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The functional sensitisation of sigma receptors following chronic selective serotonin reuptake inhibitor treatment

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Abstract

The purpose of the present study was to investigate the potential impairment of normal motor function following chronic selective serotonin reuptake inhibitor treatment that may result from sensitisation of σ receptors. Rats were chronically treated with either sertraline, citalopram, paroxetine or fluvoxamine and a selective σ receptor ligand, di-*o*-tolylguanidine (DTG), for 28 days. All animals then received an acute intra-rubral injection of either DTG or saline. Following the direct injection of DTG into the red nucleus, rats chronically treated with DTG exhibit a maximal behavioural response characterised as a pronounced dystonia. Animals chronically treated with sertraline and citalopram elicited a response similar to that of control animals following the acute DTG challenge, whereas chronic treatment with paroxetine and fluvoxamine significantly decreased and increased the dystonic response, respectively. Facial spasticity and vacuous chewing movements were associated with, and reflected the extent of, the DTG-induced dystonia. Changes in regional biogenic amine concentrations were also determined. The concentrations of serotonin and noradrenaline were determined in the brain stem and cerebellum following the intra-rubral injection of either saline or DTG in animals that had been chronically treated with a selective serotonin reuptake inhibitor or DTG. There was a significant increase in serotonin concentration in the brain stem as a result of chronic DTG and fluvoxamine treatments. The increase in serotonin correlated with the reported potentiation of dystonia in animals that received 28 days treatment with these drugs. The potentiation of dystonia following chronic DTG and fluvoxamine treatments suggests that these drugs sensitise the σ_2 receptors, an effect that does not appear to be shared by citalopram, sertraline or paroxetine.

Keywords: Selective serotonin reuptake inhibitor; σ Receptor; Red nucleus; Behaviour; Sensitisation; DTG (Di-*o*-tolylguanidine)

1. Introduction

The major advantage of the selective serotonin reuptake inhibitors compared to the older tricyclic antidepressants is their reduced anticholinergic side effects, reduced cardiotoxicity and their safety in overdose (Leonard, 1992; Mitchell, 1994). Nevertheless, a number of side effects that are associated with some selective serotonin reuptake inhibitors include dry mouth, nausea, insomnia, tremor and gastrointestinal tract disturbances (Hyttel, 1994). The anticholinergic activity does not explain the prevalence of motor impairments associated with selective serotonin reuptake inhibitor treatment which includes acute dystonia (Brod, 1989; George and Trimble, 1993), akathisia (Lipinski et al., 1989; Baldwin et al., 1991), dyskinesia (Arya and Szabadi, 1993) and the development of Parkinsonian symptoms (Meltzer et al., 1979; Caley and Friedman, 1992; Chouinard and Sultan, 1992; Steur, 1993). Although serotonin has been implicated in the development of extrapyramidal side effects, the ability of selective serotonin reuptake inhibitors to increase serotonergic activity is not necessarily a prelude to elicit an impairment in motor function (Leonard and Faherty, 1996). Moreover, activity at sites other than serotonergic neurons may contribute to the reported movement disorders following selective serotonin reuptake inhibitor treatment (Leo, 1996).

One possible explanation for motor impairment following selective serotonin reuptake inhibitor treatment is their action on σ receptors (Walker et al., 1988; Schmidt et al., 1989; Tulloch et al., 1995; Narita et al., 1996). Although there is strong evidence to suggest the presence of at least

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two subtypes of σ receptor (σ_1 and σ_2), it is thought that the σ_2 subtype is primarily involved in motor function and control (Walker et al., 1990; Quirion et al., 1992; Leitner et al., 1994). It is known that σ receptors occur in a high density in a number of brain regions that control movement. These regions include many of the central nuclei involved in muscle control such as the trigeminal, oculomotor and hypoglossal nuclei, the substantia nigra, cerebellum, brain stem and the red nucleus (Gundlach et al., 1986; Walker et al., 1990).

The red nucleus is a major component of the rubrocerebellar circuit and has proven to be a useful site for the investigation of the potential role of σ receptors in motor control (Matsumoto and Walker, 1988, 1992; Matsumoto et al., 1990). The high density of σ receptors, and very low densities of other receptors with affinity for σ receptor ligands (e.g., dopamine, opiate, phencyclidine, 5-HT receptors or adrenoceptors), make the red nucleus an ideal site for such investigations. Microinjection of a variety of σ receptor ligands into the red nucleus, including (+) *N*-allyl-normetazocine ((+)-SKF 10,047), (+)-pentazocine and di-*o*-tolylguanidine (DTG) results in dystonia in rats (Matsumoto et al., 1989; Walker et al., 1990).

The purpose of the present study was to investigate adaptive changes in σ receptors which may occur as a result of chronic selective serotonin reuptake inhibitor treatment in a behavioural model known to be sensitive to the actions of σ receptor ligands. In addition, regional changes in serotonin and noradrenaline concentrations were also determined in an attempt to assess whether any changes in motor function were correlated with regional changes in biogenic amines.

2. Methods and materials

2.1. Animals and drug treatment

Male Sprague–Dawley rats (250–280 g) were obtained from Harlan Olac (Bicester, UK) and allowed 1 week acclimatisation before the start of the experiment. Animals were housed in standard polypropylene cages ($45 \times 28 \times 20$ cm) with food and water available ad libitum. They received an intraperitoneal (i.p.) injection of sertraline, fluvoxamine, paroxetine, citalopram, DTG or physiological saline daily for 28 days. All selective serotonin reuptake inhibitors were dissolved in saline on the day of administration and injected in a volume of 1 ml/kg at a dose of 5 mg/kg. DTG was dissolved in dilute hydrochloric acid, saline was then added at pH 6.7 and the resultant solution administered in a volume of 1 ml/kg at a dose of 5 mg/kg. All selective serotonin reuptake inhibitors were a gift from Pfizer (Sandwich, UK), Solvay Duphar (Weesp, Netherlands), SmithKline&Beecham, (Harlow, UK) and Lundbeck (Copenhagen, Denmark).

2.2. Surgery

Three days prior to behavioural testing, animals were anaesthetised with chloral hydrate (300 mg/kg i.p.) and mounted in a Kopf stereotaxic apparatus. A guide cannula, constructed from 24-gauge thinwall stainless steel tubing, was stereotaxically implanted with its tip 4.00 mm above the left red nucleus (coordinates: 2.9 mm anterior, 1.1 mm lateral, 4.00 mm ventral from lambda and the skull surface (Paxinos and Watson, 1982). Cannula were secured with stainless steel screws and dental acrylic cement. The duration of the surgical procedure was 10–12 min; each animal was singly housed following cannulation. The surgical procedure was based on that of Matsumoto et al. (1988).

2.3. Behavioural testing

Following the intra-rubral injection (0.5 μl/72 s) of saline or DTG each animal was placed in a clear plastic cylindrical observation chamber (20×50 cm). Each animal was assigned a behavioural score to express the extent of dystonia (Table 2). The scoring system employed is a modification of that previously described by Contreras et al. (1988) and is a direct indication of the extent of dystonia at each time period. The extent of facial spasticity, vacuous chewing or grooming behaviour was not quantified. Two independent observers, who were 'blind' to the nature of the drug administered, scored the motor changes. Before the designation of a single behavioural score, both observers were in agreement as to the extent of the dystonia. Each animal was killed by decapitation 40 min following the intra-rubral injection of either saline or DTG, the brains rapidly dissected and stored at -20°C for histological and biochemical analyses.

2.4. Histological analysis

Histological verification of each brain was made using a Bright's cryostat. A 20-μm coronal section was taken throughout the injection site. The sections were stained using standard haematoxylin and eosin procedures. Only animals with histologically verified cannula placements were included in the data analysis.

2.5. Biochemical analysis

The whole cerebellum and brain stem were rapidly dissected on ice, sonicated in 1 ml buffer (mobile phase) containing 2 ng/50 μl *N*-methyl dopamine as an internal standard and stored at -20°C for biochemical analysis. Samples were analysed using an automated high performance liquid chromatography (HPLC)-electrochemical detection system (Shimadzu). The mobile phase contained 0.1 M citric acid, 0.1 M sodium dihydrogen phosphate, 1.4 mM octane-L-sulfonic acid, 0.1 mM ethylenediaminete-

traacetic acid and 9% methanol. The pH of the mobile phase was then adjusted to 2.8 with 4 M NaOH. The retention times of biogenic amines varied between 5–30 min on an LI Chrosorb RP-18 column. The HPLC method used was based on that of Seyfried et al. (1986). The flow rate of the mobile phase through the HPLC system was 1 ml/min at a pressure of approximately 200 bar. The column oven was maintained at 30°C. All standards were purchased from Sigma (Poole, Dorset, UK).

2.6. Treatment groups

The drug treatment of groups 1–12 are listed in Table 1.

2.7. Statistical analysis

Behavioural data was treated with a Friedman two-way analysis of variance (ANOVA) by ranks followed by a post hoc analysis using the Friedman multiple comparison procedure (Friedman, 1937, 1940). The biochemical data was treated with a two-way ANOVA followed by a post hoc analysis using the Student–Newman–Keuls test.

3. Results

3.1. Effect of intra-rubral injection of saline and DTG on dystonia

There were significant changes in dystonia at times corresponding to 1 min ($S = 112.07$, $df = 11$, $P = 0.000$), 5 min ($S = 152.21$, $df = 11$, $P = 0.000$) and 15 min ($S = 116.16$, $df = 11$, $P = 0.000$) after intra-rubral injections (Table 2).

Table 1
Drug treatment of groups 1–12

Group	Chronic treatment (i.p.)	Challenge (i.r.)
1	Saline	saline
2	DTG	saline
3	fluvoxamine	saline
4	paroxetine	saline
5	sertraline	saline
6	citalopram	saline
7	Saline	DTG
8	DTG	DTG
9	fluvoxamine	DTG
10	paroxetine	DTG
11	sertraline	DTG
12	citalopram	DTG

i.p.: Intraperitoneal.
i.r.: Intra-rubral.
DTG: Di-*o*-tolylguanidine.

Table 2
Changes in dystonia following direct injection of DTG into the left red nucleus of the rat

	Group	*n*	1 min	5 min	15 min
Intra-rubral Saline (0.89%)					
Intraperitoneal					
Saline	1	12	0(0–0)	0(0–0)	0(0–0)
DTG	2	10	0(0–0)	0(0–0)	0(0–0)
Fluvoxamine	3	10	0(0–0)	0(0–0)	0(0–0)
Paroxetine	4	10	0(0–0)	0(0–0)	0(0–0)
Sertraline	5	10	0(0–0)	0(0–0)	0(0–0)
Citalopram	6	10	0(0–0)	0(0–0)	0(0–0)
Intra-rubral DTG (18.6 nmol)					
Intraperitoneal					
Saline	7	15	1(1–1)^{A}	1(0.5–1)^{A}	0(0–0)
DTG	8	19	3(3–3)^{B}	2(1–2)^{B}	1(0.5–1)
Fluvoxamine	9	13	2(2–2)^{B}	1(1–1)	0(0–0)
Paroxetine	10	13	0(0–0)^{B}	0(0–0)	0(0–0)
Sertraline	11	13	1(1–1)	0(0–0)	0(0–0)
Citalopram	12	14	1(1–1)	0(0–0)	0(0–0)

Behavioural scoring corresponding to 24 h following the last i.p. injection of drugs: 0 = no dystonia, 1 = mild dystonia, 2 = moderate dystonia, 3 = pronounced dystonia.
DTG: di-*o*-tolylguanidine.
Results expressed as the median behavioural score with interquartile ranges in parentheses ($Q1-Q3$).
$^{A}P < 0.05$ compared to group 1; $^{B}P < 0.05$ compared to group 7 (Friedman multiple comparison).

3.1.1. Effect of intra-rubral injection of saline on dystonia

To analyse the effect that intra-rubral injected vehicle (saline) had on dystonia group 1 was compared to groups 2, 3, 4, 5, 6. There were no significant changes in dystonia following the intra-rubral injection of saline (Table 2).

3.1.2. Effect of intra-rubral injection of DTG on dystonia

To verify that DTG elicits dystonia and is therefore a viable ligand to challenge the σ receptor system group 1 was compared to group 7. There was a significant increase in the development of dystonia following the intra-rubral injection of DTG (Table 2).

To establish the effect that chronic selective serotonin reuptake inhibitor treatment had on σ receptor sensitisation group 7 was compared to groups 8, 9, 10, 11, 12. There were significant increases in dystonia in animals that had received 28 days treatment with DTG and fluvoxamine while those that had received paroxetine exhibited a significant suppression of the intra-rubral DTG-induced dystonia (Table 2).

Animals that were dystonic following intra-rubral injections also exhibited associated behavioural traits that included vacuous chewing movements, grooming, exophthalmos; in some cases, piloerection was also noted. These associated behavioural traits were not quantified but did seem to reflect the severity and duration of dystonia.

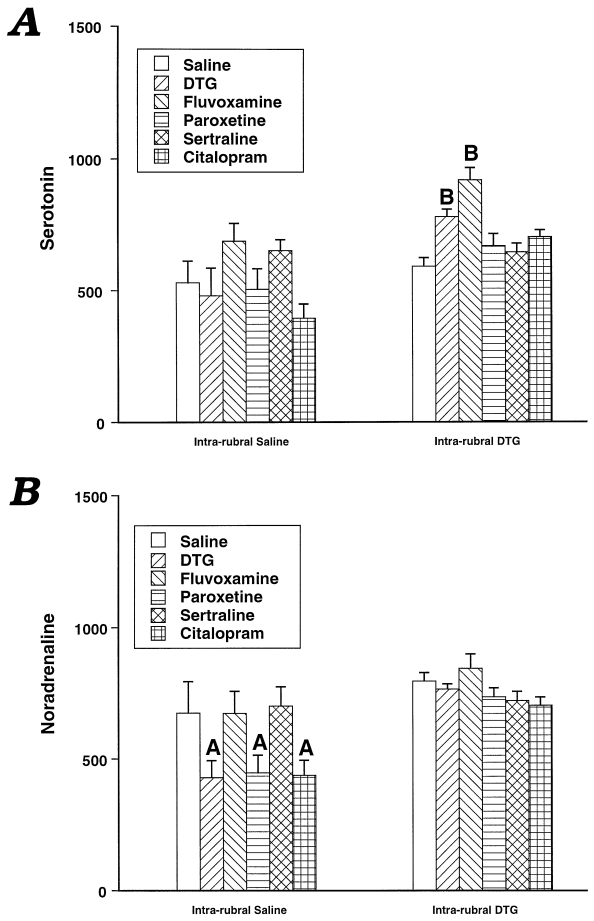

Fig. 1. Changes in (A) serotonin and (B) noradrenaline concentration in the brain stem following the direct injection into the red nucleus of the rat. Results expressed as mean ng/g fresh tissue weight ± standard error of the mean (S.E.M.). $^{A}P < 0.05$ comparing group 1 to groups 2, 3, 4, 5, 6; $^{B}P < 0.05$ comparing group 7 to groups 8, 9, 10, 11, 12 (see Table 1) (Student–Newman–Keuls). DTG: di-*o*-tolylguanidine.

3.2. Effects of intra-rubral injection of saline and DTG on biogenic amine concentration

3.2.1. The effect of intra-rubral injection of saline in the brain stem

To analyse the changes in biogenic amine concentration as a result of 28-day pretreatment alone, group 1 was compared to groups 2, 3, 4, 5, 6. There were significant changes in noradrenaline concentration ($F(5,112) = 4.79$ $P = 0.0005$). Post hoc analysis revealed a significant decrease in noradrenaline concentration in animals that had received 28 days preteatment with DTG, paroxetine and citalopram (Fig. 1b).

3.2.2. Effect of intra-rubral injection of DTG in the brain stem

To analyse the changes in biogenic amine concentration as a result of the σ receptor ligand DTG alone, group 1 was compared to group 7. There was no significant change in biogenic amine concentration.

To analyse the effect that chronic selective serotonin reuptake inhibitor treatment had on biogenic amine concentration following intra-rubrally injected DTG, group 7 was compared to groups 8, 9, 10, 11, 12. There was a significant change in serotonin concentration ($F(5,111) = 2.8$ $P = 0.03$). Post hoc analysis revealed a significant increase in serotonin in animals that had received 28 days treatment with DTG and fluvoxamine (Fig. 1a).

3.2.3. The effect of intra-rubral injection of saline in the cerebellum

To analyse the changes in biogenic amine concentration as a result of 28 day pretreatment alone, group 1 was compared to groups 2, 3, 4, 5, 6. There were no changes in biogenic amine concentration as a result of drug pretreatment (Fig. 2).

3.2.4. The effect of intra-rubral injection of DTG in the cerebellum

To analyse the changes in biogenic amine concentration as a result of the σ receptor ligand DTG alone, group 1 was compared to group 7. There were no significant changes in biogenic amine concentration (Fig. 2).

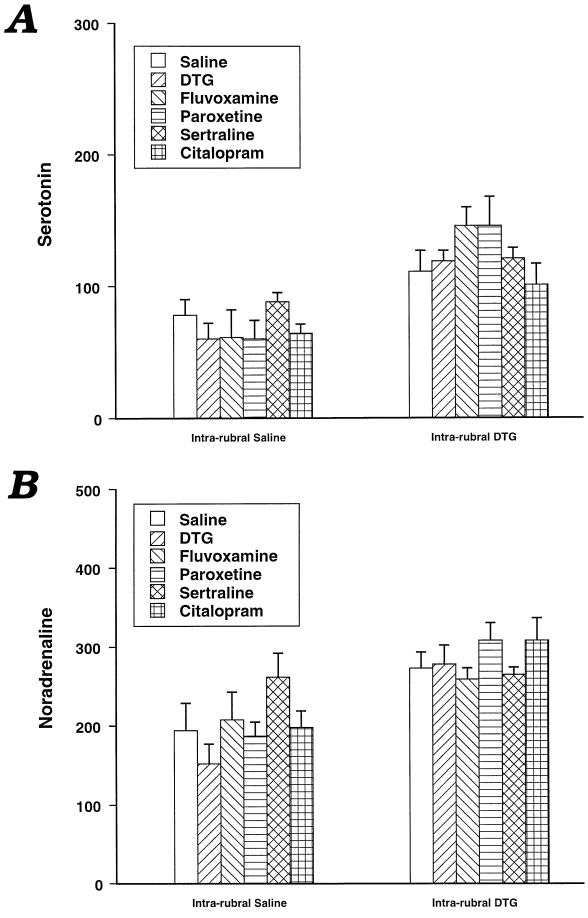

Fig. 2. Changes in (A) serotonin and (B) noradrenaline concentration in the cerebellum following the direct injection into the red nucleus of the rat. Results expressed as mean ng/g fresh tissue weight ± standard error of the mean (S.E.M.). DTG: di-*o*-tolylguanidine.

To analyse the effect that chronic selective serotonin reuptake inhibitor treatment had on biogenic amine concentration following intra-rubrally injected DTG, group 7 was compared to groups 8, 9, 10, 11, 12. There were no changes in biogenic amine concentration (Fig. 2).

4. Discussion

In an attempt to determine the antidepressant-induced adaptive changes in σ receptors, animals were chronically treated with a number of selective serotonin reuptake inhibitors and a known σ receptor ligand. The σ receptors were then challenged by intra-rubral administration of the potent σ receptor ligand, DTG, an action that has previously been demonstrated to elicit severe dystonia in rats (Matsumoto et al., 1990, 1996). A previous experiment in this laboratory demonstrated the ability of fluoxetine and fluvoxamine to elicit an acute dystonic reaction, that was comparable to DTG, when intra-rubrally injected in the rat (Faherty et al., 1997). Therefore, it was our intention to extend the preliminary study and investigate the role σ receptors have in the development of motor impairments as a result of chronic antidepressant treatment.

In the previous study, the order of potency of selective serotonin reuptake inhibitors to elicit dystonia when intra-rubrally injected in naive rats was fluoxetine = fluvoxamine > sertraline = citalopram = paroxetine (Faherty et al., 1997). This finding is reflected in the present study where the order of potency to elicit dystonia as a result of intra-rubrally injected DTG, following chronic administration, was fluvoxamine > sertraline = citalopram > paroxetine. The ability to elicit dystonia in either naive or chronically treated rats is similar to the in vitro binding affinity of these antidepressants for σ_1 receptors (Narita et al., 1996). However, there is a dissociation between the motor effects produced by (+)-pentazocine and the binding to σ_1 receptors whereas both drug-induced and age related changes in the number and affinity of [^{3}H]-DTG labelled σ receptor have functional ramifications for the control of movement and posture (Hemstreet et al., 1993; Matsumoto et al., 1990, 1996). Although σ_1 and σ_2 receptors are abundant in the rat brain, the ratio of σ_2/σ_1 often exceeds 2–3 in a number of regions intimately associated with the control of movement (Leitner et al., 1994). Moreover, because of their overlying distribution it is probable that these receptors are functionally related and can co-ordinate biological effects in vivo. For example, if σ_1 receptors were to act in an autoregulatory fashion then long-term exposure to an antagonist could lead to sensitisation of σ_2 receptors postsynaptically and subsequent potentiation of the physiological response.

Chronic treatment with DTG resulted in a potentiation of dystonia following the intra-rubral injection of DTG, an action that would strongly suggest the sensitisation of σ receptors. The increased dystonic behaviour was also observed in animals that had received 28-day treatment with the selective serotonin reuptake inhibitor, fluvoxamine. The changes in motor behaviour indicate an adaptive change in σ_2 receptors, these receptors being associated with the control of movement (Walker et al., 1990; Quirion et al., 1992; Leitner et al., 1994). σ Receptors have previously been implicated in behavioural sensitisation although the precise neural mechanism involved is undetermined (Akiyama et al., 1994; Leonard, 1996). Furthermore, a recent study by Ela et al. (1996) showed that different subtypes of the σ receptors are responsible for both attenuation and augmentation of the physiological response as a result of desensitisation and sensitisation, respectively. The other changes in motor behaviour noted in the present study included facial spasms and grooming behaviour, vacuous chewing movements and exophthalmos. It is possible that these changes result from stimulation of the cranial nerves originating in the red nucleus that innervate the facial muscles (Gundlach et al., 1986).

A number of selective serotonin reuptake inhibitors have been reported to cause extrapyramidal side effects (reviewed by Leo (1996)). Fluvoxamine and fluoxetine have been reported to cause dystonias (Meltzer et al., 1979; George and Trimble, 1993; Stoukides and Stoukides, 1991), dyskinesia (Budman and Brunn, 1991; Lipinski et al., 1989; Rothschild and Locke, 1991; Hamilton and Opler, 1992) and Parkinsonism (Caley and Friedman, 1992; Steur, 1993). These extrapyramidal side effects are predominantly associated with the motor centres of the brain and may arise from a non-selective activation of the rubro-cerebellar circuit (Bouchard et al., 1989; Baldessarini and Marsh, 1990; Mitchell, 1994; Leonard and Faherty, 1996). It should be emphasised that the effects of the selective serotonin reuptake inhibitors, when intra-rubrally injected, are not attributable to serotonin as the direct intra-rubral injection of 100 nmol serotonin did not elicit dystonia (Faherty, unpublished). This observation is further supported by the lack of dystonia following the intra-rubral injection of serotonin in the cat (Schmied et al., 1991). The fact that intra-rubral serotonin does not elicit dystonia is not surprising as serotonin has previously been shown to possess negligible binding affinity for either σ_1 or σ_2 receptors (Weber et al., 1986; Walker et al., 1990).

Dystonia has previously been associated with lesions of the brain stem, cerebellum, locus coeruleus and the red nucleus (Castaigne et al., 1981; Jankovic and Patel, 1983; Stanley et al., 1983; Jankovic et al., 1987). There has also been a number of neurochemical studies in patients suffering from dystonia. These studies have demonstrated an increased utilisation of cerebral glucose, an action that is proposed to result in the overactivity of the basal ganglia and supplementary motor area projections (Chase et al., 1988; Eidelberg et al., 1990; Brooks et al., 1992; Playford et al., 1992). An increase in cerebral glucose utilisation has also been demonstrated following the systemic administra-

tion of the σ receptor ligand, DTG (Hohmann et al., 1992). This σ receptor ligand-induced increase in cerebral glucose utilisation was reported in a number of regions including cerebellar and brain stem nuclei (Hohmann et al., 1992).

In the present study a significant increase in serotonin concentration in animals that had been chronically treated with DTG and fluvoxamine was observed following the acute injection of DTG into the red nucleus. The changes in brain stem serotonergic activity reflect the observed behavioural sensitisation manifested as a potentiation of dystonia following intra-rubral DTG injection. The increased excitation within motor circuits may explain the increase in serotonin concentration in the present study, the brain stem containing a high density of serotonergic neurons. The changes in serotonin concentration, following the intra-rubral DTG-induced dystonia, supports the finding that the genetically engineered hamster that elicits dystonia in response to environmental stimuli also exhibits an increase in the concentration of serotonin (Loscher et al., 1994). Although σ receptors have been shown to affect the dopaminergic system, these experiments usually involve the direct injection of σ receptor ligands into regions highly innervated by dopamine neurons (Patrick et al., 1993; Gudelsky, 1995; Weiser et al., 1995). In this respect the effect a direct injection of DTG into the raphé nucleus is unknown but may help determine whether σ receptor ligands can directly influence serotonergic activity. The fact that both σ and 5-HT receptors are found in abundance in both midbrain and brain stem nuclei and are also associated with the control of movement suggests a possible interaction that functions to regulate the motor circuits in the brain (Walker et al., 1990; Schmied et al., 1991; Jacobs and Fornal, 1993).

In conclusion, chronic treatment with DTG and fluvoxamine leads to a potentiation of dystonia following an intra-rubral injection of DTG, an action that would indicate a sensitisation of σ_2 receptors, this being causally linked to motoric control. Few changes in amine neurotransmitters were detected but the potentiation of behaviour was correlated with an increase in the concentration of serotonin in the brain stem. Although the extent to which the σ and the serotonergic systems interact is an open question the present study provides some indication that adaptive changes in at least one of these systems may be the underlying cause of many antidepressant related motor impairments.

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