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EFFECTS OF BUSPIRONE ON DOPAMINERGIC SUPERSENSITIVITY

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Summary

The effects of buspirone treatment on dopaminergic supersensitivity induced by long-term haloperidol administration were studied; both spontaneous activity (locomotion and rearing frequencies) of rats observed in an open-field and apomorphine-induced stereotypy were used as experimental parameters. Buspirone *per se* (3.0 mg/kg, twice daily, for 30 days) did not produce dopaminergic supersensitivity. When buspirone was given in combination to haloperidol (2.0 mg/kg, once daily, for 30 days), it decreased the neuroleptic withdrawal symptoms as detected in open-field behavior but not in apomorphine-induced stereotypy. Although single administration of buspirone *per se* decreased both open-field and apomorphine-induced stereotypy behavior, buspirone single administration did not modify the acute effects of haloperidol on these two behavioral models. Taken together with previous behavioral results showing that buspirone reverses haloperidol-induced catalepsy, the present data suggest that buspirone co-administration may lead to important clinical advantages concerning different extrapyramidal side effects of neuroleptic treatment.

Key Words: haloperidol, buspirone, dopaminergic supersensitivity, open-field stereotypy, stereotypy

In rats, abrupt withdrawal from long-term haloperidol (1,2,3), bromopride (4), metoclopramide (5), sulpiride (6) and droperidol (7) treatment not only enhanced general activity observed in an open-field but also the responses to apomorphine-induced stereotyped behavior. These effects have been considered to be a consequence of the development of supersensitivity of central dopaminergic (DA) pathways (8). In this regard, the induction of dopamine receptor supersensitivity by repeated administration of neuroleptic drugs in rodents seems to be related to the emergence of drug-induced extrapyramidal side effects such as tardive dyskinesia in humans (9,10). Indeed, although this hypothesis is not universally accepted (one of the reasons, for

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instance, is the fact that the time course for DA-2 receptor sensitivity during neuroleptic administration is much much shorter than the time for induction of tardive dyskinesia), it has dominated the conceptual approaches to studying tardive dyskinesia over the last decades (11).

In recent years, nonbenzodiazepine anxiolytics have joined benzodiazepines on the anxiolytic market. One such agent is buspirone, a pyrimidinylpiperazine derivative, which is structurally unrelated to the benzodiazepines (12). In fact, buspirone has no affinity for benzodiazepine-GABA receptor complex (13) but shows high affinity for dopaminergic and serotoninergic binding sites (14,15). Several lines of pharmacological evidence have indicated that the dopaminergic activity of buspirone cannot be considered to be that of a typical neuroleptic, although buspirone shares some biochemical effects with these drugs (16). Indeed, as is the case for classical neuroleptics, acute buspirone administration raises striatal levels of the dopamine metabolites homovanillic acid and dihydroxyphenylacetic acid (14). On the other hand, in contrast to typical neuroleptics the drug does not modify the levels of 3-methoxytyramine, the extraneuronal metabolite of dopamine (14,16) and decreases dopamine concentration in striatal tissue (16). In addition to these unique biochemical effects we have found that buspirone also presents unique pharmacological effects in behavioral terms involving dopaminergic transmission. In fact, the drug was able to reduce apomorphine-induced yawning and stereotyped behavior (indicating a dopaminergic antagonist activity), but also inhibited haloperidol-induced catalepsy (suggesting a dopamine agonist property) (17).

In the work presented here, using both general activity of rats observed in an open-field and apomorphine-induced stereotyped behavior as experimental parameters, we have examined the possible development of behavioral supersensitivity after long-term administration of buspirone. The influence of buspirone treatment on haloperidol-induced supersensitivity was also studied. Finally, we have tried to verify the relationships between buspirone and haloperidol effects on open-field behavior and on apomorphine-induced stereotypy after single drug administration.

Materials and Methods

Subjects

Genetically similar male Wistar rats weighing 250 - 300 g and about 90 days of age were used at the beginning of the experiments. Groups of 5 animals were kept in Plexiglass cages with free access to food and water in a room with controlled temperature (22 ±1 °C) and in a 12 h light/dark cycle with lights on at 7:00 am. The animals were maintained and used in accordance to the guidelines of the Committee on Care and Use of Experimental Animal Resources, School of Veterinary Medicine and Animal Science of the University of São Paulo, Brazil.

Drugs and treatment

Buspirone (RBI) and apomorphine hydrochloride (Merck) were freshly diluted in distilled water. NaCl 0.9% was used as buspirone control solution. Haloperidol (Cristalia, Brazil), was suspended in 0.9% NaCl plus tween-80 (3-4 drops). The control solution for haloperidol was 0.9% NaCl plus tween-80. The drugs and saline were administered intraperitoneally (except apomorphine that was used subcutaneously) in the volume of 1.0 ml/kg body weight.

Behavioral measures

The open-field was constructed as described by Broadhurst (18) and rats were observed individually. Hand-operated counters were employed to score ambulation frequency (number of floor units entered) and rearing frequency (number of times the animal stood on hind legs). The open-field was washed with a solution of water and alcohol (5.0 %) before the placement of the animals to obviate possible bias due to odor clues left by previous subjects. To avoid differences in the open-field behavior of experimental and control groups of rats due to circadian changes, experimental and control observations were alternated.

The animals were observed for stereotyped behavior in wire mesh cages (16 x 30 x 19 cm) without food and water. Stereotypy was quantified every 10 minutes for 100 minutes after apomorphine administration (0.6 mg/kg). The 0.6 mg/kg apomorphine dose was used because previous experiments performed in our laboratory showed that the stereotypy induced by this dose can be easily antagonized or potentiated. Stereotypy was quantified according to the scoring system proposed by Setler et. al. (19). Briefly, scores varying from 0 to 6 were attributed to the animal's behavior. The grading system was as follows: 0, asleep or stationary; 1, active; 2, predominantly active but with bursts of stereotyped sniffing and/or rearing; 3, constant stereotyped activity such as sniffing or rearing but with locomotion activity still present; 4, constant stereotyped activity maintained in one location; 5, constant stereotyped activity but with bursts of licking and/or gnawing and biting; 6, continually licking and/or gnawing of cage grids. This criterion was not subjective, as shown by the excellent scoring agreement (Pearson's correlation, $v=0.98$) of two different and independent observers. The total sum of stereotypy scores obtained for each animal during the 100 min observation period was used to obtain the mean value of stereotypy scores within each group.

Procedure

Three experiments were performed. In the first and second experiments, buspirone and haloperidol were acutely administered. In both experiments rats were divided randomly into 4 groups of 12 animals each, which received acutely two injections of saline (SAL+SAL group), 3.0 mg/kg buspirone + saline (BUS+SAL group), saline + 2.0 mg/kg haloperidol (SAL+HAL group) and 3.0 mg/kg buspirone + 2.0 mg/kg haloperidol (BUS+HAL group). Saline or buspirone were administered 30 min prior to saline or haloperidol. Thirty minutes after the second injection, rats were placed individually in the center of the open-field arena for observation of behavioral parameters (first experiment) or were injected with apomorphine (0.6 mg/kg) for observation of stereotyped behavior (second experiment).

In the third experiment, buspirone and haloperidol were long-term administered to the animals. Thus, rats were divided at random into 4 groups of 12 animals each, which, in the morning (8:00 a.m.) received either two injections of saline (SAL+SAL group), buspirone and saline (BUS+SAL group), saline and haloperidol (SAL+HAL group) and buspirone and haloperidol (BUS+HAL group). In the afternoon (5:00 p.m.) the animals of the SAL+SAL and SAL+HAL groups received only a saline injection and the rats of the BUS+SAL and BUS+HAL groups received only a buspirone injection. Buspirone was administered at the same dose (3.0 mg/kg) both in the morning and in the afternoon. In the morning, it was administered 30 min prior to haloperidol (2.0 mg/kg) or saline. This protocol of treatment was performed for 30 consecutive days. On the morning of the 30th day the rats received their last saline/buspirone and saline/haloperidol injections and, 30 min after the second injection (saline or haloperidol), they

were placed individually in the center of the open-field arena for observation of behavioral parameters over a period of 5 min. This procedure was also performed 24, 48, 72, 480 and 720 h after withdrawal. Seventy-six, 484 and 724 h after withdrawal, i.e., 4 h after the three last open-field sessions, rats of all groups were injected with apomorphine (0.6 mg/kg) and were observed for stereotyped behavior. Since open-field and stereotypy were evaluated in the same animals in this experiment, it might be speculated that the alternation between the two experimental tests could lead to behavioral interactions. However, we have verified that previous exposure (5 minutes) to an open-field does not modify apomorphine- (0.6 mg/kg, s.c.) induced stereotypy, evaluated four hours later. In addition, previous exposure to apomorphine- (0.6 mg/kg, s.c.) induced stereotypy did not modify open-field behavior of rats observed 48 hours later (unpublished data).

The three experiments were conducted blind and each rat was used in only one experiment. Buspirone and haloperidol doses were selected on the basis of our previous study (17) in which 3.0 mg/kg buspirone was able to reduce significantly both apomorphine-induced stereotypy and 2.0 mg/kg haloperidol-induced catalepsy. In the third experiment, buspirone was administered twice daily because of its short half-life (30 minutes in the rat) (20).

Statistical analysis

Since homocedasticity is necessary for the analysis of variance, Bartlet's test was applied to the open-field data. It was concluded that all results were parametric. Thus, an analysis of variance (ANOVA) followed by Duncan's test was used to study locomotion and rearing frequencies observed in the acute experiments and a two-way analysis of variance, followed by Duncan's test was used to study open-field data observed in the long-term experiments. The mean values of the stereotypy scores were treated by Kruskal-Wallis analysis of variance for non-parametric data followed by the two-tailed Mann-Whitney U-test. A probability of $p < 0.05$ was considered to show significant differences for all comparisons made.

<u>Results</u>

First experiment

The effect of single buspirone and/or haloperidol treatments on the open-field behavior of rats is shown in Fig.1 (A). In relation to the control (SAL+SAL) group, both locomotion [$F_{(3,44)} = 70.1$; $p < 0.05$] and rearing frequencies [$F_{(3,44)} = 54.0$; $p < 0.05$] were reduced in the BUS+SAL, SAL+HAL and BUS+HAL groups. Rats of the SAL+HAL and BUS+HAL groups also showed a significant decrease in locomotion and rearing frequencies when compared to those of the BUS+SAL group ($p < 0.05$). However, no differences in locomotion and rearing frequencies were observed between the SAL+HAL and the BUS+HAL groups.

Second experiment

Figure 1 (B) shows the effect of single buspirone and/or haloperidol treatment on apomorphine-induced stereotyped behavior. Rats of the BUS+SAL, SAL+HAL and BUS+HAL groups showed a significant decrease in the stereotypy scores when compared to that of the animals of the control (SAL+SAL) group (H=22.7; $p < 0.05$). In relation to the BUS+SAL group, the stereotypy scores were also significantly reduced in the SAL+HAL and BUS+HAL groups

(p<0.05). As observed for open-field behavior, there was no significant difference in stereotypy intensity between the SAL+HAL and the BUS+HAL groups.
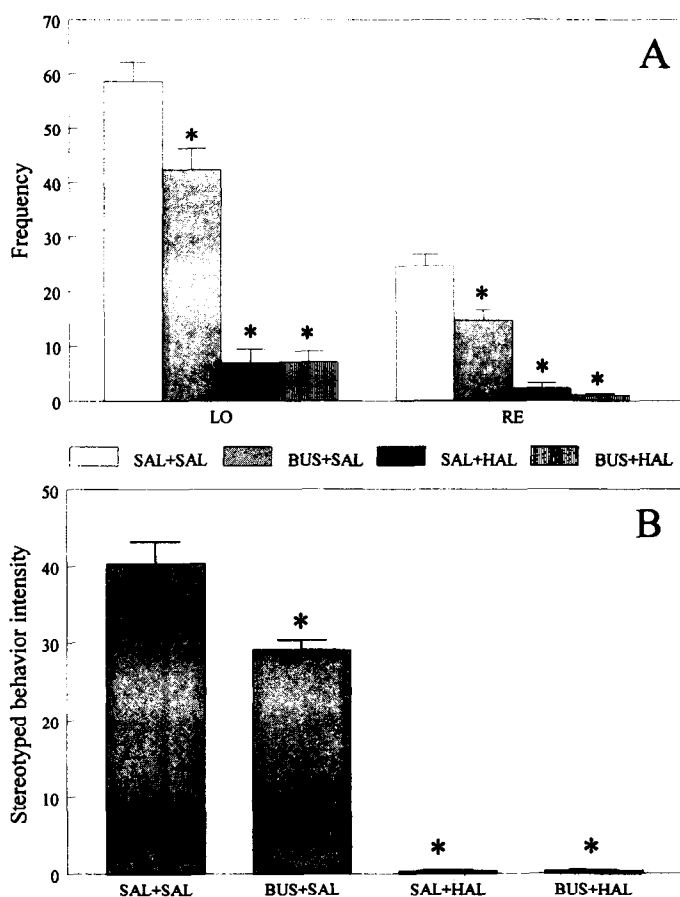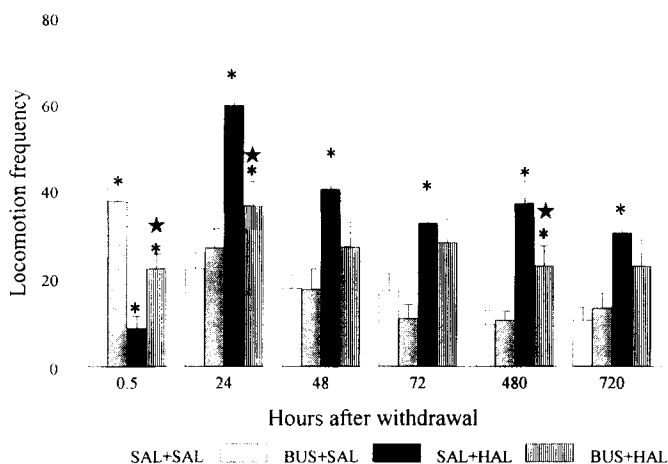

Fig.1
Effects of single administration of buspirone (BUS, 3.0 mg/kg) or saline (SAL) plus haloperidol (HAL, 2.0 mg/kg) or saline on locomotion (LO) and rearing (RE) frequencies of rats observed in an open-field (A), as well as on the stereotyped behavior induced by 0.6 mg/kg apomorphine (B). Data are reported as the mean ± SEM.
* p<0.05 compared to the SAL+SAL group (analysis of variance, Duncan's test for open-field data and Kruskal-Wallis analysis of variance followed by two-tailed Mann-Whitney U-test for stereotypy data).

Third experiment

The open-field behavior of rats abruptly withdrawn from long-term buspirone and/or haloperidol treatments are shown in Fig.2 (locomotion frequency) and in Fig.3 (rearing frequency). Concerning locomotion frequency, two-way ANOVA (with group as a between-

Fig.2

Effects of withdrawal from long-term administration (30 days) of buspirone (BUS, 3.0 mg/kg) or saline (SAL) plus haloperidol (HAL, 2.0 mg/kg) or saline on locomotion frequency of rats observed in an open-field. Data are reported as the mean ± SEM.
* p<0.05 compared to the SAL+SAL group,
★ p<0.05 compared to the SAL+HAL group (two-way ANOVA, Duncan's test).
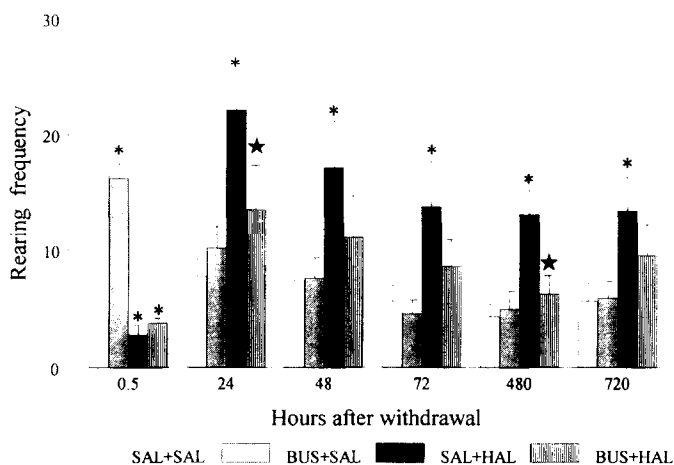
Fig.3

Effects of withdrawal from long-term administration (30 days) of buspirone (BUS, 3.0 mg/kg) or saline (SAL) plus haloperidol (HAL, 2.0 mg/kg) or saline on rearing frequency of rats observed in an open-field. Data are reported as the mean ± SEM.
* p<0.05 compared to the SAL+SAL group,
★ p<0.05 compared to the SAL+HAL group (two-way ANOVA, Duncan's test).

subject factor and observation sessions as within-subject factor) revealed significant group $[F(3,44)=6.25$, p<0.01], sessions $[F(5,220)= 12.42$, p<0.001] and group x session interaction $[F(15,220)= 11.15$, p<0.01] effects. As regards rearing frequency, two-way ANOVA revealed significant session $[F(5,220)=6.35$, p<0.01] and group x session interaction $[F(15,220)= 9.06$,

p<0.01] effects. Post hoc analysis revealed that thirty minutes after the last injection of their respective treatments, both locomotion and rearing frequencies were reduced in the BUS+SAL, SAL+HAL and BUS+HAL groups, in relation to the control (SAL+SAL) group. In this first session, buspirone co-treatment reduced significantly the decrease in locomotion frequency produced by the haloperidol treatment (rats of the BUS+HAL group had higher locomotion frequency when compared to the animals of the SAL+HAL group). Repeated haloperidol treatment was able to induce dopaminergic supersensitivity. Indeed, in relation to the SAL+SAL group, rats of the SAL+HAL group showed a significant increase in locomotion and rearing frequencies 24, 48, 72, 480 and 720 hours after withdrawal. Long-term treatment with buspirone *per se* did not induce dopaminergic supersensitivity since no significant differences in locomotion and rearing frequencies were observed between the BUS+SAL and SAL+SAL groups. Finally, buspirone co-treatment reduced significantly the behavior manifestations of the haloperidol-induced dopaminergic supersensitivity. Indeed, in relation to the SAL+SAL group, rats of the BUS+HAL group showed a significantly higher locomotion frequency only in sessions performed 24 and 480 h after withdrawal, and no significant differences in rearing frequencies were observed. In addition, in relation to the SAL+HAL group, animals of the BUS+HAL group showed decreased locomotion and rearing frequencies during all the withdrawal period, reaching statistical significance in sessions performed 24 and 480 h after withdrawal.
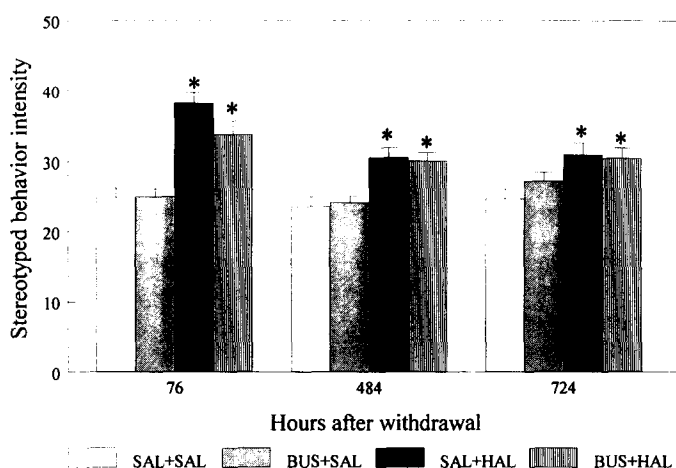

Fig.4
Effects of withdrawal from long-term administration (30 days) of buspirone (BUS, 3.0mg/kg) or saline (SAL) plus haloperidol (HAL, 2.0 mg/kg) or saline on the stereotyped behavior induced by 0.6 mg/kg apomorphine. Data are reported as the mean ± SEM.
* $p < 0.05$ compared to the SAL+SAL group (Kruskal-Wallis analysis of variance, followed by two-tailed Mann-Whitney U-test).

　　　　Figure 4 shows the effects of withdrawal from long-term buspirone and/or haloperidol treatment on apomorphine-induced stereotyped behavior. Once more, haloperidol-induced dopaminergic supersensitivity was clearly shown. Indeed, stereotypy scores were higher in the animals of the SAL+HAL group than in the rats of the SAL+SAL group 76, 484 and 724 h after abrupt removal (H=26.9 , 21.0, 10.7, p<0.05, respectively). Long-term treatment with buspirone alone did not resulted in an increased stereotyped behavior after withdrawal since no differences

in stereotypy scores were observed between BUS+SAL and SAL+SAL groups. In addition, repeated buspirone co-treatment was not able to modify haloperidol-induced dopaminergic supersensitivity when stereotyped behavior was used as experimental parameter. Thus, the intensities of stereotypy scores recorded for the animals of the BUS+HAL group were higher than those for group SAL+SAL rats and not different from those for group SAL+HAL animals in all the three observation sessions.

Discussion

The major findings of the present study were that [1] buspirone *per se* did not produce dopaminergic supersensitivity, [2] buspirone attenuated haloperidol-induced dopaminergic supersensitivity measured by open-field behavior and [3] buspirone was not able to modify haloperidol-induced dopaminergic supersensitivity measured by apomorphine-induced stereotyped behavior.

Apomorphine is a direct-acting dopamine agonist that, at stereotypic doses, is thought to produce its effects by stimulation of postsynaptic dopamine receptors (21,22). Therefore, the fact that long-term treatment of buspirone alone did not produce behavioral supersensitivity measured by apomorphine-induced stereotypy suggests the absence of up-regulation of postsynaptic dopamine receptors. This finding is consistent with previous binding data (14,23) which showed there is no up-regulation of dopamine receptors after long-term administration of buspirone. However, it is noteworthy that buspirone, at the dose used in the above mentioned long-term experiment, seems to be able to block postsynaptic dopamine receptors. Indeed, the fact that acute administration of the drug decreased apomorphine-induced stereotypy is suggestive of such a blockade.

Concerning buspirone effects *per se*, similar results were obtained in the open-field experiments. Indeed, whereas acute administration of buspirone decreased both locomotion and rearing frequencies in the open-field, withdrawal from long-term treatment did not increase the frequency of these behavioral parameters. These paradoxical data could be explained, at least in part, by the alleged preferential blockade of buspirone on the presynaptic dopamine receptors (24,25). Behaviorally, for example, Conceição and Frussa-Filho (17) verified that buspirone inhibits apomorphine-induced yawning in smaller doses than those necessary to inhibit apomorphine-induced stereotypy. Thus, during the long-term treatment, the strong antagonism action of buspirone on presynaptic receptors could lead to a great release of dopamine which might attenuate the weak blockade on postsynaptic receptors, thereby hindering the development of dopaminergic supersensitivity.

Although buspirone alone did not produce dopaminergic supersensitivity measured either by open-field behavior or by apomorphine-induced stereotypy, it affected differently haloperidol-induced behavioral supersensitivity. Indeed, buspirone co-treatment attenuated haloperidol-induced supersensitivity measured by open-field behavior, but not by apomorphine-induced stereotypy. In this regard, our stereotypy results are in accord with the data of Young et al. (26) who demonstrated that subchronic treatment with buspirone did not affect neuroleptic-induced striatal D_2 receptor up-regulation or the resulting supersensitivity to an apomorphine challenge.

The ability of buspirone to attenuate haloperidol-induced supersensitivity measured by open-field behavior but not by apomorphine-induced stereotypy could also indicate a preferential action of buspirone on presynaptic dopamine mechanisms. Indeed, whereas stereotypy depends

only on postsynaptic receptors, spontaneous open-field behavior depends on the endogenous dopamine action on these receptors and, therefore, it also depends on dopamine release, reuptake and many factors, including DA autoreceptors. Thus, the ability of buspirone to attenuate haloperidol-induced supersensitivity measured by open-field behavior but not measured by apomorphine-induced stereotypy could be related to the development of a strong presynaptic supersensitivity which would attenuate the effects of a postsynaptic supersensitivity. In this context, Taminga (27) proposed that if both auto and postsynaptic DA receptors became equally supersensitive, the synaptic activity would remain balanced and, potentially, extrapyramidal motor symptoms of tardive dyskinesia would perhaps be absent or decreased. According to this analysis, we have recently verified that the withdrawal from long-term treatment of buspirone (at the same dose and schedule used in the present study) produced a significant increase in the yawning frequency induced by low doses of apomorphine in rats (unpublished data). In this way, there is substantial evidence suggesting that apomorphine-induced yawning is mediated by dopamine autoreceptors and requires intact nigrostriatal projections (28). In further support of this assumption, using the accumulation of DOPA after administration of NSD-1015 as an experimental parameter, Tunnicliff et al. (29) verified that the withdrawal from repeated treatment with buspirone led to marked reductions in the synthesis of dopamine in the rat striatum. In this respect, a previous study by McMillen (23) had showed that repeated administration of buspirone produced no sign of altered dopaminergic metabolism except for a small decrease in response to acute buspirone challenge. However, the small dose of buspirone (1.0 mg/kg) used compared to that used in the study of Tunnicliff (29) (3.0 mg/kg) might account for the different findings. Indeed, we have verified that a smaller dose of buspirone/ per day was not able to modify haloperidol-induced dopaminergic supersensitivity measured by open-field behavior (unpublished data). Interestingly, concerning acute buspirone administration, our behavioral results are also consistent with the biochemical data reported by Tunnicliff et al. (29). Indeed, whereas acute administration of buspirone attenuated neither haloperidol-induced decreases in locomotion and rearing frequencies nor the reduction of stereotyped behavior induced by this neuroleptic, Tunnicliff et al. (29) found that the striatal synthesis of dopamine was not significantly changed after the acute dose of buspirone. These results agree well with the notion that the ability of buspirone to attenuate haloperidol-induced supersensitivity measured by open-field behavior depends on the development of a plastic phenomenon.

There are several other alternative manners in which buspirone co-treatment could attenuate the development of haloperidol-induced dopaminergic supersensitivity measured by open-field behavior but not by apomorphine-induced stereotypy. For example, locomotion and stereotypy can be differentially manipulated through selective lesions of dopaminergic systems, the nigrostriatal pathway being crucial for stereotypy and the mesolimbic dopaminergic neurons more involved in locomotion (30,31). Thus, buspirone treatment could differently modify these two neuroanatomic substrates. However, buspirone co-treatment attenuated haloperidol-induced supersensitivity measured not only by locomotion frequency but also by rearing frequency in the open-field. In this regard, these two responses have been previously shown to be differently affected by dopaminergic agonists treatment (32,33) and linked to different dopamine neurocircuitry. Indeed, whereas caudato-putamen seems to have a greater role in rearing, nucleus accumbens seems to have a greater one in locomotion (34).

Alternatively, open-field behavior and apomorphine-induced stereotypy could be differently affected by other neurotransmission systems. Notably, in binding studies, buspirone has been found to bind to $5HT_{1A}$ sites with high affinity (15). In addition, besides buspirone, other $5HT_{1A}$ receptor ligands are able to inhibit neuroleptic-induced catalepsy (35). In this respect, there

is convincing evidence that raphe serotonergic projections inhibit dopamine function at two levels: at the level of the midbrain they inhibit the firing of the dopamine cells projecting from the substantia nigra, and in the striatum and cortex they inhibit the synaptic release of dopamine and probably the synthesis of dopamine (see 36 for review). According to Elliot et al. (37) the mechanism by which catalepsy is reduced by $5HT1_A$ agonists is likely to result from a decrease in the firing of raphe cells induced by theses agents (38,39) and a consequential decrease in the inhibitory effects of serotonergic transmission in both the substantia and striatum. In support of this assumption, $5HT1_A$ agonists as 8-OH-DPAT and 5-MeO-DMT have been reported to increase the firing rate of nigrostriatal DA neurons. However, as regards the anti-cataleptic action of buspirone, in particular, data reported by McMillen & McDonald (40) strongly suggests that this effect is efferent from the dopaminergic system. Indeed, the mechanism by which buspirone causes decreased catalepsy does not seem to require presynaptic dopamine as catalepsy was reversed by buspirone in the dopamine-depleted rat. In addition, these authors showed that switching subcutaneous to intraperitoneal administration markedly decreased the effects of buspirone on dopamine metabolism but not on catalepsy. In this context, whereas the selective $5HT1_A$ agonist 8-OH-DPAT was found to stimulate spontaneous locomotor activity (41) and not to modify stereotypy behavior (37), under our experimental conditions buspirone (probably because of its antidopaminergic effects) reduced these both behaviors (although these reductions were much smaller than those produced by haloperidol). Taken together, the above results suggest that buspirone effects on different parameters of motor function may result from peculiar actions on dopaminergic and/or serotonergic and/or other neurotransmission systems.

The reduction of haloperidol-induced behavioral supersensitivity produced by buspirone co-treatment could also be related to a pharmacokinetic phenomenon. This possibility, however seems to be very unlikely because if buspirone decreased blood haloperidol levels, dopaminergic supersensitivity evaluated by apomorphine-induced stereotypy would also be attenuated. On the other hand, it should be noted that increases in haloperidol levels in serum of 26% have been previously documented during concurrent administration with buspirone, in clinical studies (42). Nevertheless, if an increase in haloperidol blood levels had happened under our experimental conditions, haloperidol-induced decreases in locomotion and rearing frequencies observed in the first open-field session (performed 30 minutes after the last treatment injection) would have been potentiated and not attenuated by buspirone co-treatment. Furthermore, increases in haloperidol blood levels would only postpone the behavioral manifestations of dopaminergic supersensitivity which, in turn, should even be more prominent.

From another standpoint, our present and previous behavioral results open the possibility that concurrent administration of buspirone and neuroleptics may lead to important clinical advantages. Indeed, under identical experimental conditions buspirone reversed haloperidol-induced catalepsy in the rat (17), but did not attenuate haloperidol-induced decrease in the stereotyped behavior produced by apomorphine (present data). Thus, whereas the latter result suggests that buspirone does not modify the action of haloperidol on postsynaptic dopamine receptors (and, presumably, its antipsychotic effects) the former encourages speculation that buspirone might ameliorate symptoms of parkinsonism. More important, the reduction of haloperidol-induced behavioral supersensitivity by buspirone co-treatment suggests that concurrent administration with buspirone could attenuate the development of tardive dyskinesia. Furthermore, taken together, our present and previous results also indicate that buspirone *per se* could be used to treat tardive dyskinesia symptoms, replacing neuroleptic treatment. Indeed, whereas acute administration of buspirone decreases apomorphine-induced stereotypy in a dose dependent manner (17), repeated administration of buspirone *per se* fails to produce the

development of dopaminergic supersensitivity. Although clinical interpretations from animal models must always be made with caution, such speculative observations are in full accordance with preliminary clinical reports. Namely, in an uncontrolled open trial, Goff et al. (42) noted that buspirone added to neuroleptic did not worsen schizophrenia symptoms and clearly improved symptoms of parkinsonism. In another uncontrolled open trial pilot study Moss et al. (43) verified that repeated buspirone treatment decreased the severity of both tardive dyskinesia and neuroleptic-induced parkinsonism. In this regard, four cases in which tardive dyskinesia was successfully treated with buspirone, with or without concomitant neuroleptic administration, were described by Neppe (44,45). Finally, concerning the clinical effects of buspirone *per se*, Medrano and Padierna (46) reported a case in which a patient's psychotic symptoms disappeared after buspirone treatment, and buspirone has not been demonstrated to produce tardive dyskinesia (47).

Acknowledgments

References

1. M.M.BERNARDI and J.PALERMO-NETO, Psycopharmacol. 65 247-250 (1979).
2. M.M.BERNARDI, H.DE SOUSA and J.PALERMO-NETO, Psycopharmacol. 73 171-175 (1981).
3. M.A.B.F.VITAL, R.FRUSSA-FILHO and J.PALERMO-NETO, Life Sci. 56 2299-2307 (1995).
4. L.F.FELICIO, A.G.NASELLO and J.PALERMO-NETO, Physiol. and Behav. 41 433-437 (1987).
5. R.FRUSSA-FILHO and J.PALERMO-NETO, Europ. J. Pharmacol. 149 323-329 (1988).
6. R.FRUSSA-FILHO and J.PALERMO-NETO, Braz. J. Med. Biol. Res. 23 463-472 (1990).
7. R.FRUSSA-FILHO and J.PALERMO-NETO, Physiol. and Behav. 50 825-830 (1991).
8. J.PALERMO-NETO, Psycopharmacol. Bull. 18 11-12 (1984).
9. H.L.KLAWANS, Am. J. Psychol. 130 82-86 (1973).
10. P.M.KARVEY, L.C.KAO, T.J.ZHANG, R.L.AMDUR, D.H.LIN, R.SINGH and H.L.KLAWANS, Pharmacol. Biochem. Behav. 35 291-300 (1990).
11. D.E.CASEY, In:Psychopharmacology: The Fourth Generation of Progress, F.E.BLOOM and D.J.KUPFER, eds., Raven Press, New York, pp.1497 (1995).
12. R.ENKELMANN, Psycopharmacol. 105 428-432 (1991).
13. T.MENNINI, M.GOBBI, F.PONZIO and S.GARATTINI, Arch. Int. Pharmacodyn. Ther. 279 40-49 (1986).
14. M.CIMINO, F.PONZIO, C.ACHILLI, G.VANTINI, C.PEREGO, S.ALGERI and S.GARATTINI, Biochem. Pharmacol. 32 1069-1074 (1983).
15. S.PEROUTKA, Biol. Psychiatr. 20 971-979 (1985).
16. S.ALGERI, A.DE LUIGI, M.G.DE SIMONI, L.IMERI, M.MARCONI, S.NAVA, C.PEREGO and G.SACCHETTI, Pharmacol., Biochem. and Behav. 29 823-826 (1988).
17. I.M.CONCEIÇÃO and R.FRUSSA-FILHO, Braz. J. Med. Biol. Res. 26 71-74 (1993).

18. P.L.BROADHURST, In: <u>Experiments in personality</u>, H.J.EYSENCK, ed., Routledge and Keegan Paul, London (1960).
19. P.SETLER, H.SARAU, G.McKENZIE, Eur. J. Pharmacol. <u>39</u> 117-126 (1976).
20. S.GARATTINI, S.CACCIA and T.MENNINI, J. Clin. Psychiatry <u>43</u> 19-22 (1982).
21. A.M.ERNST, Psychopharmacol. <u>10</u> 316-324 (1967).
22. M.T.C.PRICE, H.C.FIBIGER, Eur. J. Pharmacol. <u>29</u> 249-252 (1974).
23. B.A.McMILLEN, J. Neural Transmission <u>64</u> 1-12 (1985).
24. B.A.McMILLEN, R.T.MATTHEWS, M.K.SANGHERA, P.D.SHEPARD and D.C.GERMAN, The J. of Neurosci. <u>3</u> 733-738 (1983).
25. A.EISON and D.L.TEMPLE, The Am. J. of Medicine <u>80</u> 1-4 (1986).
26. K.A.YOUNG, R.ZAVODNY, P.B.HICKS, J. Neural Transm. <u>86</u> 223-228 (1991).
27. C.A.TAMINGA, In: <u>Neuroreceptors, basic and clinical aspects</u>, E.USDIN, W.E.J.BUNNEY and J.M.DAVIS, eds., John Willey & Sons Chichester, pp. 231-241 (1981).
28. A.J.STOESSL, C.T.DOURISH and S.D.IVESEN, Psychopharmacol. <u>93</u> 336-342 (1987).
29. G.TUNNICLIFF, J.J.BROKAW, J.A.HAUSZ, G.K.WHITE, Neuropharmacol. <u>31</u> 991-995 (1992).
30. I.CREESE and S.D.IVERSEN, Brain Res. <u>83</u> 419-536 (1975).
31. P.H.KELLY, P.W.SEVIOUR and S.D.IVERSEN, Brain Res. <u>94</u> 507-522 (1975).
32. M.M.BERNARDI and J.PALERMO-NETO, Gen. Pharmacol. <u>14</u> 545-547 (1983).
33. M.M.BERNARDI and J.PALERMO-NETO, Gen. Pharmacol. <u>15</u> 363-365 (1984).
34. I.M.H.AL-KHATIB, I.DÖKMECI and M.FUJIWARA, Jpn. J Pharmacol. <u>67</u> 69-77 (1995).
35. J.G.P.PIRES, S.R.SILVA and H.A.FUTURO-NETO, Braz. J. Med. Biol. Res. <u>27</u> 2437-2441 (1994).
36. S.KAPUR and G.R.REMINGTON, Am. J. Psychiatry <u>153</u> 466-476 (1996).
37. P.J.ELLIOT, D.M.WALSH, S.P.CLOSE, G.A.HIGGINS and A.G.HAYES, Neuropharmacol. <u>29</u> 949-956 (1990).
38. J.S.SPROUSE and G.K.AGHAJANIAN, Eur. J. Pharmacol. <u>128</u> 295-298 (1986).
39. J.S.SPROUSE and G.K.AGHAJANIAN, Synapse <u>1</u> 3-9 (1987).
40. B.A.McMILLEN and C.C.McDONALD, Neuropharmacol. <u>22</u> 273-278 (1983).
41. K.A.YOUNG, R.ZAVODNY, P.B.HICKS, Psychopharmacol. <u>110</u> 97-102 (1993).
42. D.C.GOFF, K.K.MIDHA, A.W.BROTMAN, S.McCORMICK, M.WAIVES and E.T.AMICO, J. Clin. Psychopharmacol. <u>11</u> 193-197 (1991).
43. L.E.MOSS, V.M.NEPPE and W.C.DREVETS, J. Clin. Psychopharmacol. <u>13</u> 204-209 (1993).
44. V.M.NEPPE, Lancet <u>2</u> 8677 (1989).
45. V.M.NEPPE, Abstract NR269 presented at the 143rd Annual Meeting of the American Psychiatric Association, New York (1990).
46. J.MEDRANO and J.A.PADIERNA, Am. J. Psychiatry <u>153</u> 293 (1996).
47. G.M.SIMPSON and H.SINGH, J. Clin. Psychiatry <u>49</u> 503 (1988).