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Effects of chronic risperidone on central noradrenergic transmission

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Abstract

In the present work, we investigated the effects of chronic risperidone administration on the activity of locus coeruleus noradrenergic neurons. In addition, the effect of chronic risperidone administration on the basal level of norepinephrine in the prefrontal cortex was evaluated. Results of this research showed that chronic risperidone administration increased the activity of locus coeruleus noradrenergic neurons. The sensitivity of α_2-adrenoceptors in the somatodendritic region of the locus coeruleus was assessed by using the ID_{50} of clonidine. Results indicated that the firing rate of locus coeruleus noradrenergic neurons was the same in risperidone-treated rats and controls. Similarly, the ID_{50} for (±)-2,5-dimetoxy-4-iodoamphetamine (DOI), an agonist of 5-HT_2 receptors which inhibits the activity of locus coeruleus neurons by acting on these receptors, did not show any differences between the firing rate of these neurons in risperidone treated rats and controls. Unlike controls, chronically treated rats showed a significant decrease in norepinephrine levels in the prefrontal cortex. The decreased release of norepinephrine following continuous risperidone administration could be explained by the sustained increase in locus coeruleus neuronal activity after chronic risperidone administration. This low norepinephrine level in the prefrontal cortex may contribute to the relief of certain negative schizophrenic symptoms and to the improvement of cognitive function.

Keywords: Risperidone; Microdialysis; Schizophrenia; Antipsychotic drug; Electrophysiology; Noradrenergic system

1. Introduction

Atypical antipsychotic drugs have been identified as a group of neuroleptic agents effective against the negative as well as the positive symptoms of schizophrenia. These drugs produce weak or no catalepsy in rodents at doses which are effective in models predicting antipsychotic activity and which promote significantly fewer extrapyramidal side effects in humans (Kane, 1993). More recently, Meltzer (1995) has proposed the lack of effects on serum prolactin concentration in humans, in addition to the low extrapyramidal side effects, as a further subclassification for atypical antipsychotics. Examples of these drugs include clozapine, risperidone, remoxipride and ziprasidone.

Although the clinical effects of antipsychotic drugs have been extensively studied, the underlying mechanism of action is not fully understood. Interaction with central dopaminergic transmission, specifically on dopamine D_2 receptors, has been inferred as the main property of antipsychotic drugs. Further effects on other neurotransmitter systems may also contribute to the clinical actions of these drugs.

Risperidone is a benzisoxazole derivative with a very high affinity for 5-HT_{2A} receptors, moderate affinity for catecholamine (mainly dopamine D_2 receptors), α_1- and α_2-adrenoceptors (Janssen et al., 1988), and poor affinity for the acetylcholine muscarinic receptors. Working with laboratory animals, Megens et al. (1988) demonstrated the low capacity of risperidone to induce catalepsy and extrapyramidal side effects. In chronic schizophrenic patients, risperidone showed a marked antipsychotic effect, improved negative and affective symptoms and reduced pre-existing extrapyramidal side effects (Bersani et al., 1990). These properties are partially shared by clozapine (Meltzer, 1995). As with clozapine, these effects have been tentatively explained by the high ratio of 5-HT_{2A}/dopamine D_2 receptor blockade (Den Boer and Westenberg, 1995).

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Clozapine, another atypical antipsychotic drug, unlike most neuroleptics, is not only a powerful 5-HT_2 receptor antagonist but also equally or nearly as potent as an α_2-adrenoceptor antagonist (Van Kammen et al., 1990; Sahakian and Hodges, 1994). Chronic clozapine increases the firing rate of noradrenergic neurons of the locus coeruleus, probably by blocking the automodulatory mechanism that operates on the α_2-adrenoceptor in the somatodendritic region of the locus coeruleus (Ramirez and Wang, 1986a). The marked enhancement of norepinephrine activity induced by chronic clozapine treatment could contribute to its low potential for causing extrapyramidal side effects, which could be the result of the selective action of clozapine on the A10 mesolimbic but not the A9 nigrostriatal dopamine system. This view is supported by the work of Cools (1983), who provided some evidence suggesting that norepinephrine selectively affects the mesolimbic but not the nigrostriatal tract at the terminal regions. However, haloperidol, a typical antipsychotic drug, was found to decrease the locus coeruleus noradrenergic firing rate (Ramirez and Wang, 1986a). On the basis of these findings, we decided to study the effects of chronic risperidone administration on central noradrenergic transmission to increase our knowledge of the mechanism of action of this drug. To this end, we studied the activity of locus coeruleus noradrenergic neurons using a single-cell recording method. In addition, the effects of chronic risperidone on the noradrenergic output in the prefrontal cortex were directly studied by means of microdialysis in freely moving rats.

2. Materials and method

2.1. Subjects

Experiments were carried out on male Wistar rats weighing 270–300 g. Animals were housed in groups of five per box under standard conditions: room temperature (22 ± 2°C); 12L:12D cycle; water and food ad libitum.

Risperidone (Janssen) was dissolved in tartaric acid 0.4 M and made up to the final volume with saline. Sodium hydroxide (0.1 N) was added until the final pH was 6–6.2. Vehicle was prepared with physiologic saline solution (0.9 g/100 ml) and tartaric acid 0.4 M was added to achieve a final pH of 6–6.2. Clonidine and (±)-2,5-dimethoxy-4-iodoamphetamine (DOI) were dissolved in saline.

Animals were s.c. injected with risperidone (0.2 mg/kg/day) or vehicle (0.1 ml/100 g/day) for 5 weeks. The risperidone dosage was selected according to doses of similar antipsychotic potency in clinical trials (Kane, 1993; Chouinard et al., 1994).

2.2. Electrophysiological procedures

At 24 h after the last injection, rats were anesthetized with chloral hydrate (400 mg/kg i.p.). Supplemental doses of anesthetic were administered through a dorsal tail vein when needed to maintain surgical anesthesia throughout the experiment. These conditions meet or exceed the standards for the care of laboratory animals as outlined in the NIH Guide for the Care and Use of Laboratory Animals. Techniques used for extracellular single-cell recording have been described in detail elsewhere (Ramirez and Wang, 1986a,b; Pavcovich and Ramirez, 1991). Briefly, rats were mounted on a stereotaxic frame, the skulls were exposed and a hole was drilled above the locus coeruleus, where an electrode was lowered (1.1–1.3 mm posterior to lambda, 1.1–1.3 mm lateral to the midline suture and 5.5–6.5 mm below the dura; atlas of Paxinos and Watson, 1986) by means of a hydraulic microdrive. The number of spontaneously active cells per track (five-track average per animal) and the firing rate were assessed. The firing rate was obtained from the counted cells which displayed a signal-to-noise ratio of 2:1 or more. Locus coeruleus noradrenergic neurons display the following characteristics: (a) positive–negative action potentials lasting approximately 2 ms, often with a notch between the initial segment and the somatodendritic spike component; (b) a firing rate of 0.5–3.0 spike/s; (c) burst of firing followed by a quiescent period in response to pinching of the contralateral paw (Cedarbaum and Aghajanian, 1977). These properties fulfil electrophysiological criteria for the identification of locus coeruleus noradrenergic cells (Aghajanian et al., 1977; Ramirez and Wang, 1986a,b; Pavcovich and Ramirez, 1991). Electrode potentials, which had been previously passed through a high-impedance amplifier, were displayed on an oscilloscope. The electrical signals were passed through a window discriminator and monitored on an audio amplifier. Integrated histograms generated by the analog output of the window discriminator were computed on line and stored for later computer analysis.

Dose–response curves for clonidine and DOI were performed by injecting successive i.v. doses of drugs at 5.0-min intervals and the percentage of spikes suppressed was assayed during this period. Only one cell per rat was tested. Upon completion of the experiments, the cell location was marked by passing a 25-mA cathodal current through the recording electrode for 15 min and a spot of Fast green dye was deposited. Rats were then perfused with phosphate-buffered 10% formaline solution. Serial frozen sections, 50-μm thick, were sliced and the dye spot was microscopically traced.

2.3. Microdialysis procedures

The microdialysis procedure was basically as described by Robinson and Justice (1991). Briefly, rats were anesthetized with chloral hydrate (400 mg/kg, i.p.) and mounted on a Stoelting stereotaxic frame with the incisor bar at −3.3 mm below interaural zero. AN69 HF dialysis fiber, inner diameter 200 μm and outer diameter 340 μm (Hospal, Meyzieu, France), was transversally inserted in

Table 1
Comparison of the effects produced by chronic administration of risperidone vs. control on the number of locus coeruleus spontaneously active cells (cells/track) and their firing rate
Data represent means ± S.E.M.

Treatment	*n* (cells)	Firing	*n* (rats)	Cells/track
Control	18	1.87 ± 0.11	8	4.84 ± 0.10
Chronic risperidone	19	2.38 ± 0.13[a]	9	6.02 ± 0.31[a]

[a] Significantly different from control, $P < 0.01$ (Newman–Keuls test).

the prefrontal cortex (coordinates vs. bregma: A +3.2; V −2.6; atlas of Paxinos and Watson, 1986). Dialysis was confined to the prefrontal cortex by covering the dialysis fiber with epoxy resin along its whole length except for 7 mm corresponding to the section in contact with cortical tissue. The probe was fastened to the skull with screws and dental cement and the skin was sutured. Rats were then placed in individual acrylic bowls and left to recover for at least 24 h.

Experiments began 24 h after the last risperidone injection. The dialysis membranes were perfused with Ringer's solution (NaCl 147 mM; KCl 4.0 mM; $CaCl_2$ 1.7 mM; $MgCl_2$ 0.8 mM; pH = 7.2) at a constant flow rate of 1.2 μl/min. After an equilibration period, samples of the dialysate were collected every 30 min into vials containing 1 μl acetic acid (0.1 N) to prevent oxidation of norepinephrine. Vials were kept at 4°C in a refrigerated fraction collector. Immediately after collection, the dialysate was analyzed on a high-performance liquid chromatography (HPLC) system. Control levels were defined as an average of these baselines. Corrections were made to account for the dead volume. At the end of the experiments, animals were killed by decapitation, brains were removed and the position of the dialysis probe track was histologically verified.

2.4. Monoamine assay

The amount of norepinephrine in the collected fractions was analyzed on an HPLC equipped with reverse-phase column (ultrasphere C18, 15 cm, 5 μm particle size, Beckman) coupled with electrochemical detection. The HPLC system consisted of a BAS LCD-4 electrochemical detector with a glass–carbon electrode and pump (Spectra Series P200). The potential was set at 600 mV (vs. Ag\AgCl reference electrode). The mobile phase containing 75 mM NaH_2PO_4, 1.0 mM sodium dodecyl sulfate, 100 μM EDTA, 1.48 mM triethylamine, 13% methanol and 15% acetonitrile (pH 5.6) was filtered and pumped throughout the system at a flow rate of 1.0 ml/min by a Spectra Series P200 pump. Under these conditions, the limit of detection was below 10 fmol. Peaks for both HPLC systems were displayed, integrated and stored with Peak Simple II Data System (SRI Instr, CA, USA). Quantification was made by comparing the peak heights of the samples to those of a standard curve.

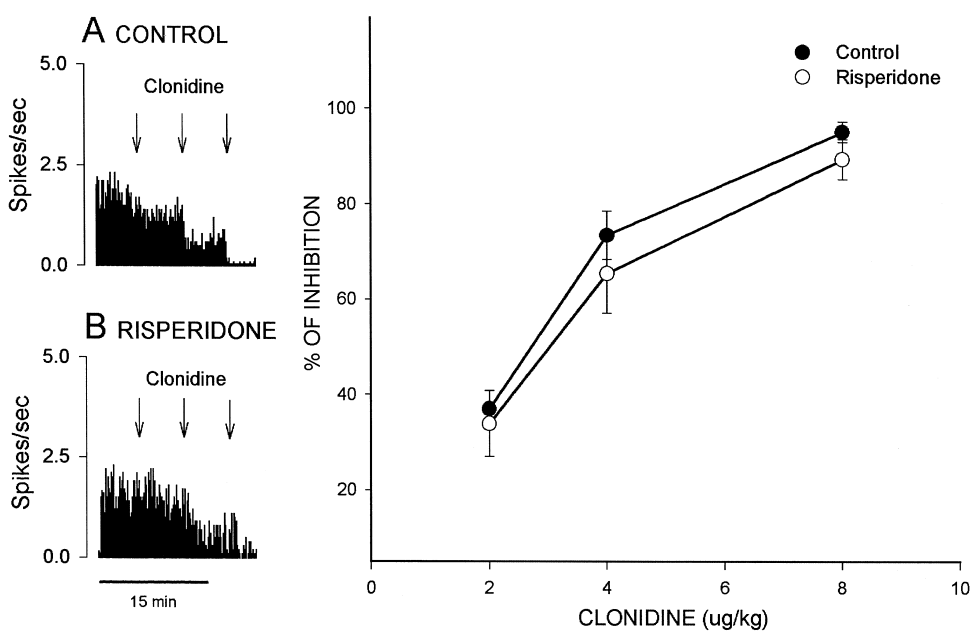

Fig. 1. Integrated firing rate histograms showing representative effects of i.v. clonidine administration on the activity of locus coeruleus noradrenergic neurons recorded from (A) control and (B) chronic risperidone (0.2 mg/kg/day)-treated rats. Arrows indicate time of injection. Cumulative dose of clonidine was 16 (2.0 + 4.0 + 8.0) μg/kg in both groups. (C) Dose–response curve of i.v. clonidine to inhibit the firing of locus coeruleus noradrenergic neurons in control and chronic risperidone-treated rats ($n = 7$).

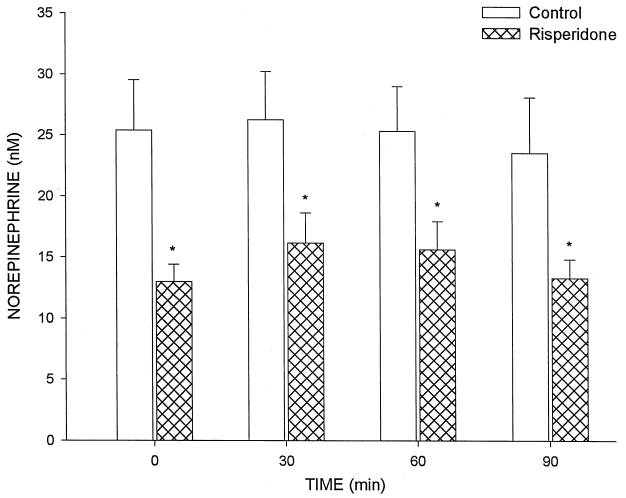

Fig. 2. Effect of chronic risperidone administration (0.2 mg/kg/day) on extracellular levels of norepinephrine in microdialysis samples from cerebral cortex of conscious, freely moving rats. Data are expressed as nanomolar (nM) concentration, means ± S.E.M. $^{*}P < 0.05$ (Student's *t*-test) compared to control group ($n = 5$).

2.5. Statistical analysis

Statistical analyses for electrophysiological results were performed using two-way analysis of variance (ANOVA), and subsequent post hoc comparisons were carried out with the Newman–Keuls test.

Values for microdialysis are expressed as means ± S.E.M. Data were analyzed by two-way ANOVA for repeated measures with treatment as between-subjects factor and time as within-subjects factor (Split-Plot ANOVA). Post hoc comparisons between groups were performed with an independent *t*-test. A P value of 0.05 or less was considered significant.

3. Results

The therapeutic effects of most neuroleptic drugs appear after chronic (3–5 weeks) administration (Meltzer et al., 1978; White and Wang, 1983). In order to explore whether chronic risperidone administration modifies the firing of locus coeruleus noradrenergic neurons, the activity of this nucleus after chronic (5 weeks) risperidone administration was investigated. The number of spontaneously active cells/track and the discharge of locus coeruleus noradrenergic neurons were increased 24 h after the last injection of chronic risperidone (0.2 mg/kg/day). Cells/track $F(1,15) = 13.16$; $P < 0.0025$ and firing rate $F(1,35) = 9.88$; $P < 0.0034$ (Table 1). These effects were due to the chronic risperidone administration rather than to the risperidone remaining after the last injection because the half-life of risperidone in brain tissue is known to be 3–4 h (Van Beijsterveldt et al., 1994). One of the mechanisms that rule the spontaneous activity of locus coeruleus noradrenergic cells is the inhibitory action mediated by α_2-adrenoceptors (Williams et al., 1985). To assess whether the sensitivity of α_2-adrenoceptors in the locus coeruleus

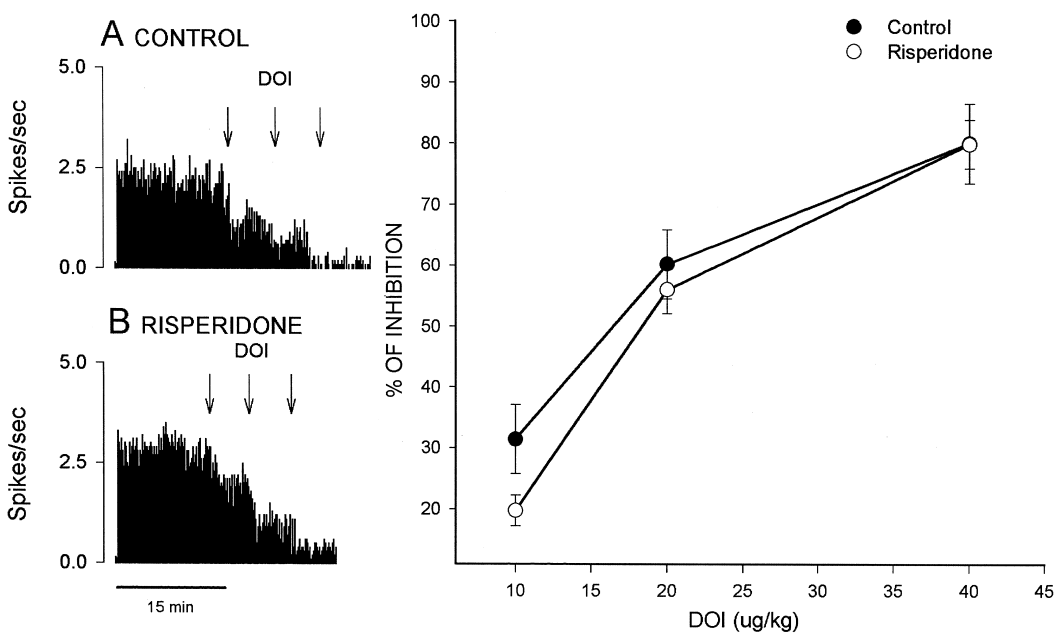

Fig. 3. Integrated firing rate histograms showing representative effects of i.v. DOI administration on the activity of locus coeruleus noradrenergic neurons recorded from (A) control and (B) chronic risperidone (0.2 mg/kg/day)-treated rats. Arrows indicate time of injection. Cumulative dose of DOI was 70 (10 + 20 + 40) μg/kg in both groups. (C) Dose–response curve of i.v. DOI to inhibit the firing of locus coeruleus noradrenergic neurons of control and chronic risperidone-treated rats ($n = 6$).

area was modified by the chronic administration of risperidone, the effect of a challenge inhibitory dose of clonidine on the firing of these cells was determined. The ID_{50} of clonidine for locus coeruleus neuronal activity of rats chronically treated with 0.2 mg/kg risperidone during 5 weeks (2.46 ± 0.45 μg/kg) did not change compared with controls (3.34 ± 0.58 μg/kg) (Fig. 1). Fig. 1A, B show an example of the effect of challenge doses of clonidine ($2.0 + 4.0 + 8.0$ μg/kg) on the spontaneous activity of locus coeruleus noradrenergic neurons.

In order to verify whether the alterations observed after chronically administered risperidone in locus coeruleus noradrenergic neuron activity, modified norepinephrine outflow in the terminals in the prefrontal cortex, we assayed the extracellular norepinephrine level in this area by the microdialysis technique. As shown in Fig. 2, chronic risperidone administration significantly decreased the basal norepinephrine level in the prefrontal cortex (14.63 ± 1.00) as compared with that of the controls (25.16 ± 1.90) [average of four samples].

Considering that the spontaneous activity of noradrenergic neurons in the locus coeruleus of the rat appears to be under the inhibitory influence of the serotoninergic raphe system (Leger and Descarries, 1978; Segal, 1979; McNaughton and Mason, 1980; Foote et al., 1983; McRae-Degueurce et al., 1985) — apparently by means of 5-HT_2 receptors (Gorea and Adrien, 1988) — and the proposed affinity of risperidone for 5-HT_2 receptors was similar to that of the atypical antipsychotic drug clozapine, we investigated the ID_{50} of DOI, a serotoninergic agonist, for the firing of locus coeruleus noradrenergic neurons in control and risperidone-treated rats. There were no differences in the sensitivity of the 5-HT_2 receptors that affect the activity of locus coeruleus noradrenergic neurons. The ID_{50} of DOI was 19.42 ± 4.41 and 22.61 ± 1.37 μg/kg for control and risperidone-treated rats, respectively (Fig. 3).

4. Discussion

In the prefrontal cortex, one of the projection areas of locus coeruleus noradrenergic neurons, a decrease in the basal norepinephrine level after chronic treatment with risperidone was found (Fig. 2). This could have been a result of depletion of norepinephrine because of increased locus coeruleus neuronal activity, in response to repeated risperidone administration. This finding is consistent with the results reported by Westerink et al. (1998) concerning a large, dose-related, increase in the overflow of norepinephrine in prefrontal cortex of the rat following acute risperidone administration.

Chronic risperidone administration was able to increase the activity of locus coeruleus noradrenergic neurons (Table 1), without changing the ID_{50} of clonidine for inhibiting the activity of locus coeruleus noradrenergic neurons (Fig. 1). This means that changes in the sensitivity of α_2-adrenoceptors, located in the locus coeruleus area, are not responsible for the increased firing of locus coeruleus noradrenergic neurons after risperidone administration. The α_2-self-inhibition is one of the mechanisms ruling the activity of locus coeruleus neurons, since the early phase of the after-hyperpolarization is relatively resistant to α_2-adrenoceptor blockade (McNaughton and Mason, 1980; Aghajanian et al., 1983). In the light of these findings, different arguments can be used to explain the increased firing rate and the number of spontaneously active cells per track observed in our experimental subjects. Changes in membrane properties, such as $I_{k(Ca)}$, induced by alteration of inhibitory norepinephrine release in the locus coeruleus area may be related to the increased activity of locus coeruleus neurons after repeated risperidone administration.

It has been demonstrated that risperidone displays high affinity for 5-HT_{2A} compared to dopamine D_2 receptors (Svartengren and Simonsson, 1990). Moreover, it has been found that risperidone inhibits the spontaneous firing of 5-HT cells in the dorsal raphe nucleus, probably by acting on 5-HT autoreceptors (Hertel et al., 1997b). There is a controversy over the nature of the inhibitory effects of 5-HT projections to the locus coeruleus nucleus. Most evidence supports an indirect effect on afferent projections to this nucleus (Rasmussen et al., 1986). Under our experimental conditions, after chronic administration of risperidone, DOI induced a dose-related inhibition of the spontaneous activity of locus coeruleus noradrenergic neurons. Moreover, the sensitivity of 5-HT_2 receptors, assessed by the ID_{50} of DOI on the activity of locus coeruleus cells, did not show any difference from that of the controls (Fig. 3).

Acute clozapine, unlike typical antipsychotic administration, decreases the firing rate of 5-HT neurons in the dorsal raphe nucleus (Gallager and Aghajanian, 1976). Similarly, risperidone inhibits the firing of this nucleus (Hertel et al., 1997a). Our results on the inhibitory effect of DOI on the locus coeruleus noradrenergic neurons may be a consequence of an increased 5-HT inhibitory input to the locus coeruleus, since inhibitory serotoninergic projections to the locus coeruleus have been described (Leger and Descarries, 1978; Segal, 1979; McRae-Degueurce et al., 1985).

The dopamine hypothesis of schizophrenia, in which schizophrenia is related to increased dopamine function (Matthyse, 1973), has been a major theory on schizophrenia. However, since the core symptoms of schizophrenia are the persistent negative symptoms as well as the cognitive deficits, and as these symptoms are notoriously unresponsive to neuroleptic treatment, awareness has grown that the original hypothesis is in need of an overhaul (Kahn and Davidson, 1995). New data suggest that the negative symptoms, as well as the cognitive deficits, may be related to decreased dopamine function in the prefrontal cortex. The positive symptoms of schizophrenia appear to

be related to increased dopamine turnover in the striatum (Kahn and Davidson, 1995). It is thought that typical antipsychotic drugs ameliorate the psychotic symptoms by decreasing dopamine activity in the A10 area after chronic administration. In contrast, it has been postulated that extrapyramidal side effects develop as a consequence of the chronic dopamine receptor inhibition in the A9 dopamine area (Chiodo and Bunney, 1983; White and Wang, 1983).

Our results show that continuous risperidone administration for 5 weeks modifies central noradrenergic transmission. Considering the different receptor interactions suggested for risperidone, the most likely receptor interactions involved are the interaction with α_1- and/or α_2-adrenoceptors because they are present in the locus coeruleus area as well as pre- and postsynaptically on adrenergic terminals. In the locus coeruleus, the stimulation of α_2-adrenoceptors induces inhibition of the firing of these cells. On prefrontal noradrenergic terminals, the α_2-adrenoceptors regulate norepinephrine release; the α_1-adrenoceptors are postsynaptically located. We cannot rule out another interaction between risperidone and 5-HT or dopamine receptors as being responsible for the decrease in the norepinephrine level observed in the prefrontal cortex under our experimental conditions. In the light of these findings, we suggest that the decreased norepinephrine level in the prefrontal cortex may be a compensatory effect which may also decrease the level of norepinephrine on the vicinity of locus coeruleus cells, enhancing the spontaneous activity of these cells. These low prefrontal norepinephrine levels found following chronic risperidone administration may contribute to the relief of certain negative symptoms observed in schizophrenia, since an increased noradrenergic activity has been associated with relapse of schizophrenia symptoms (Van Kammen et al., 1990). In fact, many neuropsychiatric disorders such as schizophrenia are also associated with high levels of norepinephrine turnover (Baldessarini et al., 1992).

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References

Aghajanian, G.K., Cedarbaum, J.M., Wang, R.Y., 1977. Evidence for norepinephrine-mediated collateral inhibition of locus coeruleus neurons. Brain Res. 136, 570–577.

Aghajanian, G.K., Vandermaelen, C.P., Andrade, R., 1983. Intracellular studies on the role of calcium in regulating the activity and reactivity of locus coeruleus neurons in vivo. Brain Res. 273, 237–243.

Baldessarini, R.J., Huston-Lyons, D., Campbell, A., Marsh, E., Cohen, B.M., 1992. Do central antiadrenergic actions contribute to the atypical properties of clozapine? Br. J. Psychiatry 160, 12–16.

Bersani, G., Bressa, G.M., Meco, G., Marini, S., Pozzi, F., 1990. Combined serotonin 5-HT_2 and dopamine D_2 antagonism in schizophrenia, clinical, extrapyramidal and neuroendocrine response in a preliminary study with risperidone (R 64 766). Hum. Psychopharmacol. 5, 225–231.

Cedarbaum, J.M., Aghajanian, G.J., 1977. Catecholamine receptors on locus coeruleus: pharmacological characterisation. Eur. J. Pharmacol. 44, 375–385.

Chiodo, L.A., Bunney, B.S., 1983. Typical and atypical neuroleptics: differential effects of chronic administration on activity of A9 and A10 midbrain dopaminergic neurons. J. Neurosci. 3, 1607–1619.

Chouinard, G., Vainer, J.L., Bélanger, M.-C., Turnier, L., Beaudry, P., Roy, J.-Y., Miller, R., 1994. Risperidone and clozapine in the treatment of drug-resistant schizophrenia and neuroleptic-induced supersensitivity psychosis. Prog. Neuro-Psychopharmacol. Biol. Psychiatry. 18, 1129–1141.

Cools, A.R., 1983. A mesolimbic system and tardive dyskinesia: new perspectives for therapy. In: Bennet, J., Belnaker, R.H. (Eds.), New Direction in Tardive Dyskinesia Research Vol. 21 Karger, Basel, pp. 111–123.

Den Boer, J.A., Westenberg, H.G.M., 1995. Atypical antipsychotics in schizophrenia: a review of recent developments. In: Den Boer, J.A., Westenberg, H.G.M., Van Praag, H.M. (Eds.), Advances in the Neurobiology of Schizophrenia. Wiley, England, pp. 275–302.

Foote, S.L., Bloom, F.E., Aston-Jones, G., 1983. Nucleus locus coeruleus: new evidence of anatomical and physiological specificity. Physiol. Rev. 63, 844–914.

Gallager, D.W., Aghajanian, G.K., 1976. Effect of antipsychotic drugs on the firing of dorsal raphe cells: I. Role of adrenergic system. Eur. J. Pharmacol. 39, 341–355.

Gorea, E., Adrien, J., 1988. Serotoninergic regulation of noradrenergic coerulean neurons: electrphysiological evidence for the involvement of 5-HT_2 receptors. Eur. J. Pharmacol. 154, 285–291.

Hertel, P., Nomikos, G.G., Schilström, B., Arborelius, L., Svensson, T.H., 1997a. Risperidone dose-dependently increases extracellular concentrations of serotonin in the rat frontal cortex: role of α_2-adrenoceptor antagonism. Neuropsychopharmacology 17, 44–55.

Hertel, P., Nomikos, G.G., Svensson, T.H., 1997b. Risperidone inhibits 5-hydroxytryptaminergic neuronal activity in the dorsal raphe nucleus by local release of 5-hydroxytryptamine. Br. J. Pharmacol. 122, 1639–1646.

Janssen, P.A., Niemegeers, C.J., Awouters, F., Schellekens, K.H., Megens, A.A., Meert, T.F., 1988. Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin-S_2 and dopamine-D_2 antagonistic properties. J. Pharmacol. Exp. Ther. 244, 685–693.

Kahn, R.S., Davidson, M., 1995. Dopamine in schizophrenia. In: Den Boer, J.A., Westemberg, H.G.M., Van Praag, H.M. (Eds.), Advances in the Neurobiology of Schizophrenia. Wiley, Chichester, pp. 205–220.

Kane, J.M., 1993. Newer antipsychotic drugs. A review of their pharmacology and therapeutic potential. Drugs 46, 585–593.

Leger, L., Descarries, S., 1978. Serotonin nerve terminals in the locus coeruleus of adult rat: a radioautographic study. Brain Res. 145, 1–13.

Matthyse, S., 1973. Antipsychotic drug actions: a clue to the neuropathology of schizophrenia?. Fed. Proc. 32, 200–205.

McNaughton, N., Mason, S.T., 1980. The neuropsychology and neuropharmacology of the dorsal ascending noradrenergic bundle: a review. Prog. Neurobiol. 14, 157–219.

McRae-Degueurce, A., Dennis, T., Leger, L., Scatton, B., 1985. Regulation of noradrenergic neuronal activity in the rat locus coeruleus by serotoninergic afferents. Physiol. Psychol. 13, 188.

Megens, A.A., Awouters, F., Niemegeers, C.J., 1988. Differential effects of the new antipsychotic risperidone on large and small motor movements in rats, a comparison with haloperidol. Psychopharmacology 95, 493–496.

Meltzer, H., 1995. The concept of an atypical antipsychotic drug. In: Den Boer, J.A., Westenberg, H.G., Van Praag, H.M. (Eds.), Advances in the Neurobiology of Schizophrenia. Wiley, England, pp. 265–273.

Meltzer, H.Y., Goode, D.J., Fang, V.S., 1978. The effect of psychotropic drugs on endocrine function: I. Neuroleptics, precursors, and agonists. In: Lipton, M.A., DiMascio, A., Killam, K.F. (Eds.), Psychopharmacology, a Genaration of Progress. Raven Press, New York, pp. 509–529.

Pavcovich, L.A., Ramirez, O.A., 1991. Time course effects of uncontrollable stress in locus coeruleus neuronal activity. Brain Res. Bull. 26, 17–21.

Paxinos, G., Watson, C., 1986. The Rat Brain in Stereotaxic Coordinates. Academic Press, New York.

Ramirez, O.A., Wang, R.Y., 1986a. Evidence for norepinephrine-containing neurons: effects produced by acute and subchronic treatment with antipsychotic drugs and amphetamine. Brain Res. 362, 165–170.

Ramirez, O.A., Wang, R.Y., 1986b. Electrophysiological evidence for locus coeruleus autoreceptor subsensitivity following subchronic administration of D-amphetamine. Brain Res. 385, 415–419.

Rasmussen, K., Glennon, R.A., Aghajanian, G.K., 1986. Phenethylamine hallucinogens in the locus coeruleus: potency of action correlates with rank order of 5-HT_2 binding affinity. Eur. J. Pharmacol. 132, 79–82.

Robinson, T.E., Justice, J.B. Jr., 1991. Microdialysis in the Neuroscience. Elsevier, Amsterdam, Netherland.

Sahakian, B.J., Hodges, J., 1994. Idazoxan improves cognitive functions in frontal lobe dementia. J. Neurol., Neurosurg. Psychiatry 57, 120–121.

Segal, M., 1979. Serotoninergic innervation of the locus coeruleus from the dorsal raphe and its action on response to noxious stimuli. J. Physiol. 286, 401–415.

Svartengren, J., Simonsson, P., 1990. Receptor binding properties of amperozide. Pharmacol. Toxicol. 66, 8–11.

Van Beijsterveldt, L.E., Geerts, R.J., Leysen, J.E., Megens, A.A., Van den Eynde, H.M., Meuldermans, W.E., Heykants, J.J., 1994. Regional brain distribution of risperidone and its active metabolite 9-hydroxy-risperidone in the rat. Psychopharmacology (Berlin) 114, 53–62.

Van Kammen, D.P., Peters, J., Yao, J., Van Kammen, W.B., Neylan, T., Shaw, D., Linnoila, M., 1990. Norepinephrine in acute exacerbations of chronic schizophrenia. Arch. Gen. Psychiatry 47, 161–170.

Westerink, B.H.C., de Boer, P., de Vries, J.B., Kruse, C.G., Long, S.K., 1998. Antipsychotic drugs induce effects on the release of dopamine and noradrenaline in the medial prefrontal cortex of the rat brain. Eur. J. Pharmacol. 361, 27–33.

White, F.J., Wang, R.Y., 1983. Differential effects of classical and atypical antipsychotic drugs on A_9 and A_{10} dopamine neurons. Science 221, 1054–1057.

Williams, J.T., Henderson, G., North, R.A., 1985. Characterization of α_2-adrenoceptors which increase potassium conductance in rat locus coeruleus neurons. Neuroscience 14, 95–101.