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Short communication

Chronic administration of *l*-sulpiride at low doses reduces A10 but not A9 somatodentritic dopamine autoreceptor sensitivity

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Abstract

The effect of chronic treatment (twice daily for 21 days) with low doses of *l*-sulpiride (2 mg/kg i.p.) on the apomorphine-induced inhibition of A10 and A9 dopaminergic neurons was compared with the effect of chronic administration of the classic antidepressant desipramine (20 mg/kg i.p. daily for 21 days). Intravenous administration of apomorphine (0.01–0.04 mg/kg), to rats treated chronically with *l*-sulpiride, produced a reduction of the spontaneous firing rate of A9 dopaminergic neurons not significantly different from that observed in control (saline-treated) rats. In contrast, apomorphine at the same doses was more potent in inhibiting A10 firing in control rats than in *l*-sulpiride-treated subjects. On the other hand, desipramine-treated rats were found normosensitive (as compared to saline-treated rats) to the inhibitory properties of apomorphine in both A9 and A10 dopaminergic neurons. It is suggested that chronic *l*-sulpiride-induced reduction of autoreceptor sensitivity in the A10 region may contribute to its clinical antidepressant effect.

Keywords: Dopamine neuron; *l*-Sulpiride; Desipramine; Autoreceptor; Depression

1. Introduction

Behavioural and biochemical studies have evidenced that chronic treatment with antidepressants selectively increases dopamine transmission in the mesolimbic system. Spyraki and Fibiger (1981) reported that chronic treatment with desipramine potentiates the hypermotility but not the stereotypes induced by amphetamine and apomorphine. Since the stimulation of locomotor activity induced by amphetamine is considered to be due to activation of dopamine receptors in the mesolimbic system, these authors first suggested that chronic treatment with antidepressants might selectively increase the sensitivity of dopamine receptors in the mesolimbic system. In support of this hypothesis, chronic administration of desipramine enhances intracranial self-stimulation from electrodes placed in the ventral tegmental area, the site of origin of dopamine neurons that project to the nucleus accumbens (see review by Serra et al., 1992).

Subsequently, other reports have demonstrated that chronic antidepressants potentiate dopamine transmission in the mesolimbic system. In different animal models of depression (behavioural despair, learned helplessness, chronic mild stress) antidepressant drugs seem to act by increasing dopamine transmission in this system (Serra et al., 1992). More recently, it has been shown that chronic antidepressants selectively increase the behavioural stimulant responses mediated by the activation of dopamine D_2 receptors in the mesolimbic system (Serra et al., 1992). Furthermore, it has been observed that chronic imipramine potentiates the stimulating effect of cocaine on motor activity and dopamine release in limbic areas (Rossetti et al., 1991), while chronic desipramine enhances the amphetamine-induced increase of dopamine release in the nucleus accumbens but not in the striatum (Nomikos et al., 1991). Brown et al. (1991) then showed that desipramine increases the effect of locally applied amphetamine on dopamine release in the nucleus accumbens.

l-Sulpiride is a blocker of dopamine D_2 receptors with a paradoxical profile: it exhibits opposite therapeutic effects depending on the doses administered. At high doses (800–1000 mg/die) (Cassano et al., 1975) it behaves as a

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traditional neuroleptic, whereas low doses produce an antidepressant effect (Bocchetta et al., 1993; Maier and Benkert, 1994). Since the mesolimbic system plays an important role in the mechanism of action of antidepressants (see Serra et al., 1992), this effect may arise from a selective blockade of dopamine autoreceptors in the mesolimbic system thus damping the self-inhibition (Groves et al., 1975) produced by endogenous dopamine and thereby potentiating dopamine transmission (Serra et al., 1992). To investigate this possibility we compared the efficacy of apomorphine at low doses to inhibit dopaminergic neurons in both A9 and A10 regions in rats chronically treated with *l*-sulpiride and with the classical antidepressant, desipramine.

2. Materials and methods

Male Sprague-Dawley rats (Charles-River, Como, Italy) weighing 225–300 g at the beginning of treatment were used. The rats were housed four per cage at 22°C with lights on from 08:00 to 20:00 h and food and water ad libitum.

The rats were divided into four groups: one ($n = 10$) received *l*-sulpiride (2 mg/kg i.p. twice a day for 21 consecutive days), one ($n = 10$) received desipramine (20 mg/kg i.p. once a day for 21 consecutive days), and two groups ($n = 20$) received a corresponding volume of saline.

Four hours after last drug or saline administration the rats were anesthetized with halothane and surgically prepared for extracellular single unit recordings as already described (Diana et al., 1991). Recordings were obtained from A10 and A9 dopaminergic neurons (A 2.0, L 0.5 and A 1.9, L 1.9 from lambda, respectively). Antidromic activation from the nucleus accumbens (for A10 region) and nucleus caudatus (for A9 region) (A 8.8, L 1.6, V 7.1 from lambda and A 1.0, L 3.6, V 3.75, from bregma, respectively) was achieved, delivering rectangular pulses (0.1–3.0 mA; 0.1–0.5 ms, 0.8 Hz) with a stainless-steel Formvar-coated bipolar electrode.

Dopamine neurons were identified by their anatomical position, their response to antidromic activation and characteristic waveform and firing pattern. After the basal firing rate had been recorded (5–10 min), apomorphine was administered i.v. at exponentially increasing doses every 120 s (0.01–0.04 mg/kg). Only one cell was recorded per rat.

3. Results

The results obtained from *l*-sulpiride- and desipramine-treated rats were compared to those obtained from saline-treated rats by means of a repeated measures analysis of variance (ANOVA). Results obtained from the two control groups (saline-treated) were pooled since no differences between them were found.

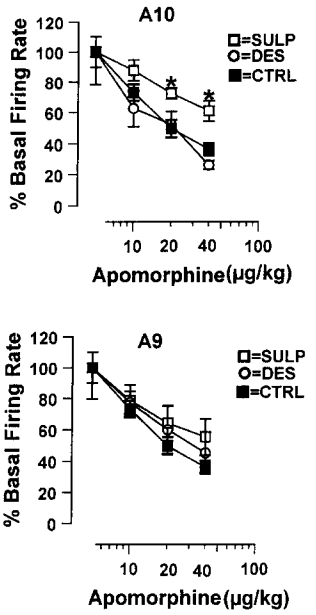

Fig. 1. Dose-response curves for the inhibitory effect of apomorphine (10–40 μg/kg i.v.) on firing rate of antidromically identified A10 (top) and A9 (bottom) dopaminergic neurons in chronic *l*-sulpiride (SULP) ($n = 10$), chronic desipramine (DES) ($n = 10$) and saline-treated rats (CTRL) ($n = 20$). Apomorphine-induced inhibition was reduced in rats treated chronically with SULP as compared with DES and CTRL. * $P < 0.05$ (ANOVA for repeated measures).

As shown in Fig. 1, repeated *l*-sulpiride administration for 3 weeks caused a significant decrease in the ability of apomorphine to inhibit the firing rate of A10 but not A9 dopamine neurons as compared to that in saline-treated rats. Chronic desipramine did not modify apomorphine sensitivity in A9 or in A10 neurons as compared to that in neurons from control rats.

4. Discussion

The present results showed that chronic administration of low doses of the dopamine D_2 receptor antagonist *l*-sulpiride reduces the ability of intravenously administered apomorphine to inhibit selectively dopamine neuronal activity in the A10 region. Accordingly, A9 dopamine neurons recorded from *l*-sulpiride-treated rats were found not significantly different from those of saline-treated controls in their response to apomorphine administration (Fig. 1).

Previous clinical investigations (Bocchetta et al., 1993; Maier and Benkert, 1994) have reported an antidepressant action of low doses of *l*-sulpiride. The mechanism by which *l*-sulpiride could produce an antidepressant action might be through blocking preferentially dopamine autoreceptors in the limbic system. Biochemical data indicate

that both striatal dopamine D_1 and D_2 receptor function (transductional mechanisms) is reduced by long-term treatment with *l*-sulpiride. This is consistent with an increased dopamine tonus on these receptors and suggests a preferential blockade of dopamine autoreceptors (Missale et al., 1990). The somatic autoreceptor blockade could impair dopamine autoinhibition (Groves et al., 1975), eventually potentiating dopamine transmission (Serra et al., 1992; Brown et al., 1991; Nomikos et al., 1991).

On the other hand, the inefficacy of chronic desipramine to prevent apomorphine-induced inhibition of dopamine neurons, although supported by some (Chiodo and Antelman, 1980) has been denied by most investigators (MacNeil and Gower, 1982; Groves et al., 1990) and thus is consistent with an antidepressant action of desipramine at a different neuronal level.

Recently, Bouthenet et al. (1991) have shown that dopamine D_3 receptor mRNA is localized mainly in limbic areas such as the ventral striatum, islands of Calleja and hippocampus, which receive dopaminergic projections from the A10 cell group where it has also been detected in dopamine perikarya. Its expression in the A10, and corresponding terminal areas, has suggested that the dopamine D_3 receptor might play an autoreceptor role (Bouthenet et al., 1991). *l*-Sulpiride displays a relatively high affinity for such receptors, and its ability to reduce the apomorphine-induced inhibition of dopamine neuronal activity, selectively so in the A10 region, might be ascribed to blockade of dopamine D_3 autoreceptors in addition to blockade of autoreceptors of the D_2 type.

In conclusion, the present findings indicate an inhibitory action of low doses of *l*-sulpiride on the autoreceptor-mediated inhibition of dopamine firing produced by apomorphine selectively in the limbic system. When considered in light of previous reports these results may provide a basis for the antidepressant effect of *l*-sulpiride in humans.

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