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EFFECTS OF BUSPIRONE ON AN ANIMAL MODEL OF TARDIVE DYSKINESIA

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Abstract

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1. The effects of buspirone were studied on an animal model of tardive dyskinesia, i.e., the quantification of orofacial dyskinesia in rats repeatedly treated with reserpine.
2. Rats were co-treated with saline [SAL] or buspirone [BUS] (3.0 mg/kg, i.p., twice daily) and vehicle [VEH] or reserpine [RES] (0.1 mg/kg, s.c., once every other day) for 19 days. On the day 20, the animals were observed for quantification of the behavioral parameters of orofacial dyskinesia: tongue protrusion and vacuous chewing movements frequencies and duration of twitching of the facial musculature.
3. Rats of the SAL+RES group exhibited a significant increase in the three behavioral parameters of orofacial dyskinesia relative to the rats of the SAL+VEH group. However, animals of the BUS+RES group showed only an increased frequency of vacuous chewing movements when compared to animals of the SAL+VEH group. In addition, the duration of the facial twitching was significantly decreased in the BUS+RES group in relation to rats of the SAL+RES group. There were no significant differences in the orofacial parameters between the BUS+VEH and the SAL+VEH groups.
4. Because it was also verified that chronic buspirone treatment was able to increase apomorphine-induced yawning behavior, the possibility is raised that buspirone attenuates reserpine-induced orofacial dyskinesia through the development of dopamine autoreceptor supersensitivity.

Keywords: buspirone, dopamine, orofacial movements, rat, reserpine, serotonin, tardive dyskinesia.

Abbreviations: buspirone (BUS), reserpine (RES), saline (SAL), vehicle (VEH).

Introduction

Tardive dyskinesia is a syndrome characterized by repetitive involuntary movements, usually involving mouth, face and tongue and sometimes limb and trunk musculature. The syndrome is considered to be an adverse effect of prolonged administration of antipsychotic drugs. It usually persists for months after the neuroleptic has been discontinued and may be irreversible (Casey, 1985; Kane, 1995).

In rats, chronic treatment with dopamine receptor blockers such as haloperidol (Bernardi et al., 1981; Vital et al., 1995), bromopride (Felicio et al., 1987), metoclopramide (Frussa-Filho and Palermo-Neto, 1988), sulpiride (Frussa-Filho and Palermo-Neto, 1990) and droperidol (Frussa-Filho and Palermo-Neto, 1991) not only enhanced general activity observed in an open-field but also the stereotyped behavior induced by the dopamine agonist apomorphine. This behavioral supersensitivity is thought to result from striatal D_2–like receptor site proliferation in response to chronic dopamine receptor blockade (Burt et al.,1977; Seeman, 1980; Vital et al., 1998) and has been proposed as a potential model for antipsychotic-induced tardive dyskinesia (Klawans, 1973; Baldessarini and Tarsy, 1979).

Although the hypothesis of dopamine supersensitivity has dominated the conceptual approaches to studying tardive dyskinesia over the last decades (Casey, 1995), some fundamental observations seem not to support this hypothesis (Gerlach, 1985; Wolfarth and Ossowoska, 1989, Waddington, 1990; Casey, 1995). Perhaps one of the most important flaws is related to the effects of age on tardive dyskinesia/ behavioral supersensitivity. In this regard, age is the single most frequently implicated risk factor for tardive dyskinesia, increasing both the severity and persistence of the condition (Wolfarth and Ossowoska, 1989; Kane et al., 1985). Conversely, old animals have a diminished capacity to develop both behavioral supersensitivity to apomorphine-induced stereotyped behaviors and dopamine receptor up-regulation after chronic treatment with neuroleptics (Waddington and Gamble, 1980; Gamble and Waddington, 1981; Randall et al., 1981; Misra et al., 1982).

More recently, Neisewander et al. (1994) have suggested that reserpine-induced oral dyskinesia may provide a new model of tardive dyskinesia. Indeed, rats treated with this monoamine-depleting agent for at least 3 days develop orofacial dyskinesia characterized by twitching of the facial musculature, vacuous chewing movements and tongue protrusion (Neisewander et al., 1991a,b; 1994; 1996; Vital et al., 1997; Bergamo et al., 1997). In this regard, although reserpine is not classified as a neuroleptic, it has been used as an antipsychotic agent and has been associated with the development of tardive dyskinesia (Shonecker, 1957; Uhrbrand and Faurbye, 1960). This reserpine-induced orofacial dyskinesia

(especially tongue protrusion frequency) in rats has also other features that are consistent with tardive dyskinesia, including persistence following termination of administration and dose-dependent blockade by a D_2-selective antagonist (Neisewander et al., 1991a,b). Furthermore, whereas at high doses of reserpine the response appears within 3 days, at low doses the response is not evident until many days of treatment (Neisewander et al., 1994), consistent with the protracted development of tardive dyskinesia in humans (Gerlach and Casy, 1988). As with tardive dyskinesia (Wolfarth and Ossowska, 1989), reserpine-induced oral dyskinesia is exacerbated by dopamine agonists like amphetamine (Neisewander et al., 1996). Importantly, the authors have recently verified that when compared to control adult rats, the significant increase in tongue protrusion frequency induced by reserpine treatment was more persistent in the old rats than in the adult animals (Bergamo et al., 1997). Finally, consistent with the clinical situation where spontaneous senile dyskinesia and tardive dyskinesia cannot be differentiated on the basis of behavioral symptoms only (Gerlach, 1985; Wolfarth and Ossowska, 1989), reserpine-induced oral dyskinesia was phenomenologically identical to age-induced spontaneous oral movements in rats (Bergamo et al., 1997).

In recent years, nonbenzodiazepine anxiolytics have joined benzodiazepines on the anxiolytic market. One such agent is buspirone, a pyrimidinylpiperazine derivate, which is structurally unrelated to the benzodiazepines (Enkelmann, 1991). In fact, buspirone has no affinity for benzodiazepine-GABA receptor complex (Mennini et al., 1986) but shows high affinity for serotonergic and dopaminergic binding sites (Cimino et al., 1983; Peroutka, 1985), where it behaves as a partial $5HT_{1A}$ agonist and a D_2-like receptor antagonist, respectively (Tunnicliff et al., 1992). However, several lines of pharmacological evidence have indicated that the dopaminergic activity of buspirone cannot be considered to be the same as that of a typical neuroleptic. Behaviorally, acute administration of buspirone was able to reduce apomorphine-induced yawning and stereotyped behavior at the same doses that inhibited haloperidol-induced catalepsy in rats (Conceição and Frussa-Filho, 1993). As regards chronic administration, whereas buspirone *per se* did not produce behavioral supersensitivity, when given in combination with haloperidol it decreased the neuroleptic-induced supersensitivity as detected in open-field behavior but not in apomorphine-induced stereotypy (Queiroz and Frussa-Filho, 1997).

In order to further study the effects of chronic buspirone treatment on animal models of tardive dyskinesia, the primary purpose of this study was to determine the effects of buspirone co-treatment on the three behavioral parameters of reserpine-induced oral dyskinesia in rats: tongue protrusion, vacuous chewing movements and twitching of the facial musculature. To further characterize the effects of buspirone on dopaminergic plasticity, apomorphine-induced

yawning behavior was also quantified since it has been considered a behavioral parameter of nigrostriatal dopaminergic pre-synaptic function (Stoessl et al., 1987), and much of buspirone D_2-like binding is to dopamine autoreceptors (McMillen et al., 1983; Tunnicliff et al., 1992).

Methods

Animals

Genetically similar male Wistar rats weighing 250-300 g and about 90 days of age were used at the beginning of the experiment. The animals were housed in Plexiglas cages (6 animals each) with free access to food and water in a room with controlled temperature (22 ±1 °C) and in a 12 hour light/ dark cycle with lights on at 7:00 am. The rats 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

Reserpine (RBI) was dissolved in glacial acetic acid and then diluted in distilled water. The control solution for reserpine consisted of the same amount of acetic acid and water as in the reserpine solution. Buspirone (RBI) and apomorphine (Merck) were freshly diluted in distilled water. NaCl 0.9% was used as buspirone control solution. All the solutions were injected in the volume of 1.0 ml/kg body weight.

Experimental Procedure

In the first experiment, the rats were randomly divided into 4 groups of 10 animals each, which received 3.0 mg/kg buspirone (BUS) or saline (SAL) i.p. twice daily (8:00 a.m. and 5:00 p.m.), everyday, and 0.1 mg/kg reserpine (RES) or vehicle (VEH) s.c. every other day (8:30 a.m.), for 19 days. On the 20th day, 24 hours after the last reserpine or vehicle injection and 15.5 hours after the last buspirone or saline injection, animals of the four groups (SAL+VEH, BUS+VEH, SAL+RES and BUS+RES) were observed for the quantification of orofacial movements.

In the second experiment, animals were allocated randomly in 2 groups of 10 rats each, which received 3.0 mg/kg buspirone or saline, i.p., twice daily (8:00 a.m. and 5:00 p.m.) for 30 days, respectively. Twenty four hours after the last administration, the animals were observed for apomorphine-induced yawning behavior. In this experiment, the duration of buspirone

treatment was increased (30 days) in order to compare the present data with previous results related to buspirone effects on apomorphine-induced stereotypy (see Discussion section).

In both experiments, buspirone was administered twice daily because of its short half-life (Garattini, 1982). Each animal was used in only one experiment.

Behavioral Testing

To quantify the occurrence of orofacial dyskinesia, hand operated counters were employed to score tongue protrusion and vacuous chewing frequencies and stopwatches were employed to score the duration (total seconds) of twitching of the facial musculature. In the present study, tongue protrusion was operationally defined as a visible extension of the tongue outside of the mouth and not directed at anything. Individual tongue protrusions during a bout of oral dyskinesia were each preceded by visible retraction of the tongue (Neisewander et al., 1996). Vacuous chewing movements were referred to as single mouth opening in the vertical plane not directed towards physical material and twitching of the facial musculature was referred to as continuous tremor of the masseter musculature. If tongue protrusion, vacuous chewing, or twitching of the facial musculature occurred during a period of grooming they were not taken into account. The behavioral parameters of orofacial dyskinesia were measured continuously for 15 minutes.

To quantify the yawning behavior, rats were injected s.c. with 0.06 mg/kg apomorphine and 5 minute later, the number of yawns was counted continuously for 30 minutes.

In both behavioral tests, mirrors were placed under the floor and behind the backwall of the experimental cage to permit observation when the animal was faced away from the observer. Both behavioral tests were conducted blind.

Statistical Analysis

Since homocedasticity is necessary for the analysis of variance, Bartlet's test (Johnson and Leoni, 1974) was performed. Since tongue protrusion, vacuous chewing and facial twitching data did not fulfill criteria for homogeneity of variance, non-parametric tests were used. Thus, these data were analyzed by Kruskal-Wallis analysis of variance followed by the two-tailed Mann-Whitney U test (Siegel, 1956). For yawning frequency, a Student t-test was employed. A probability of $p<0.05$ was considered to show significant differences for all comparisons made.

Results

The effects of chronic buspirone and/or reserpine treatments on orofacial movements in rats are shown in Fig.1. Kruskal-Wallis analysis of variance revealed significant differences among groups for tongue protrusion ($H=17.6$; $p<0.005$) and vacuous chewing ($H=23.4$; $p<0.0005$) frequencies as well as for duration of facial twitching ($H=24.5$; $p<0.0005$). Mann-Whitney U test revealed that in relation to the control group (SAL+VEH), animals chronically treated with reserpine (SAL+RES group) showed increased tongue protrusion and vacuous chewing frequencies as well as twitching of the facial musculature duration. However, rats of the BUS+RES group showed only an increased vacuous chewing frequency, when compared to the SAL+VEH group. In addition, the facial twitching duration presented by animals of the BUS+RES group was significantly lower than that of the SAL+RES group. Finally, there were no significant differences in orofacial movements between the BUS+VEH and SAL+VEH groups.

Figure 2 shows that chronic treatment with buspirone induced a significant increase in the frequency of apomorphine-induced yawning behavior ($T(18)= 2.13$; $p<0.05$).

Discussion

The major findings of the present study were that: [1] rats treated chronically with reserpine developed an orofacial dyskinesia characterized by tongue protrusion, vacuous chewing movements and twitching of the facial musculature, [2] buspirone co-treatment attenuated reserpine-induced orofacial movements and [3] chronic buspirone treatment *per se* did not modify spontaneous orofacial movements, but significantly increased apomorphine-induced yawning.

Behavioral Parameters of Reserpine-Induced Orofacial Dyskinesia

The development of an orofacial dyskinesia characterized by tongue protrusion, vacuous chewing movements and twitching of the facial musculature in rats repeatedly treated with reserpine has been extensively reported (Neisewander et al., 1991a,b; 1994; 1996; Vital et al., 1997; Bergamo et al., 1997). However, except for the paper of Bergamo et al. (1997), the duration of the twitching of the facial musculature and the frequency of vacuous chewing movements were not quantified in the other studies. In the present investigation, the frequency of vacuous chewing movements, though the most prominent behavior in reserpine-treated animals, was the only reserpine-induced orofacial parameter that was not significantly modified by buspirone co-treatment. However, it should be noted that the magnitude of the reduction in

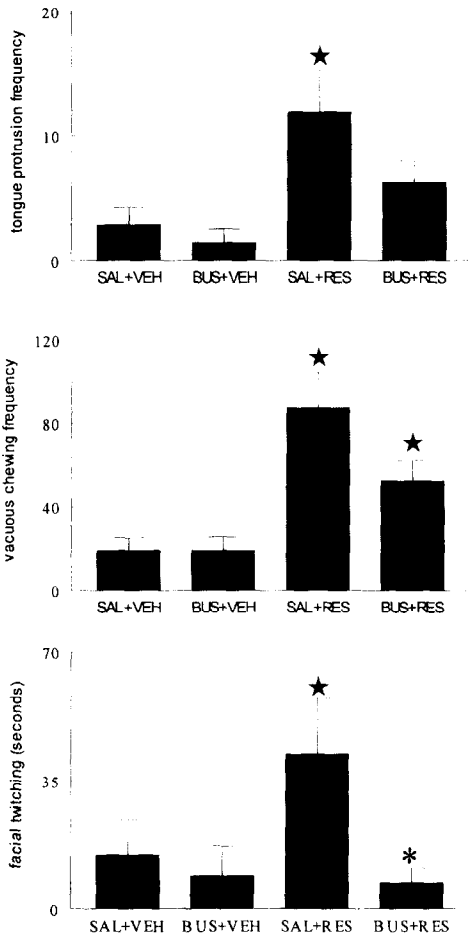

Fig.1 Effects of long-term administration (19 days) of buspirone (BUS, 3.0 mg/kg) or saline (SAL) plus reserpine (RES, 0.1 mg/kg) or vehicle (VEH) on tongue protrusion and vacuous chewing frequencies and twitching of the facial musculature duration (seconds). Data are reported as the mean ± SEM. ★$p<0.05$ compared to the SAL+VEH group, * $p<0.05$ compared to the SAL+RES group. Kruskal-Wallis analysis of variance, followed by two-tailed Mann-Whitney U-test.

vacuous chewing frequency in the BUS+RES group compared to the SAL+RES group was not substantially different from the drug effects on tongue protrusions. Vacuous chewing movements induced by long-term neuroleptic treatment have also been extensively studied Waddington, 1990). However, it is still debatable whether neuroleptic-induced purposeless

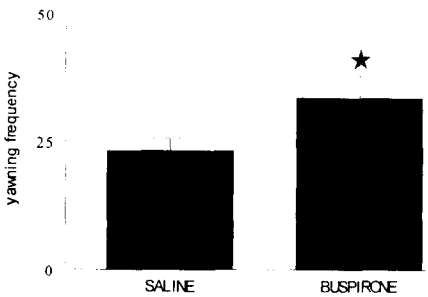

Fig.2 Effects of long-term administration (30 days) of buspirone (3.0 mg/kg) or saline on apomorphine (0.06 mg/kg)-induced yawning. Data are reported as the mean ± SEM. ★ $p<0.05$ compared to the SALINE group. Student t-test.

chewing movements are a model of tardive dyskinesia or acute distonia. In fact, the latter possibility is supported by the observation that the number of vacuous chewing movements increases just after the first dose of neuroleptic (Wolfarth and Ossowska, 1989). Interestingly, (high doses of reserpine have also been reported to increase vacuous chewing frequency 90 minutes after the first drug administration (Steinpreis and Salamone, 1993; Baskin and Salamone, 1993). Concerning this issue, reserpine-induced tongue protrusion is decreased in animals observed 6 hours after the first reserpine injection (Neisewander et al., 1991a; 1994). Indeed, the increase in tongue protrusion is not observed until 24 hours after the second injection of a high dose (1.0 mg/kg) of reserpine and appears much later during the course of administration at lower doses (Neisewander et al., 1994). These findings suggest that tongue protrusion is not an acute reserpine-elicited effect, but rather a spontaneous oral dyskinesia that develops as an adaptive response to reserpine repeated administration. Finally, the clearest effects of buspirone were seen in the facial twitching parameter. Whereas preliminary data from our laboratory suggests that this parameter is not modified six hours after a single 1.0 mg/kg reserpine administration, we have reported that it was significantly increased for several days after the second 1.0 mg/kg reserpine injection (Bergamo et al., 1997). Clearly, more extensive experimentation is necessary to characterize and differentiate the behavioral parameters of reserpine-induced orofacial dyskinesia in order to determine the extent to which each one may provide a better index of dyskinesia.

Effect of Buspirone on the Plasticity of Dopamine Autoreceptors and Attenuation of Reserpine-Induced Oral Dyskinesia

The findings that reserpine-induced oral dyskinesia is reversed by the acute administration of a dopamine D_2-like receptor antagonist (Neisewander et al, 1991b) and by nigrostriatal 6-hydroxydopamine lesions (Neisewander et al, 1996), but is exacerbated by the acute administration of amphetamine (Neisewander et al, 1996) suggest that residual endogenous dopamine may be involved in this response. Thus, the ability of buspirone to attenuate reserpine-induced orofacial dyskinesia could be related to the alleged preferential blockade of buspirone on the pre-synaptic dopamine receptors as compared to the postsynaptic ones (McMillen et al., 1983; McMillen, 1985). Behaviorally, for example, Conceição and Frussa-Filho (1993) verified that buspirone inhibits apomorphine-induced yawning in smaller doses than those necessary to inhibit apomorphine-induced stereotypy. In this respect, whereas apomorphine-induced yawning seems to be mediated by pre-synaptic dopamine receptors (Stoessl et al., 1987), apomorphine-induced stereotypy is thought to result from stimulation of postsynaptic dopamine receptors (Ernst, 1967; Price and Fibiger, 1974). Specifically, the ability of chronic buspirone treatment to attenuate reserpine-induced orofacial dyskinesia could be related to the development of a pre-synaptic dopamine receptor supersensitivity (leading to a decreased availability of dopamine in the synaptic cleft).

Different lines of experimental evidence seem to be in accord with the possibility mentioned above. First, whereas we have previously verified that the chronic buspirone treatment (3.0 mg/kg, twice daily, for 30 days) did not increase apomorphine-induced stereotyped behavior (Queiroz and Frussa-Filho, 1997), the present study shows a significant increase in apomorphine-induced yawning after an identical buspirone chronic treatment. Second, Tunnicliff et al. (1992) 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 (1985) had shown 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 et al (1992) (3.0 mg/kg) might account for the different findings. Third, when given in combination with haloperidol, buspirone decreased the effects of chronic neuroleptic treatment as detected in the open-field behavior but not in apomorphine-induced stereotyped behavior (Queiroz and Frussa-Filho, 1997). Thus, whereas stereotypy depends only on postsynaptic receptor, spontaneous open-field behavior depends on the endogenous dopamine action on these receptors and, therefore, it also depends on dopamine release, reuptake and many other factors, including dopamine autoreceptors. Forth, there is behavioral evidence that

chronic administration of a low dose of haloperidol (blocking preferentially the pre-synaptic dopamine receptors) can produced a dopamine autoreceptor supersensitivity in the absence of postsynaptic dopamine receptor supersensitivity (Frussa-Filho et al., 1997). Finally, it is important to stress that an adaptive phenomenon seems to be necessary for the inhibitory effect of buspirone on reserpine-induced oral dyskinesia. Indeed, preliminary results in our laboratory indicate that the acute administration of 3.0 mg/kg buspirone does not modify the expression of reserpine-induced orofacial dyskinesia (unpublished data).

Effect of Buspirone on Serotonergic Neurotransmission and Attenuation of Reserpine-Induced Orofacial Dyskinesia

There are several other alternative manners in which buspirone co-treatment could attenuate reserpine-induced orofacial dyskinesia. As mentioned earlier, in binding studies, buspirone has been found to bind to 5-HT_{1A} sites with high affinity (Mennini et al., 1986). There is autoradiographic (Weissmann-Nanopoulos et al., 1985; Verge et al., 1985), electrophysiological (Sprouse and Aghajanian, 1987; Sinton and Fallon, 1988) and neurochemical (Higgins et al., 1988; Hjorth and Magnusson, 1988; Hutson et al., 1989; Hillegaart et al., 1990) evidence that 5-HT_{1A} autoreceptors are presented on serotonergic neurons within the raphe nuclei. Consequently, activation of these 5-HT_{1A} autoreceptors can reduce serotonergic neuronal activity and decrease release of serotonin in the terminal regions (Yoshimoto and McBride, 1992). In this respect, there is convincing evidence that raphe serotonergic projections inhibit dopamine nigrostriatal function at two levels: at the level of midbrain they inhibit the firing of the dopamine cells projecting from the substantia nigra, and in the striatum they inhibit the synaptic release of dopamine and probably the synthesis of dopamine (Kapur and Remington, 1996 for review). In addition, Liminga et al. (1993) showed that whereas infusion of a selective 5-HT_{1A} agonist (8-OH-DPAT) into the substantia nigra caused a dose-dependent decrease in oral movements, the non-selective 5-HT agonists TFMPP and m-CPP increased them (probably via 5-HT_{1B} receptors). Furthermore, both systemic and direct administration of agonists of 5-HT_{2C} receptors into the subthalamic nucleus have been reported to increase orofacial movements in rats (Stewart et al., 1989; Eberle-Wang et al., 1996). Taken together, the above data suggest that the effects of chronic buspirone treatment on reserpine-induced orofacial dyskinesia may result from a complex and plastic interaction between dopaminergic and serotonergic neurotransmission systems and receptor subtypes.

Clinical Implications

Irrespective from the exact mechanism by which buspirone co-treatment attenuates reserpine-induced orofacial movements the present data suggests that chronic buspirone

administration could be an effective pharmacological tool in the treatment of tardive dyskinesia. Although clinical interpretations from animal models must always be made with caution, such a speculative observation is in full accordance with preliminary clinical reports. Namely, four cases in which tardive dyskinesia was successfully treated with buspirone, with or without concomitant neuroleptic administration, were described by Neppe (1989; 1990). These clinical case reports were supported by an uncontrolled open-label pilot study in which Moss et al. (1993) verified that repeated buspirone treatment was efficacious in the treatment of tardive dyskinesia.

Conclusion

This study has demonstrated that buspirone co-administration has an inhibitory effect on an animal model of tardive dyskinesia. Although the exact mechanisms that may underlie the attenuating effect of buspirone on reserpine-induced orofacial dyskinesia remain to be investigated systematically, this observation is in full accordance with preliminary clinical reports.

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References

BALDESSARINI, R.J. and TARSY, D. (1979) Relationship of the actions of neuroleptic drugs to the patophysiology of tardive dyskinesia. Int. Rev. Neurol. 21: 1-45.

BASKIN, P. and SALAMONE, J.D. (1993). Vacuous jaw movements in rats induced by acute reserpine administration: interactions with diffecnt doses of apomorphine. Pharmacol. Biochem. Behav. 46(4): 793-797.

BERGAMO, M.; ABÍLIO, V.C.; QUEIROZ, C.M.T.; BARBOSA-JÚNIOR, H.N.; ABDANUR L.R.A. and FRUSSA-FILHO, R. (1997). Effects of age on a new model of tardive dyskinesia. Neurobiol. Aging. 18(6): 623-629.

BERNARDI, M.M.; De SOUSA, H. and PALERMO-NETO J. (1981) Effect of single and long-term haloperidol administration on open-field behavior of rats. Psycopharmacol. 73: 171-175.

BURT, D.R.; CREESE, I. and SNYDER, S.H. (1977) Anti-schizophrenic drugs – chronic treatment elevates DA receptor binding in the brain. Science 196: 326-7.

CASEY, D.E. (1985) Tardive dyskinesia reversible and irreversible. In: Dyskinesia: Research and treatment, D.E.Casey, T.N.Chase, A.V.Christensen and J.Gerlach (Eds.), pp 88-98, Springer-Verlag, Berlim.

CASEY, D.E. (1995) Tardive Dyskinesia – Patophysiology. In: Psychopharmacology: The Fourth Generation of Progress, F.E.Bloom and D.J.Kupfer (Eds), pp 1497-1502, Raven Press, New York.

CIMINO, M.; PONZIO, F.; ACHILLI, C.; VANTINI, G.; PEREGO, C.; ALGERI, S. and GARATTINI, S. (1983) Dopaminergic effects of buspirone, a novel anxiolytic agent. Biochem. Pharmacol. 32: 1069-1074.

CONCEIÇÃO, I.M. and FRUSSA-FILHO, R. (1993) Effects of single administration of buspirone on catalepsy, yawning and stereotypy in rats. Brazilian J. Med. Biol. Res. 26: 71-74.

EBERLE-WANG, K.; LUCKI, I. and CHESSELET, M.F. (1996) A role for the subthalamic nucleus in 5-HT2C-induced oral dyskinesia. Neurosci 172: 117-128.

ENKELMANN, R. (1991) Alprazolam versus buspirone in the treatment of outpatients with generalized anxiety disorder Psychopharmacol. 105: 428-432.

ERNST, A.M. (1967) Mode of action of apomorphine and dexamphetamine on gnawing compulsion in rats. Psychopharmacol. 10: 316-324.

FELICIO, L.F.; NASELLO, A.G. and PALERMO-NETO, J. (1987) Dopaminergic supersensitivity after long-term bromopride treatment. Physiol. and Behav. 41: 433-437.

FRUSSA-FILHO, R. and PALERMO-NETO, J. (1988) Effects of single and long-term metoclopramide administration on open-field and stereotyped behavior of rats. Europ. J. Pharmacol. 149: 323-329.

FRUSSA-FILHO, R. and PALERMO-NETO, J. (1990) Effects of single and long-term sulpiride administration on open-field and stereotyped behavior of rats. Brazilian J. Med. Biol. Res. **23** 463-472.

FRUSSA-FILHO, R. and PALERMO-NETO, J. (1991) Effects of single and long-term droperidol administration on open-field and stereotyped behavior of rats. Physiol. and Behav. 50: 825-830.

FRUSSA-FILHO, R.; ABÍLIO, V.C.; BERGAMO, M. and PALERMO-NETO, J. (1997) Behavioural subsensitivity induced by long-term administration of a low dose of haloperidol to rats. J. Pharm. Pharmacol. 49(4) 412-415.

GAMBLE, S.J. and WADDINGTON, J.L. (1981) Multiplicity of dopamine-mediated behaviours during six months phenotiazine neuroleptic treatment in young but not aged rats. Br. J. Pharmacol. 74: 225.

GARATTINI, S.; CACCIA, S. and MENNINI, T. (1982) Notes on buspirone's mechanism of action. J. Clin. Psychiat. 43: 19-22.

GERLACH, J. (1985) Patophysiological mechanisms underlying tardive dyskinesia. In: Dyskinesia: Research and treatment, D.E.Casey, T.N.Chase, A.V.Christensen, J.Gerlach (Eds), pp 99-104, Springer-Verlag, Berlim.

GERLACH, J. and CASEY, D.E. (1988) Tardive dyskinesia. Acta Psychiatry Scan. 77: 369.

HIGGINS, G.A.; BRADBURY, A.J.; JONES, B.J. and OAKLEY, N.R. (1988) Behavioural and biochemical consequences following activation of 5HT1-like and GABA receptors iin the dorsal raphe nucleus of the rat. Neuropharmacol. 27: 993-1001.

HILLEGAART, V.; HJORTH, S. and AHLENIUS, S. (1990) Effects of 5-HT and 8-OHDPAT on forebrain monoamine synthesis after local application into the median and dorsal raphe nuclei of the rat. J. Neural Transm. 81: 131-145.

HJORTH, S. and MAGNUSSON, T. (1988) The 5-HT1A receptor agonist, 8OHDPAT, preferentially activates cell body 5-HT autoreceptors in rat brain in vivo. N.-Sch. Arch. Pharmacol. 338: 463-471.

HUTSON, P.H.; SARNA, G.S.; O'CONNELL, M.T. and CURZON, G. (1989) Hippocampal 5-HT synthesis and release in vivo is decreased by infusion of 8-OHDPAT into the nucleus raphe dorsalis. Neurosci. Lett. 100: 276-280.

JOHNSON, N. and LEONE, F. (1974) Statistics and experimental design. In: Engineering and physical sciences, J.Wiley (Ed), New York.

KANE, J.M. (1995) Tardive dyskinesia: Epidemiological and clinical presentation. In: Psychopharmacology: The Fourth Generation of Progress, F.E.Bloom and D.J.Kupfer (Eds), pp 1485-1495, Raven Press, New York.

KANE, J.M.; WOERNER, M. and LIEBERMAN, J. (1985) Tardive dyskinesia: prevalence, incidence and risk factors. In: Dyskinesia: Research and Treatment, D.E.Casey, T.N.Chase, A.V.Christensen, J.Gerlach (Eds), pp 72-78, Springer-Verlag, Berlim.

KAPUR, S. and REMINGTON, G. (1996) Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry 153: 466-476.

KLAWANS, H.L. (1973) The pharmacology of tardive dyskinesia. Am. J. Psychol. 130: 82-86.

LIMINGA, U.; JOHNSON, A.E.; ANDRÉN, P.E. and GUNNE, L.M. (1993) Modulation of oral movements by intranigral 5-hydroxytryptamine receptor agonists in the rat. Pharmacol Biochem and Behav 46: 427-433.

McMILLEN, B. A. (1985) Comparative chronic effects of buspirone or neuroleptics on rat brain dopaminergic neurotransmission. J. Neural Transm. 64: 1-12.

McMILLEN, B.A.; MATTHEWS, R.T.; SANGHERA, M.K.; SHEPARD, P.D. and GERMAN, D.C. (1983) Dopamine receptor antagonismby the novel anti-anxiety drug, buspirone. J. Neurosci. 3 733-738.

MENNINI, T.; GOBBI, M.; PONZIO, F. and GARATTINI, S. (1986) Neurochemical effects of buspirone in rat hippocampus: evidence for selective activation of 5-HT neurones .Arch. Int. Pharmacodyn. Ther. 279: 40-49.

MISRA, C.H. SHELAT, H. and SMITH, R.C. (1982) Age affects dopamine receptors changes during chronic administration of fluphenazine. Eur. J. Pharmacol. 85: 343-346.

MOSS, L.E.; NEPPE, V.M. and DREVETS, W.C. (1993) Buspirone in the treatment of tardive dyskinesia. J. Clin. Psychopharmacol. 13: 204-209.

NEISEWANDER, J.L., CASTAÑEDA, E. and DAVIS, D.A. (1994) Dose-dependent differences in the development of reserpine-induced oral-dyskinesia in rats: support for a model of tardive dyskinesia. Psychopharmacol. 116: 79-84.

NEISEWANDER, J.L., CASTAÑEDA, E., DAVIS, D.A.; ELSON, H.J. and SUSSMAN, A.N. (1996) Effects of amphetamine and 6-hydroxydopamine lesions on reserpine-induced oral dyskinesia. Eur. J. Pharmacol. 305: 13-21.

NEISEWANDER, J.L.; LUCKI, I. and McGONIGLE, P. (1991a) Neurochemical changes associated with the persistence of spontaneous oral dyskinesia in rats following chronic reserpine treatment. Brain Res. 558: 27-35.

NEISEWANDER, J.L.; LUCKI, I. and McGONIGLE, P. (1991b) Behavioral and neurochemical effects of chronic administration of reserpine and SKF-38393 in rats. J. Pharmacol. Exp. Ther. 257; 850-860.

NEPPE, V.M. (1989) High-dose buspirone in case. Lancet 2: 8677.

NEPPE, V.M. (1990) High dose buspirone treatment in tardive dyskinesia. (Abtract NR269) Presented at the 143rd Annual Meeting of the American Psychiatry Association, New York.

PEROUTKA, S. (1985). Selective interaction of novel anxyolitic with 5-hydrosytriptamine 1A receptor. Biol. Psychiatr. 20: 971-979.

PRICE, M.T.; FIBIGER, H.C. (1974) Apomorphine and amphetamine stereotypy after 6-hydroxydopamine lesions of the substantia nigra. Eur. J. Pharmacol. 29(2) 249-252.

QUEIROZ, C.M.T. and FRUSSA-FILHO, R. (1997) Effects of buspirone on dopaminergic supersensitivity. Life Sci. 61(4): 371-382.

RANDALL, P.K. SEVERSON, J.A. and FINCH, C.E. (1981) Aging and the regulation of striatal dopaminergic mechanisms in mice. J. Pharmacol. Exp. Ther. 219: 695-700.

SEEMAN, P. (1980) Brain dopamine receptors. Pharmacol. Rev. 32: 229-313.

SHONECKER, M. (1957) Ein eigentumliches syndrom in earlen Bereich bei. Megaphen Applikation Nervenartz 28: 34.

SIEGEL, S. (1956) Non-parametric statistic for the behavioral sciences, pp 117-127, McGraw-Hill, New York.

SINTON, C.M. and FALLON, S.C. (1988) Electrophysiological evidence for a functional diferentiation between subtypes of the 5-HT1 receptor. Eur. J. Pharmacol. 157: 173-181.

SPROUSE, J.S. and AGHAJANIAN, G.K. (1987) Electrophysiological responses of serotonergic dorsal raphe neurones to 5-HT1A and 5-HT1B agonists. Synapse 1: 3-9.

STEINPREIS, R.E. and SALAMONE, J.D. (1993) Effects of acute haloperidol and reserpine administration on vacuous jaw movements in three different age groups of rats. Pharmacol. Biochem. Behav. 46(2): 405-409.

STEWART, B.R.; JENNER, P. and MARSDEN, C.D. (1989) Induction of purposeless chewing behaviour in rats by 5-HT agonist drugs. Eur J Pharmacol. 162: 101-107.

STOESSL, A.J.; DOURISH, C.T. and IVESEN, S.D. (1987) Apomorphine-induced yawning in rats is abolished by bilateral 6-hydroxydopamine lesions of the substantia nigra. Psychopharmacol. 93: 336-342.

TUNNICLIFF, G.; BROKAW, J.J.; HAUSZ, J.A.; MATHESON, G.K. and WHITE, G.W. (1992) Influence of repeated treatment with buspirone on central 5-hydroxytryptamine and dopamine synthesis. Neuropharmacol. 31(10): 991-995.

UHRBRAND, L. and FAURBYE, A. (1960) Reversible and irreversible dyskinesia after treatment with perphenazine, chlorpromazine, reserpine and electroconvulsive therapy. Psychopharmacologia 1 408-418.

VERGE, D.; DAVAL, G.; PATEY, A.; GOZLAN, H.; El MESTIKAWY, S. and HAMON, M. (1985) Presynaptic 5-HT autoreceptors on serotoninergic cell bodies and/or dendrites but not terminals are of 5HT1A subtype. Eur. J. Pharmacol. 113: 463-462.

VITAL, M.A.B.F.; FLÓRIO, J.C.; FRUSSA-FILHO, R.; De LUCIA, R.; TUFIK, S. and PALERMO-NETO, J. (1998) Effects of haloperidol and GM1 ganglioside treatment on striatal D2 receptor binding and dopamine turnover. Life Sci. 62(13): 1161-1169.

VITAL, M.A.B.F.; FRUSSA-FILHO, R. and PALERMO-NETO J. (1995) Effects of monosialoganglioside on dopaminergic supersensitivity. Life Sci. 56: 2299-2307.

VITAL, M.A.B.F.; FRUSSA-FILHO, R. and PALERMO-NETO, J. (1997) Effects of monosialoganglioside on a new model of tardive dyskinesia. Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 21: 1169-1179.

WADDINGTON, J.L. (1990) Spontaneous orofacial movements induced in rodents by very long-term neuroleptic drug administration: phenomenology, pathophysiology and putative relationship to tardive dyskinesia. Psychopharmacol. 101: 431-447.

WADDINGTON, J.L. and GAMBLE, S.J. (1980) Defferential effects of ageing on distinct features of apomorphine stereotypy in the adult rat. Neurosci. Lett. 20: 95-99.

WEISSMANN-NANOPOULOS, D.; MACH, E.; MAGRE, J.E.; DEMASSY, Y. and PUJOL, J.F. (1985) Evidence for the localisation of 5-HT1A binding sites on serotonin containing neurons in the raphe dorsalis and raphe centralis nuclei of the rat brain. Neurochem. Int. 7: 1061-1072).

WOLFARTH, S. and OSSOWSKA, K. (1989) Can supersensitivity of rodents to dopamine be regarded as a model of tardive dyskinesia? Prog. Neuropsychopharmacol. Biol. Psychiat. 13: 789-840.

YOSHIMOTO, K. and McBRIDE, W.J. (1992) Regulation of nucleus accumbens dopamine release by the dorsal raphe nucleus in the rat. Neurochem. Res. 17(5): 401-407.

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