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The dopamine D_2 receptor antagonist sulpiride causes long-lasting serotonin release

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Abstract

The effects of the dopamine D_2 receptor antagonist sulpiride on extracellular levels of serotonin (5-hydroxytryptamine, 5-HT) and the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) were examined by using in vivo voltammetry. Sulpiride (1 or 3 mM; 2 μl over 24 min) was administered to freely moving rats via a cannula implanted in the striatum and 5-hydroxyindole levels were measured by using a carbon fiber voltammetry electrode implanted in the ipsilateral striatum. Six to 8 h after injection, 5-hydroxyindole levels increased 3-fold, peaked 1 to 2 days post-injection, and returned to normal levels within 2 to 4 days. These effects were suppressed by pretreatment with *p*-chlorophenylalanine. Two days after sulpiride injection, high-performance liquid chromatography of striatal homogenates revealed that although the 5-HT concentration was unchanged, the 5-HIAA concentration was increased significantly. These results suggest that the long-lasting elevation of 5-hydroxyindole concentrations was primarily due to increased 5-HT release.

Keywords: Voltammetry, in vivo; Dopamine D_2 receptor antagonist; 5-HT (5-hydroxytryptamine, serotonin); Depression; Schizophrenia

1. Introduction

Depression is thought to be related to dysfunction of the serotonergic system (Ashcroft et al., 1966; Cervo et al., 1991). Recent evidence indicates that selective uptake inhibitors of serotonin (5-hydroxytryptamine, 5-HT) are very effective in the treatment of depression (Bodnoff et al., 1989; Martin et al., 1990; Boyer, 1992; Fuller, 1994). In addition, the atypical antipsychotic drug clozapine, a mixed dopamine receptor and 5-HT receptor antagonist, is effective in the treatment of some forms of schizophrenia (Kane et al., 1988; Meltzer et al., 1989; Coward, 1992), suggesting that 5-HT function also may be involved in this disease.

Sulpiride, a specific dopamine D_2 receptor antagonist, is widely used as a very effective treatment for depression and schizophrenia. This drug is reported to increase the extracellular dopamine concentration (Zetterström et al., 1984; Imperato and Di Chiara, 1988), but this increase does not persist longer than 1 day (Horikawa et al., 1997). The mechanism underlying this effect is unclear, however. Neurochemical studies (Benloucif and Galloway, 1991; Dewey et al., 1995) have shown that the administration of 5-HT stimulates dopamine release. Taken together, these data suggest that there are significant interactions between the dopamine and 5-HT systems and raise the possibility that sulpiride may cause an increase in 5-HT release.

To investigate this possibility, sulpiride was injected into the striatum of freely moving rats, and changes in the levels of extracellular 5-hydroxyindoles (5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA)) were measured for an extended period by using in vivo voltammetry (Cespuglio et al., 1981; Kennett and Joseph, 1982; Rivot et al., 1988; Nakazato and Akiyama, 1998).

2. Materials and methods

2.1. In vivo voltammetric measurement of 5-hydroxyindoles (5-HT and 5-HIAA)

The voltage paradigm for measurement of 5-hydroxyindoles consisted of a triangular activation pulse (±1275

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mV) followed after 2 s by a triple-stepped measuring pulse (Fig. 1). The activation and measuring pulses were applied as a pair every 30 s in vitro and every 45 s in vivo. The measuring pulse was stepped from 350 to 450 mV to determine the level of 5-hydroxyindoles (Nakazato and Akiyama, 1988). Although the 5-HT current intensity at measuring pulse steps from 350 to 450 mV was 13 times that of 5-HIAA in vitro (Table 1), 5-HT and 5-HIAA cannot be differentiated well. Therefore, 5-HT and 5-HIAA were measured together as 5-hydroxyindoles.

The extracellular levels of 5-hydroxyindoles were calculated from the difference between the current intensity observed at 350 mV and that at 450 mV (Nakazato and Akiyama, 1998), thus excluding the influence of substances with the most efficient oxidation potential below 350 mV (e.g., dopamine and its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC); Table 1; Akiyama et al., 1985). Likewise, the presence of sulpiride did not affect measurement of the 5-hydroxyindole current intensity because sulpiride itself did not produce a detectable change in current intensity in vitro with measuring pulse steps from 350 to 450 mV (Fig. 2).

2.2. Surgery

Male Wistar rats ($n = 22$), 350 to 400 g, were anesthetized with pentobarbital. A measuring electrode, consisting of a glass capillary tube containing a carbon fiber (7 μm in diameter) that extended 300 to 400 μm from the tip of the glass, was inserted unilaterally into the right striatum (coordinates: 0.5 mm anterior and 3.0 mm lateral to bregma; 5.0 mm ventral to the dura mater). In some cases ($n = 6$), electrodes were implanted bilaterally in the striatum. An auxiliary electrode and a reference electrode (Ag/AgCl) were placed on the dura mater. A stainless steel cannula (0.6 mm outer diameter) for drug administration was placed ipsilaterally, approximately 1 mm distant to the measuring electrode, and inserted 2.5 mm into the brain above the striatum. In animals with bilateral measuring electrodes, only one cannula was implanted. The cannula assembly consisted of an inner and outer cannula. The inner cannula was made of a stainless-steel tube into which a fused silica tube (0.15 mm outer diameter) had been threaded. The length of the inner cannula matched that of the outer cannula. The fused silica tube protruded approximately 1 to 1.5 mm from the tip of the cannula. The cannula was sealed with a dummy inner cannula until 1 h before drug administration. Animals were allowed to recover for at least 4 weeks before drug administration.

Table 1
In vitro sensitivity of the measuring electrode

Drugs	Concentration (10^{-7} M)	Current intensity	
		250–350 mV	350–450 mV
5-HT	1	8	130
5-HIAA	10[a]	7	100
Dopamine	1	−10	−20
DOPAC	10[a]	25	10

A current intensity of 200 corresponds to 1 nA.
[a]Note that these compounds were used in higher concentrations than dopamine and 5-HT.
Current intensity was measured ($n = 20$) in phosphate-buffered saline as the potential was raised from 250 to 350 mV and from 350 to 450 mV.

2.3. Drugs

In one group of animals, sulpiride (1 mM or 3 mM; Fujisawa Yakuhin Kogyo, Japan) was dissolved in Krebs-

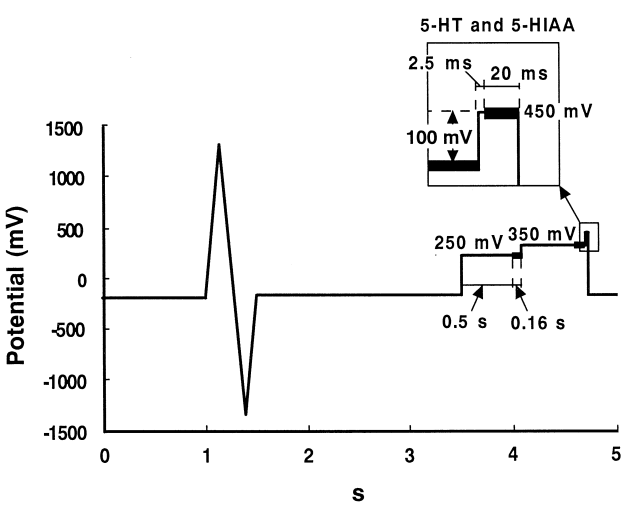

Fig. 1. Voltage paradigm used for the measurement of 5-HT and 5-HIAA. The current intensities were measured every 30 s in vitro during the time indicated by the thick lines.

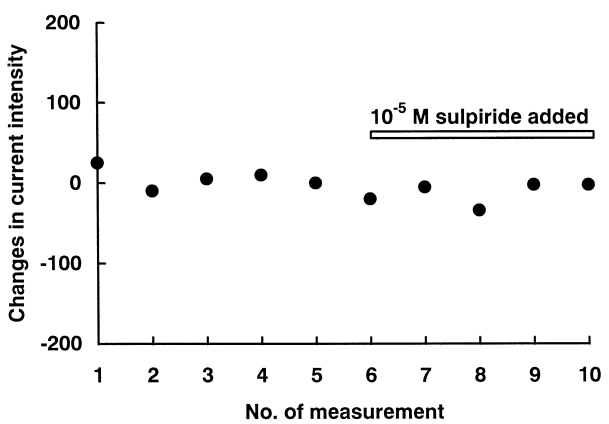

Fig. 2. No change in current intensity due to sulpiride itself was observed with measuring steps from 350 to 450 mV in vitro. Sulpiride (100 μl; 10 mM) was added five times to 100 ml phosphate-buffered saline, and the current intensity was measured at the measuring steps used for 5-hydroxyindoles (350 to 450 mV). The final concentration of sulpiride was 50 μM. Data points are normalized values that represent percent changes from the baseline value measured immediately prior to sulpiride addition (measurement number 5), thus the change in current intensity at measurement number 5 is 0.

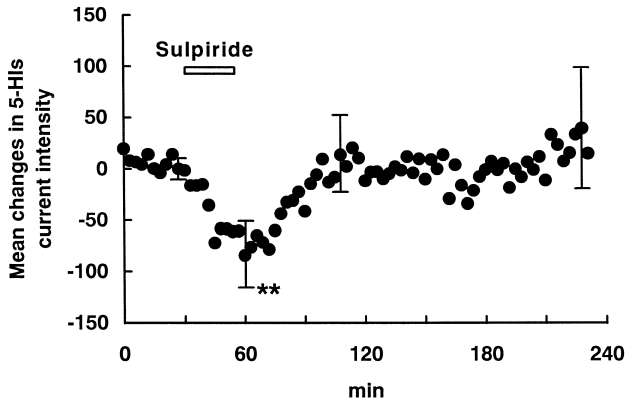

Fig. 3. Immediate effect of sulpiride on 5-hydroxyindole levels. Sulpiride (3 mM) was administered intrastriatally ($n = 6$) during the time indicated by the open bar. 5-Hydroxyindole levels decreased significantly during the injection relative to the control values prior to the injection, but returned to control values approximately 80 min after the start of drug injection. Data points are normalized values that represent the means of the percent changes from the baseline values measured immediately prior to the sulpiride injections. Error bars represent standard deviations. 5-HIs, 5-hydroxyindoles. $**$, significant changes ($P < 0.01$) with respect to the last preinjection value.

Ringer solution and 2 μl of this solution, or Krebs-Ringer solution alone (vehicle), was injected over 24 min into the striatum of freely moving rats, whereafter the release of 5-hydroxyindoles was measured. In another group of animals, intraperitoneal injections of sulpiride (25, 50, or 100 mg/kg) or vehicle were administered, and 5-hydroxyindoles were measured on five consecutive days following the injection. In a third group of animals, following intraperitoneal injection of the 5-HT synthesis blocker *p*-chlorophenylalanine (200 mg/kg) once a day for 3 consecutive days, sulpiride (3 mM) was injected intrastriatally ($n = 5$) and 5-hydroxyindoles were measured. *p*-Chlorophenylalanine was injected 2 days, 1 day, and 3 h before the sulpiride injection.

2.4. Measurement of striatal 5-HT and 5-HIAA levels by high-performance liquid chromatography (HPLC)

Two days after the sulpiride or vehicle injection, rats were anesthetized with pentobarbital and killed, and brains were removed rapidly and frozen. The striatum was dissected, homogenized in 40 μl of 1 M $HClO_4$ per 1 mg of brain tissue, and centrifuged at $7000 \times g$ for 10 min. The supernatant was subjected to HPLC, using electrochemical detection, and 5-HT and 5-HIAA levels were measured. The column used was MD-50DS (Eicom, Japan). The mobile phase consisted of 85% 0.1 M sodium acetate–0.1 M citric acid (pH 3.5), 15% methanol, 100 mg/ml octane sulfonate, and 5 mg/l disodium EDTA. The flow rate was 1 ml/min.

2.5. Statistical analysis

The current intensities of the 5-hydroxyindoles are presented as mean percent increases above baseline values and concentrations are presented as mean values. Statistical analyses were performed using either Student's *t*-tests or ANOVAs followed by post-hoc tests.

3. Results

3.1. Effect of sulpiride on extracellular 5-hydroxyindole levels

During the intrastriatal injection of 3 mM sulpiride ($n = 6$), a transient decrease in the level of extracellular 5-hydroxyindoles was found in the striatum, but this decrease began to reverse soon after the end of the injection (Fig. 3). Approximately 4 h after the injection, the level of 5-hydroxyindoles appeared to increase slightly, though not significantly. Approximately 6 to 8 h after the intrastriatal injection (1 or 3 mM sulpiride), the level of 5-hydroxyindoles increased 3-fold relative to baseline (Fig. 4). Approximately 1 to 2 days after the injection, the level fad further increased significantly. Subsequently, 2 to 4 days after the injection, the level returned to baseline levels. In the contralateral striatum, which was not injected with sulpiride, no significant change in the level of 5-hydroxyindoles was observed (data not shown). After intraperitoneal injection of sulpiride (25, 50, or 100 mg/kg) in the

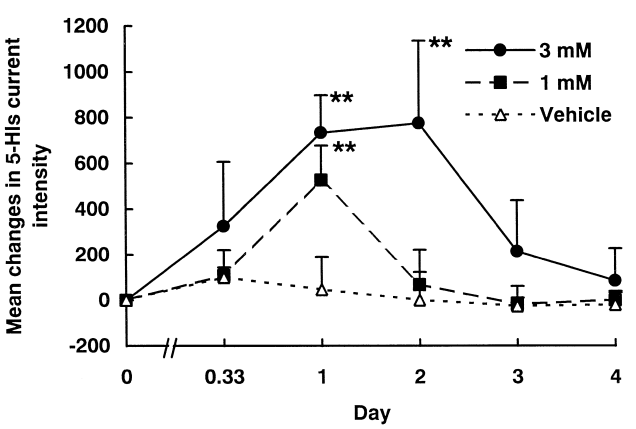

Fig. 4. Long-lasting increase in 5-hydroxyindole levels following intrastriatal administration of sulpiride (1 mM, $n = 6$; 3 mM, $n = 6$). Extracellular 5-hydroxyindole levels began to increase approximately 6 to 8 h after the injection and remained elevated for 1 to 3 days. The transient decrease in 5-hydroxyindoles observed after the injection of sulpiride shown in Fig. 3 is not shown in this figure. Data points are normalized values that represent the means of the percent changes from the baseline values measured immediately prior to the sulpiride injections. Krebs–Ringer solution was injected as vehicle ($n = 6$). Error bars represent standard deviations. 5-HIs, 5-hydroxyindoles. $**$, significant difference ($P < 0.01$, Student's *t*-test) compared to vehicle.

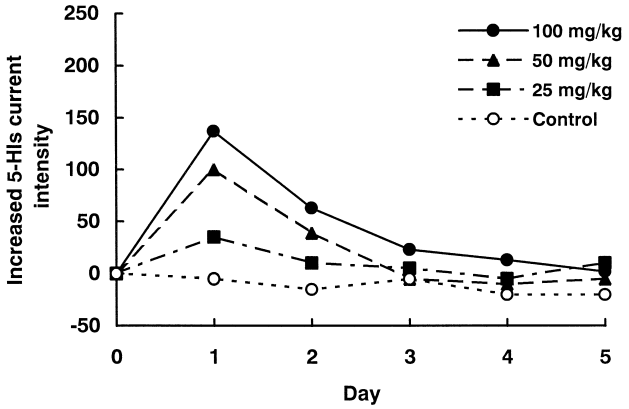

Fig. 5. Intraperitoneal administration of sulpiride (25, 50, or 100 mg/kg) resulted in a dose-dependent increase in 5-hydroxyindole levels. Data points are normalized values that represent the percent change from the baseline values measured immediately prior to the sulpiride injection on day 0. A representative case is shown. 5-HIs, 5-hydroxyindoles.

same rat, the levels of 5-hydroxyindoles increased in a dose-dependent manner. A representative case is shown in Fig. 5. The increases in the levels of 5-hydroxyindoles were slight following intraperitoneal injections compared to those following intrastriatal injections. Pretreatment with *p*-chlorophenylalanine suppressed the sulpiride-induced increase in the levels of 5-hydroxyindoles (Fig. 6).

3.2. Measurement of striatal 5-HT and 5-HIAA concentrations

HPLC analysis of striatal 5-HT and 5-HIAA concentrations showed that 2 days after intrastriatal administration of sulpiride the concentration of 5-HT was almost unchanged, whereas the concentration of 5- HIAA was increased significantly compared with that of controls (Fig. 7).

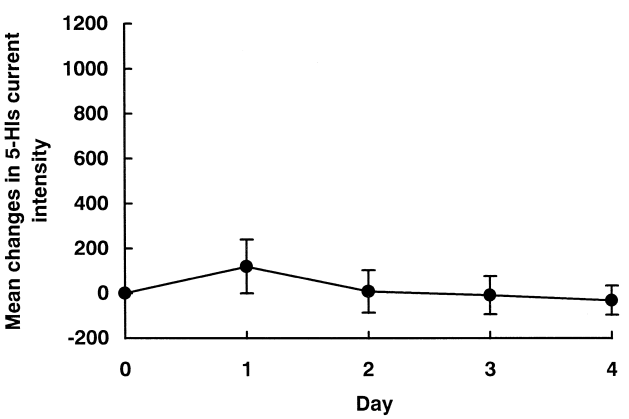

Fig. 6. Suppression of the sulpiride-induced increase in 5-hydroxyindole levels after pretreatment with *p*-chlorophenylalanine ($n = 5$). After administration of *p*-chlorophenylalanine (200 mg/kg, i.p.) for 3 days, sulpiride (3 mM) administration did not cause an increase in 5-hydroxyindole levels. Data points are normalized values that represent the means of the percent changes from the baseline values measured immediately prior to the sulpiride injections. Error bars represent standard deviations. 5-HIs, 5-hydroxyindoles.

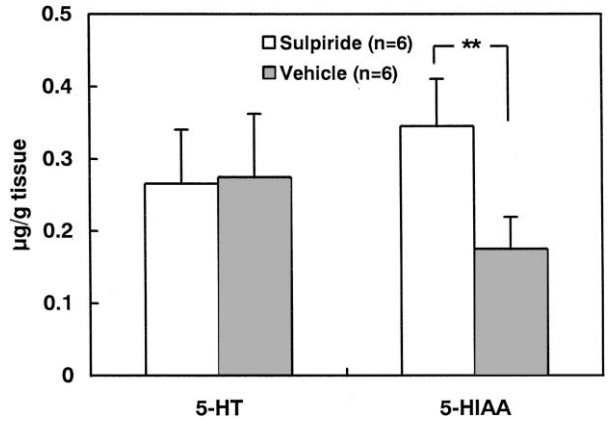

Fig. 7. 5-HT and 5-HIAA concentrations in striatal homogenates. These concentrations were measured ipsilaterally by HPLC 2 days after intrastriatal administration of sulpiride (3 mM) or vehicle. 5-HT concentration was not changed, but 5-HIAA concentration was increased significantly compared to that of controls. Error bars represent standard deviations. **, significant between-group difference ($P < 0.01$, Student's *t*-test).

4. Discussion

Some dopamine receptor antagonists have been shown to act as 5-HT receptor antagonists (Bürki et al., 1975; Ferré and Artigas, 1995). We therefore were interested in investigating the effects of the dopamine D_2 receptor antagonist sulpiride on 5-HT levels in vivo. The results of the present study indicate that in addition to its known dopamine receptor antagonist function, sulpiride, when injected in the striatum, can cause a significant increase in the level of 5-hydroxyindoles.

4.1. Interpretation of changes in extracellular 5-hydroxyindoles measured by in vivo voltammetry

5-HT and 5-HIAA cannot be well differentiated by in vivo voltammetry (Nakazato and Akiyama, 1998), therefore 5-HT was measured together with its metabolite. Suppression of the sulpiride-induced increase in the levels of 5-hydroxyindoles following the administration of the 5-HT synthesis inhibitor *p*-chlorophenylalanine confirmed that the measured substances were 5-hydroxyindoles. The results of the HPLC analysis also support the conclusion that the increase in 5-hydroxyindoles measured by in vivo voltammetry was due to an increase in 5-HT release.

4.2. Mechanism of changes in 5-hydroxyindole release

In the present study, sulpiride induced a short-term decrease in 5-hydroxyindoles followed by a long-term increase in 5-hydroxyindoles. This short-term decrease is consistent with a previous report by Wong et al. (1995), in

which 5-HIAA release was measured using microdialysis after intraperitoneal administration of the dopamine D_2 receptor antagonist eticlopride. They described a short-term suppression of release that appeared to last longer than that observed in the present study. The short-term suppression may be due to an indirect action of sulpiride on γ-aminobutyric acid (GABA) release. An increase in GABA has been shown to decrease 5-HT release (Becquet et al., 1990). It has been demonstrated (Van der Heyden et al., 1980; Girault et al., 1986b) that stimulation of dopamine D_2 receptors inhibits GABA release in the dorsal striatum of the rat. It also has been reported (Euvrard et al., 1979; Stoof and Kebabian, 1982; Lehmann and Langer, 1983) that stimulation of dopamine D_2 receptors inhibits the release of acetylcholine, and that acetylcholine increases GABA release (Girault et al., 1986a). Taken together, these results indicate that administration of a dopamine D_2 receptor antagonist should result in an increase in GABA release and a decrease in 5-HT release. This is one explanation for the sulpiride-induced short-term suppression of 5-HT release observed in the present study.

There are several possible explanations for the long-lasting elevation in 5-hydroxyindole levels. It is well established (Klawans and Rubovits, 1972; Sayers et al., 1975; Baldessarini, 1980) that chronic administration of dopamine antagonists results in upregulation of dopamine receptors. Recent evidence shows (Eastwood et al., 1994; Fitzgerald et al., 1995; Healy and Woodruff, 1997) that antipsychotic drugs affect dopamine receptor mRNA levels in the rat striatum. Furthermore, exogenous sulpiride remains in the extracellular space in the brain for an extended time (more than 6 h) because it is not taken up and metabolized efficiently (Horikawa et al., 1997). Taken together, these results raise the possibility that the extended presence of sulpiride caused dopamine D_2 receptor upregulation or other intracellular changes that may have resulted in the suppression of GABA release and a subsequent increase in 5-HT release. An alternative possibility is that sulpiride may have had neurotoxic effects on acetylcholine or GABA neurons via dopamine D_2 receptors at the high concentrations used in the present study, although evidence of neuronal loss was not apparent in the histological investigations performed in the present study (data not shown). This does not exclude that a more subtle effect on the functioning of these cell may have caused an increase in 5-HT release.

4.3. Clinical implications of the long-lasting release of 5-hydroxyindoles induced by sulpiride

5-HT-selective uptake inhibitors have been shown to be effective in the treatment of depression (Bodnoff et al., 1989; Martin et al., 1990; Boyer, 1992; Fuller, 1994), consistent with the hypothesis that the serotonergic system is involved in this disease (Ashcroft et al., 1966; Den Boer et al., 1987; Cervo et al., 1991). Recently, atypical antipsychotic drugs, such as clozapine (a dopamine and 5-HT receptor antagonist), have been used in the treatment of schizophrenia (Kane et al., 1988; Meltzer et al., 1989; Coward, 1992), raising the possibility that the serotonergic system is involved in this disease also. The results of the present study indicate that sulpiride causes the long-lasting release of 5-HT. This finding is consistent with the fact that 5-HT uptake inhibitors are effective in the treatment of depression and that the drugs such as clozapine are also effective in the treatment of schizophrenia. The effect of sulpiride on serotonergic neurons raises the possibility that other dopamine D_2 receptor antagonists also affect serotonergic neurons. A similar effect was observed with haloperidol, a dopamine D_1 and D_2 receptor antagonist (unpublished data), and the magnitude of the changes was lower than that observed with sulpiride. Further research will determine whether this is a general characteristic of dopamine antagonists. Investigation of the dopamine D_2 receptor antagonist-induced effects on serotonergic neurons is not only important for characterizing the mechanism of the action of sulpiride, but also may lead to the development of new drugs as therapy for psychiatric disorders.

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