Amersham, ^{3}H-Hyperfilm) were developed using Kodak D-19 developer.

Analysis of the Results

The analysis of the results was carried out by means of the computerized microdensitometry, using the Tesak VDC 501 image analyzer, equipped with the Digital PDP 11 computer (16). The main steps required by the software procedure were the following: 1) loading of the image through a standard black and white TV camera; 2) standardization of the image according to two (light and dark) reference grey tones; 3) conversion of the grey tones range of the autoradiogram into the grey tones scale of the image analyzer (from 0 = black to 256 = white); 4) selection of the sampling area on the TV screen through a magnetic pen; 5) subtraction of the background value from each measurement; 6) conversion of the optical density values into pmol/mg protein, according to the standard ^{3}H-microscale (Amersham, England). Specific binding of ^{3}H-spiperone was defined as the difference between total ^{3}H-spiperone bound and ^{3}H-spiperone bound in the presence of 1 μM (+)butaclamol. In each animal and for each level three consecutive sections were measured. Analysis of the variance (ANOVA) and the Dunnett test were used for the statistical analysis of the autoradiographic data.

RESULTS

The effects of chronic treatment with thioridazine were studied in light of 1) the modifications of apomorphine-induced behavior; 2) DA receptor changes.

Effects of Thioridazine Chronic Treatment on Apomorphine-Induced Behavior

Acute apomorphine administration (1 mg/kg IP in 1 ml saline) resulted in behavioral differences when compared with the saline control group (Table 1). Whereas locomotion was not affected, stereotypies were significantly greater. Of the stereotypies sniffing, licking, chewing and gnawing were significantly greater and grooming was significantly less; there was no significant difference in rearings scores.

Figure 1 shows the effects of chronic thioridazine and saline treatment on apomorphine-induced behavior. Animals chronically treated with thioridazine show a significantly greater duration of sniffing relative to both the behavior recorded before the chronic treatment (T = 5, $p<0.005$, Wilcoxon matched-pairs signed-ranks test) and to animals treated with chronic saline (U = 14, $p<0.001$ Mann-Whitney U-test). No significant differences were observed between postsaline and pretreatment conditions.

Figure 2 shows the effects of chronic thioridazine treatment on apomorphine-induced locomotion. The drug provokes a significant increase in locomotor activity in the final 15-min observation. These differences were statistically significant both when compared with animals treated with chronic saline and with locomotion evaluated before chronic treatment. After chronic saline treatment, locomotion did not change. Following chronic thioridazine treatment duration of grooming significantly decreased ($p = <0.046$), whereas the number of rearings did not change (data not shown).

DA Receptor Modifications After Thioridazine Chronic Treatment

The analysis of the autoradiographic results was carried out in

TABLE 1

BEHAVIORAL EFFECTS OF ACUTE APOMORPHINE ADMINISTRATION (1 mg/kg IP)

Behaviors	Saline (n = 12) A ± SEM	Apomorphine (N = 24) A ± SEM	z	p
Forward Locomotion*	14.47 ± 2.53	13.57 ± 1.73	0.41	—
Stereotypies				
Rearing†	3.14 ± 0.42	3.00 ± 0.37	0.27	—
Gnawing‡	21.25 ± 4.86	49.60 ± 7.24	2.01	<0.022
Chewing‡	15.31 ± 1.71	101.20 ± 8.63	4.75	<0.001
Sniffing†	54.42 ± 5.62	410.00 ± 17.04	4.63	<0.001
Licking‡	6.55 ± 0.99	207.00 ± 10.14	5.10	<0.001
Grooming‡	125.38 ± 7.02	60.57 ± 4.77	3.42	<0.001

*Average ± SEM distance (arbitrary units) covered during locomotion by the rats; †Average ± SEM number of rearings; ‡Average ± SEM duration in sec of stereotypies. Statistical analysis was performed by means of the Mann-Whitney U-test.

order to separately measure the target regions of mesostriatal and mesolimbo-cortical DA systems at three different rostrocaudal levels (A9410, A8620 and A7890) according to the König and Klippel stereotaxic atlas of the rat (26). At all rostro-caudal levels, the cerebral cortex was divided into 3 portions: medial, dorsal and lateral, respectively, corresponding to the cingulate cortex, the frontoparietal motor cortex and the frontoparietal somatosensory cortex. The region of the basal ganglia was divided into the olfactory tubercle (OT), nucleus accumbens (NAS) and six portions of the striatum: dorso-medial (DM), dorso-central (DC), dorso-lateral (DL), ventro-medial (VM), ventro-central (VC) and ventro-lateral (VL) (Fig. 3). The quantitative analysis of the autoradiograms showed a significant difference between ^{3}H-spiperone binding in treated and untreated animals, $F(1,10) = 144$,

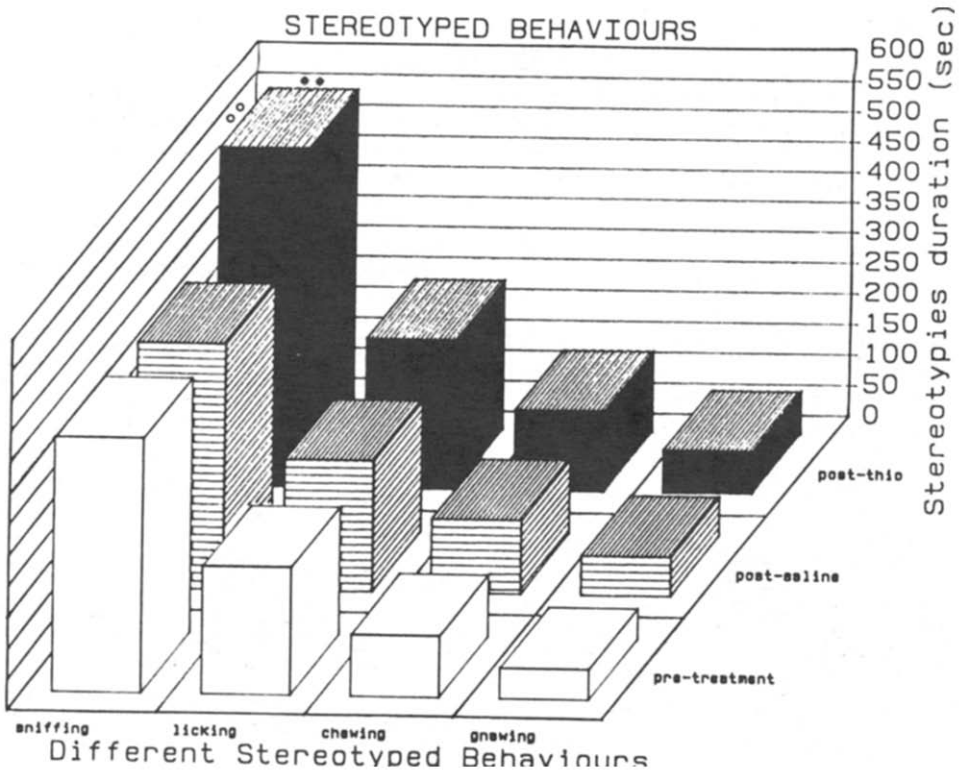

FIG. 1. Durations (in sec) of different stereotypies induced by apomorphine (1 mg/kg in 1 ml saline IP), before (blank bars) and after chronic treatment with saline 0.9% NaCl (hatched bars) or with thioridazine (5 mg/kg) (black bars). **$p<0.001$; Mann-Whitney U-test (compared to saline-chronic treatment). °$p<0.005$ Wilcoxon matched-pair signed-rank test (compared to pretreatment data).

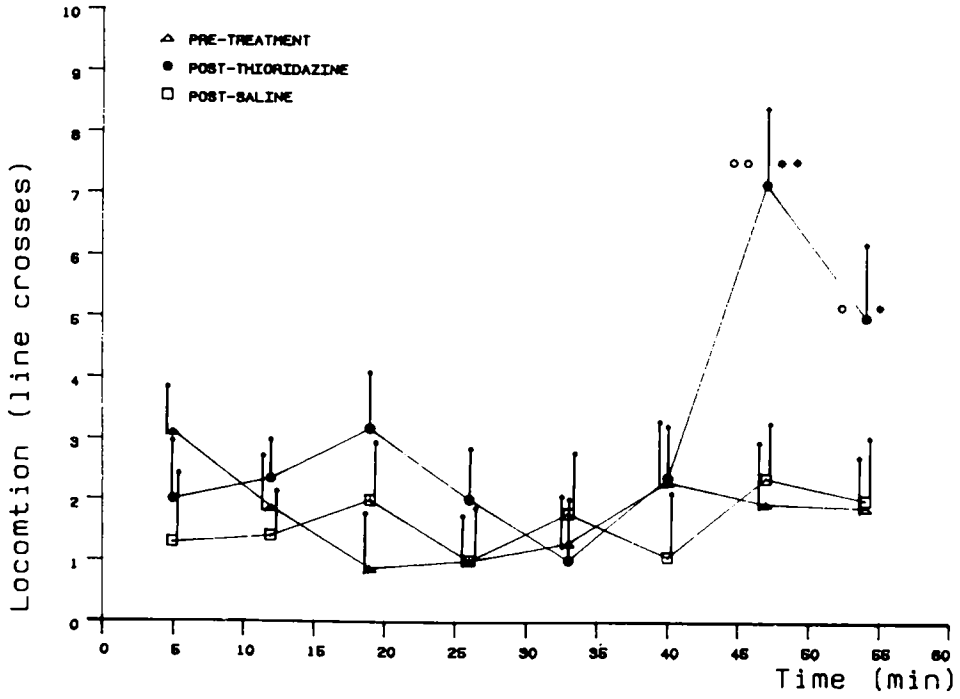

FIG. 2. Time-course of locomotor activity (number of line crosses ± SEM) induced by apomorphine (1 mg/kg in 1 ml saline IP) before (triangles) and after chronic treatment with saline 0.9% NaCl (blank squares) or with thioridazine (5 mg/kg) (circles). $*p<0.01$; $**p<0.005$, Mann-Whitney U-test (compared to saline chronic treatment). $°p<0.01$; $°°p<0.005$, Wilcoxon matched-pair signed-rank trest (compared to pretreatment data).

$p<0.001$. Table 2 shows significantly more DA receptors in the medial cortex at the three levels studied and more in the dorsal cortex at the most anterior level (A9410). Fewer DA receptors appear in the lateral cortex at all levels. In the nucleus accumbens, there were significantly fewer DA receptors. In the dorsal and in ventro-lateral striatum there were more DA receptors, while in the ventro-central and in the ventro-medial regions there were no differences between control and thioridazine treatment. Finally, DA receptors were significantly more numerous in the olfactory tubercle.

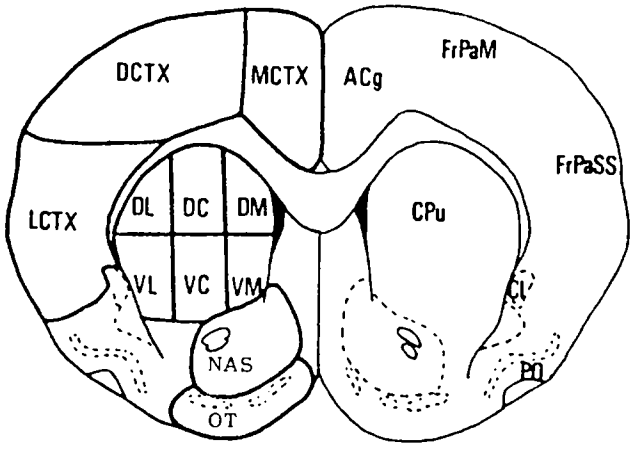

FIG. 3. Sampling scheme used in the analysis of the results. MCTX: medial cerebral cortex; ACg: anterior cingulate cortex; DCTX: dorsal cortex; FrPaM: frontoparietal motor cortex; LCTX: lateral cortex; FrPaSS: fronto parietal somatosensory cortex; Cl: claustrum; CPu: caudato putamen; DC: dorso-central striatum; DL: dorso-lateral striatum; DM: dorso-medial striatum; VC: ventro-central striatum; VL: ventro-lateral striatum; VM: ventro-medial striatum; NAS: nucleus accumbens; PO: primary olfactory area; OT: olfactory tubercle.

DISCUSSION

Chronic thioridazine administration causes a behavioral supersensitivity to apomorphine, i.e., an increase in both locomotion and stereotypies, which suggests that thioridazine acts both on the nigro-striatal DA system, that is thought to be responsible for stereotypies, and on the mesolimbic mesocortical DA system that is thought to be responsible for locomotion. However, the effect of thioridazine on stereotyped behavior compared with that observed after typical neuroleptic administration (28,41) appears to be weaker, in that among the studied stereotypies, only sniffing was greater. DA receptor differences revealed by the autoradiographic study after chronic thioridazine treatment are in agreement with the observed behavioral supersensitivity: the greater number of DA receptors in the dorsal and ventro-lateral striatum, which receive fibers from A9 neurons, could be responsible for increases in sniffing; while the greater number of DA receptors in the olfactory tubercle and/or in the medial and central cortex could be responsible for the greater degree of locomotor activity. Although the modification of DA receptors is evident both in the O.T. and in the cerebral cortex, it needs to be pointed out that the number of DA-2 receptors in O.T. is greater than in the cortex: the O.T. seems more involved in the control of the locomotor activity (18, 19, 24); moreover, the time course of the locomotor activity shown in our results is similar to that observed in animals with 6-OHDA lesion of the O.T. (18).

The partial inhibition of apomorphine-induced stereotypies and

TABLE 2

MODIFICATIONS OF ^{3}H-SPIPERONE BINDING SITES INDUCED BY CHRONIC TREATMENT WITH THIORIDAZONE (5 mg/kg ORALLY ADMINISTERED FOR 22 DAYS)

	^{3}H-Spiperone (pmol/mg protein)	
Brain Region	Saline	Thioridazine
A9410		
MTCX	0.074 ± 0.012	0.338 ± 0.023†
DCTX	0.104 ± 0.017	0.133 ± 0.011*
LCTX	0.081 ± 0.012	0.045 ± 0.007†
DM	0.387 ± 0.028	0.546 ± 0.083*
DC	0.626 ± 0.103	0.988 ± 0.089†
DL	0.892 ± 0.178	1.437 ± 0.051†
VM	0.225 ± 0.042	0.281 ± 0.059
VC	0.531 ± 0.101	0.579 ± 0.050
VL	0.631 ± 0.073	1.118 ± 0.062†
NAS	0.278 ± 0.041	0.074 ± 0.012†
OT	0.598 ± 0.062	1.134 ± 0.197*
A8620		
MTCX	0.068 ± 0.008	0.101 ± 0.009*
DCTX	0.127 ± 0.018	0.139 ± 0.014
LCTX	0.116 ± 0.011	0.042 ± 0.006†
DM	0.372 ± 0.013	0.648 ± 0.074*
DC	0.571 ± 0.043	1.136 ± 0.087†
DL	0.802 ± 0.072	1.926 ± 0.149†
VM	0.236 ± 0.058	0.318 ± 0.051
VC	0.312 ± 0.056	0.362 ± 0.071
VL	0.523 ± 0.061	1.218 ± 0.094†
NAS	0.225 ± 0.018	0.132 ± 0.028*
OT	0.398 ± 0.042	0.835 ± 0.096*
A7890		
MTCX	0.013 ± 0.012	0.154 ± 0.025*
DCTX	0.120 ± 0.005	0.121 ± 0.015
LCTX	0.047 ± 0.002	0.032 ± 0.002†
DM	0.432 ± 0.025	0.541 ± 0.074
DC	0.388 ± 0.062	0.487 ± 0.098
DL	1.082 ± 0.163	1.816 ± 0.168†
VM	0.226 ± 0.012	0.284 ± 0.032
VC	0.301 ± 0.032	0.392 ± 0.037*
VL	0.740 ± 0.103	1.017 ± 0.087*

The values of the optical density were converted into molar quantities of bound ligands using a metacrilate standard scale (Amersham). The unspecific binding [cold (+)butaclamol] was substracted to each value. The results are expressed as mean (±SEM). The statistical analysis was carried by the Dunnett test, after ANOVA.

*$p = <0.01$; †$p = <0.001$. See text for abbreviation.

the less pronunced elevation in striatal DA (7,29) probably reflect the weaker antidopaminergic and greater anticholinergic activity of thioridazine relative to other neuroleptics (33). The different DA-ergic and cholinergic balance induced by thioridazine respect to other neuroleptics could be responsible for its atypical spectrum activity.

Indeed, chronic thioridazine administration is associated with a down-regulation of DA receptors in the NAS and in the LCTX, which is in agreement with biochemical and electrophysiological data. Acute thioridazine administration increases DA release in the NAS but not in the striatum probably through autoreceptors of A10 neurons (27) and induces a corresponding activation of the neuronal firing of A10 but not of A9 neurons (8,40). The greater availability of the neurotransmitter in the NAS could therefore be responsible for the receptor down-regulation in this nucleus. The down-regulation observed in the LTCX is more difficult to explain because the existence of autoreceptors in this region has been questioned (2, 3, 17).

On the other hand, DA receptor down-regulation observed in the NAS and in the LCTX could explain the depolarization block of A10 neurons claimed to be responsible for the therapeutic effects of neuroleptics (38). In fact, thioridazine binding with autoreceptors in A10 cells could release them from their self-inhibition and the decrease in DA receptors in NAS neurons could reduce their sensibility to DA, which normally activates the inhibitory loop from NAS to A10 neurons (36). These two combined effects could result in the depolarization block of A10 neurons observed after thioridazine chronic treatment (8, 9, 40).

Our autoradiographic data seem to confirm a specific action of the atypical neuroleptic thioridazine on mesolimbic mesocortical DA system; this emphasizes the importance of DA receptor decrease as a possible anatomical substrate for the selective inactivation of A10 neurons. Moreover, the different changes in DA receptors observed after chronic thioridazine in the projection areas of A9 and A10 neurons (dorsal vs. ventral striatum, NAS vs. O.T., medial vs. lateral cortex) underline the need for a thorough functional and pharmacological investigation of each projection area of the mesencephalic DA systems, in order to understand the role played by A10 neuronal inactivation in inducing antipsychotic effects of neuroleptics.

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