

Enhancing action of LSD on neuronal responsiveness to serotonin in a brain structure involved in obsessive–compulsive disorder

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Abstract

Potent serotonin (5-HT) reuptake inhibitors are the only drugs that consistently exert a therapeutic action in obsessive–compulsive disorder (OCD). Given that some hallucinogens were reported to exert an anti-OCD effect outlasting their psychotomimetic action, possible modifications of neuronal responsiveness to 5-HT by LSD were examined in two rat brain structures: one associated with OCD, the orbitofrontal cortex (OFC), and another linked to depression, the hippocampus. The effects of concurrent microiontophoretic application of LSD and 5-HT were examined on neuronal firing rate in the rat OFC and hippocampus under chloral hydrate anaesthesia. In order to determine whether LSD could also exert a modification of 5-HT neuronal responsiveness upon systemic administration, after a delay when hallucinosis is presumably no longer present, it was given once daily (100 µg/kg i.p.) for 4 d and the experiments were carried out 24 h after the last dose. LSD attenuated the firing activity of OFC neurons, and enhanced the inhibitory effect of 5-HT when concomitantly ejected on the same neurons. In the hippocampus, LSD also decreased firing rate by itself but decreased the inhibitory action of 5-HT. The inhibitory action of 5-HT was significantly greater in the OFC, but smaller in the hippocampus, when examined after subacute systemic administration of LSD. It is postulated that some hallucinogens could have a beneficial action in OCD by enhancing the responsiveness to 5-HT in the OFC, and not necessarily in direct relation to hallucinosis. The latter observation may have theoretical implications for the pharmacotherapy of OCD.

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Introduction

Obsessive–compulsive disorder (OCD), with a lifetime prevalence of about 2%, is the fourth most common psychiatric disorder. It is more common than schizophrenia and bipolar affective disorder, which both have a 1% prevalence rate. Clinically, OCD is characterized by persistent and recurrent thoughts, or images (obsessions) and/or repetitive behaviours or mental acts (compulsions), which cause a significant impairment in the daily functioning of the individuals affected. It often begins early in life, it waxes and wanes over time, and remission is rare (APA, 1994). Among various pharmacotherapies, only the potent serotonin (5-HT) reuptake inhibitors (SRIs) have consistently

been shown to exert a clear therapeutic effect in OCD (Goodman, 1999). With regards to pathophysiology, positron emission tomography studies have brought forward compelling evidence implicating a neuronal circuitry involving the orbitofrontal cortex (OFC), the head of the caudate nucleus and the thalamus, showing elevated glucose metabolic rates in OCD patients compared to controls (Baxter et al., 1987). Strikingly, this hyperactivity is attenuated following clinical improvement with either behavioural and/or pharmacotherapy (Baxter et al., 1992). Furthermore, OCD patients who responded to an SRI have decreases in metabolic activity in the right caudate, right ventrolateral prefrontal cortex, bilateral orbitofrontal cortex (OFC), and thalamus but depressed patients, who responded to the same drug, have not (Saxena et al., 2002). Taken together, these observations indicate that 5-HT transmission, in the forebrain structures mentioned above, plays an important role in the anti-OCD response with SRIs.

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There are case reports describing that hallucinogens such as psilocybin and lysergic acid diethylamide (LSD) have an anti-OCD effect that clearly outlasts their psychotomimetic action (Brandrup and Vanggaard, 1977; Hanes, 1996; Leonard and Rapoport, 1987; Moreno and Delgado, 1997). Since these two drugs are endowed with significant affinity for various 5-HT-binding sites (Titeler et al., 1988), it is thus conceivable that their putative anti-OCD effects are mediated through a modification of 5-HT signalling. The present in-vivo electrophysiological studies were thus undertaken to explore the potential of LSD to alter neuronal responsiveness to 5-HT in the OFC, in comparison to the hippocampus, a brain region classically associated with depression and the antidepressant response (Blier and de Montigny, 1999; Duman et al., 2001; Sheline et al., 1999). These experiments appear all the more important in light of the capacity of a single dose of LSD to increase expression of a small set of genes involved in synaptic plasticity, glutamatergic signalling and cytoskeletal architecture (Nichols and Sanders-Bush, 2002).

Materials and methods

Male Sprague–Dawley rats with a body weight of 200–300 g (Charles River, St. Constant, Quebec, Canada) were used in the study. The rats were housed in groups of two in standard marcolone cages with sawdust bedding that was changed three times per week. The animals were kept on a 12:12 h light–dark cycle under controlled conditions for regular indoor temperature and humidity. The animals had free access to standard rodent food (Charles River) and water during the study. For the second set of experiments, rats were given LSD daily (100 µg/kg i.p.) for 4 d and controls were given physiological saline injections, also daily for 4 d. In these rats, the experiments were carried out 24 h after the last injection. This regimen was used on the basis of the above-mentioned case reports whereby the obsessions could be decreased during times when the hallucinogens were exerting their psychotomimetic effect but also for variable periods afterwards.

Experimental design

The present study was comprised of two separate sets of experiments. In the first series, the effect of local microiontophoretic application of the hallucinogen LSD was examined on the responsiveness of OFC neurons to 5-HT, also applied through the same microelectrode. For this purpose, 5-HT and LSD were ejected, first alone and then concurrently, in the OFC

and the inhibitory effect of the same current of 5-HT upon neuronal firing activity was compared in the presence and in the absence of LSD. Identical experiments were conducted in the hippocampus. In the second set of experiments, the effects of systemic administration of LSD were investigated on the responsiveness of OFC neurons to 5-HT 24 h after the last dose in order to determine whether LSD could induce alterations in neuronal sensitivity to 5-HT at a time the drug would presumably no longer exert hallucinosis in animals. It was reported that LSD, in the dose range utilized in the present experiments, exerts behavioural signs of hallucinosis in cats that last for up to approx. 8 h (Trulson and Jacobs, 1977). It is, however, impossible to ascertain the presence of hallucinosis in laboratory animals given the subjective nature of the phenomenon and the fact that the best available model has yielded at least one false positive (Marini et al., 1981). Nevertheless, LSD, even at doses higher than that used in the present study, is cleared from the rat brain within 1 h (Rosecrans et al., 1967). This paradigm was thus aimed at mimicking the conditions for which an anti-OCD action of LSD was reported in humans. For this purpose, pairs of rats from the same arrivals were treated with LSD or saline, and tested on the same day using the same microiontophoretic pipette to study the responsiveness of the OFC neurons to 5-HT. A mean inhibitory effect for each current of 5-HT was determined for each rat and these mean values were used for the statistical analyses. This procedure was deemed optimal to minimize intra- and inter-experiment variability. Identical experiments and procedures were also conducted in the hippocampus.

Extracellular single-unit recording and microiontophoresis

Five-barrelled glass micropipettes (ASI Instruments, Warren, MI, USA) were pulled with a vertical electrode puller. The diameter of the micropipettes (5–10 µm) was checked under a microscope. The central barrel and one of the side barrels contained 2 M NaCl for recording and current balancing, respectively. For the first series of experiments, the three other barrels were filled with quisqualate (1.5 mM in 400 mM NaCl; pH 8), 5-HT (2 mM in 200 mM NaCl; pH 4), and LSD (2 mM in 100 mM NaCl; pH 4) and the 5-HT and LSD ejecting currents ranged from 1–10 nA. For the second series of experiments, two barrels were filled with 5-HT (2 mM in 200 mM NaCl; pH 4) and the last one with quisqualate. The impedance of the central barrel and of the side barrels ranged from 1–4 and 30–80 MΩ, respectively. Quisqualate was ejected as

anions and retained in the barrel with a current of +10 nA, while 5-HT and LSD were ejected as cations and retained with a current of -10 nA. The 5-HT ejection currents used were 10, 20, and 30 nA. These rats were anaesthetized with chloral hydrate (400 mg/kg i.p.) followed by subsequent 100 mg/kg doses approximately every 60 min to maintain complete anaesthesia. Body temperature was maintained at 36–37 °C throughout the experiments. The rats were placed in a stereotaxic frame and the skull exposed. A burr hole was drilled and the micropipette was lowered into the OFC (A, 3.7 mm; L, 2.0 mm from bregma; V, 2.5–4.0 mm below cortical surface) or the hippocampus (A, 4.2 mm; L, 4.2 mm from lambda, into the CA3 pyramidal neuron layer; V, 4.0–6.0 mm below cortical surface). The coordinates for the OFC in rats correspond to those for humans which delineate Brodmann area 47 (Rajkowska et al., 1998). Extracellular unitary activity was amplified and displayed on an oscilloscope (1200B; Hewlett-Packard, Boise, ID, USA). Action potentials were discriminated from background noise by means of a differential amplitude discriminator (Fintronics Inc., Orange, CT, USA). The frequency of neuronal discharges was integrated over 10-s intervals with a rate meter. The pyramidal neurons recorded in both the hippocampus and OFC were firing spontaneously but the majority fired at a low rate, or were quiescent, and were thus activated by the application of quisqualate. All procedures were approved by the McGill Animal Ethics Board.

Drugs

The drugs used were 5-HT creatinine sulphate and quisqualate (Sigma Chemical Co., St. Louis, MO, USA); and LSD (Ministry of Health and Welfare, Ottawa, ON, Canada). The concentrations and the doses used for these experiments were chosen on the basis of previous experiments carried out in our laboratories.

Statistical analyses

All results are expressed as means + S.E.M. The *n* values refer to the number of neurons tested. In the microiontophoretic experiments whereby 5-HT and LSD were ejected, the responsiveness to 5-HT in the presence and the absence of LSD was compared using the two-tailed Student's *t* test. In the experiments where LSD was given systemically, the responsiveness to 5-HT in controls and treated rats was compared using a two-way analysis of variance (ANOVA) followed by Tukey tests. These two analyses were carried out after ensuring the data passed a normality test.

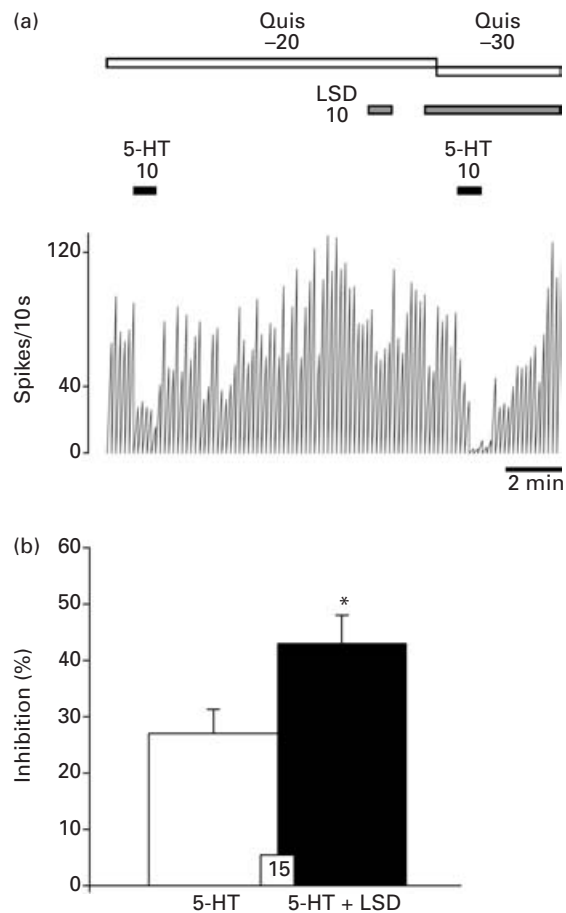


Figure 1. (a) Integrated firing rate histograms of an OFC neuron showing its responsiveness to 5-HT and LSD applied directly through the recording microiontophoretic pipette. The bars above the trace represent the periods of application of these two agents, and of quisqualate (Quis) used to activate the neuron. The numbers above these rectangles indicate the currents used (in nA) to eject these compounds. 5-HT and LSD were ejected as positive ions and quisqualate as negative ions. Note the greater degree of inhibition of firing produced by 5-HT during the ejection of LSD. (b) Histograms representing the degree of inhibition of OFC neurons produced by the same microiontophoretic current of 5-HT in the absence (white histogram) and in the presence of the concomitant microiontophoretic application of LSD (black histogram). **p* < 0.001 using the two-tailed paired Student's *t* test.

Results

Effect of microiontophoretic application of 5-HT and LSD on the firing activity of OFC neurons

As previously reported for experiments carried out under identical conditions in the rat, mouse and guinea pig OFC (Bergqvist et al., 1999b; El Mansari and Blier, 1997a; Rueter et al., 2000), microiontophor-

etic applications of 5-HT consistently produced a suppression of firing of OFC neurons (Figures 1a, 3). Applications of LSD through the same micropipette also decreased the firing rate of the same neurons that were inhibited by 5-HT. To test for the presence of an interaction of this hallucinogen with 5-HT, a current of LSD that produced a small but significant inhibition of firing was iontophoretically applied onto each neuron. This ensured that LSD was, indeed, coming out of the electrode. The firing rate of the neuron was then restored to that previously used to examine the responsiveness to 5-HT by increasing the ejection current of quisqualate. This was done to avoid a potential bias in the evaluation of 5-HT responsiveness due to different firing rates. Under such conditions, the responsiveness to 5-HT was significantly increased in the presence of LSD in 10 rats (d.f. = 11, $t = 5.16$, $p < 0.001$; Figure 1b).

Effect of microiontophoretic application of 5-HT and LSD on the firing activity of hippocampus pyramidal neurons to 5-HT

In order to determine whether the potentiation of the responsiveness of OFC neurons to 5-HT by LSD was a brain region-specific effect, identical experiments were carried out in the hippocampus, a brain region classically associated with depression, but not OCD. Microiontophoretic application of 5-HT consistently lowered the firing activity of CA3 pyramidal neurons (Figures 2a, 4). Similarly, the application of LSD also produced an inhibitory action of the firing rate of the same pyramidal neurons, as previously reported (Blier and de Montigny, 1983). Upon concurrent ejection of LSD, the inhibitory response to 5-HT was significantly attenuated when compared to that achieved in the absence of LSD in 8 rats (d.f. = 19, $t = 6.37$, $p < 0.001$; Figure 2b).

Effect of the systemic administration of LSD on the responsiveness of OFC neurons to 5-HT

The responsiveness of OFC neurons to 5-HT was then studied following the systemic administration of LSD for two reasons. First, it was aimed at determining whether the potentiating effect of LSD could be achieved with the drug given systemically, and second to determine if this action could outlast the presence of hallucinosis, as is apparently the case in the human subjects who reported the long-lasting anti-OCD effect of LSD (Brandrup and Vanggaard, 1977; Hanes, 1996; Leonard and Rapoport, 1987; Moreno and Delgado, 1997). Hence, 5-HT was ejected microiontophoretically at currents of 10, 20 and 30 nA onto OFC neurons in

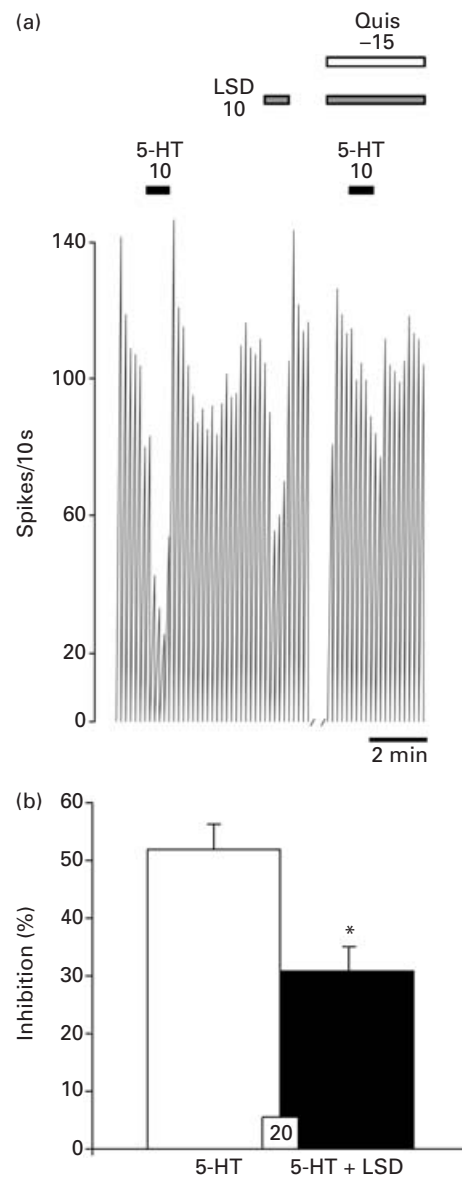


Figure 2. (a) Integrated firing rate histograms of a hippocampus CA3 pyramidal neuron showing its responsiveness to 5-HT and LSD applied directly through the recording microiontophoretic pipette. The bars above the trace represent the periods of application of these two agents, and of quisqualate (Quis) used to activate the neuron. The numbers above these rectangles indicate the current used (in nA) to eject these compounds. 5-HT and LSD were ejected as positive ions and quisqualate as negative ions. The two slashes at the bottom of the trace indicate an interruption of the trace. Note the smaller degree of inhibition of firing produced by 5-HT during the ejection of LSD. (b) Histograms representing the degree of inhibition of hippocampus neurons produced by the same microiontophoretic current of 5-HT in the absence (white histogram) and in the presence of the concomitant microiontophoretic application of LSD (black histogram). * $p < 0.001$ using the two-tailed paired Student's t test.

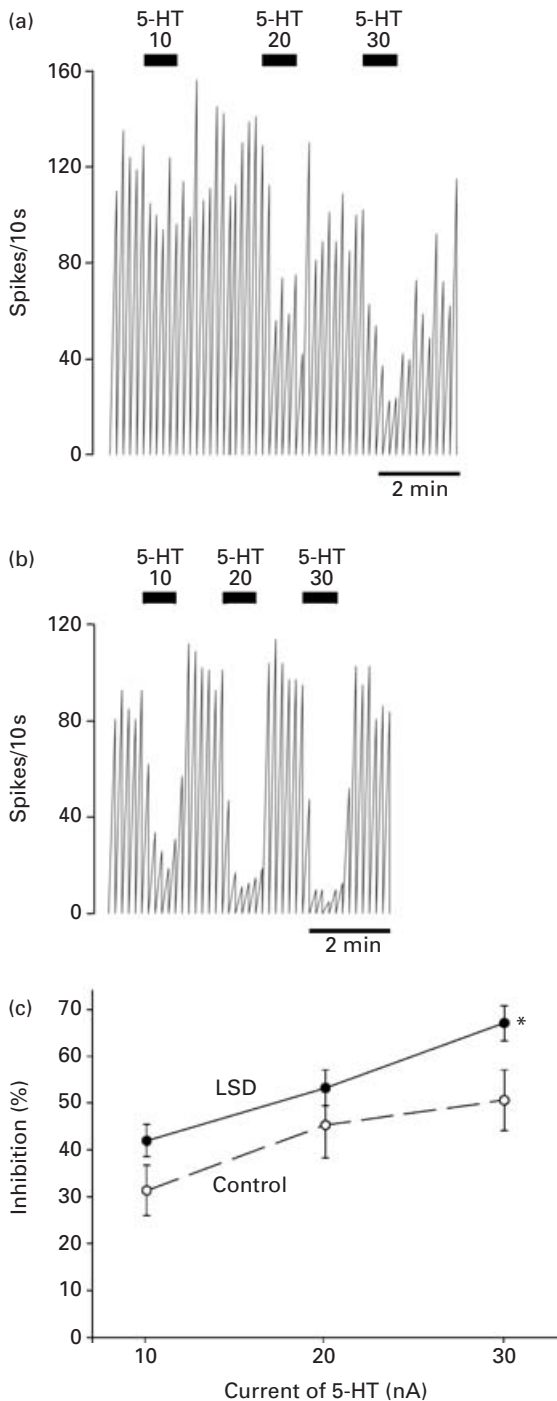


Figure 3. Integrated firing rate histograms of an OFC neuron recorded in (a) a saline-treated rat and (b) a LSD-treated rat, with the same micropipette on the same day, showing their responsiveness to 5-HT applied directly through the recording microiontophoretic electrode. The bars above the traces represent the periods of application of 5-HT and the numbers above these rectangles indicate the currents used (in nA) to eject 5-HT (as positive ions). Time base applies to both traces. Note the greater degree of inhibition of firing

7 pairs of LSD-treated ($n=31$ neurons) and saline-treated ($n=27$ neurons) rats using the same microelectrode in each pair. As illustrated in Figure 3, the inhibitory action of the three currents of 5-HT was greater in the LSD-treated rats compared to their matched controls. There were both significant current and treatment effects ($F_{2,41}=9.26$, $p<0.001$ and $F_{1,41}=7.64$, $p=0.009$, respectively), but no treatment $\times$ current effect ($F_{2,41}=0.36$, $p=0.70$).

Effect of the systemic administration of LSD on the responsiveness of hippocampus pyramidal neurons to 5-HT

Experiments identical to those described above for the OFC were carried out in the hippocampus of rats treated with saline and LSD for 4 d. 5-HT was ejected microiontophoretically at currents of 10, 20 and 30 nA in the hippocampus of 6 matched pairs of LSD- and saline-treated rats using the same electrode. As can be seen in Figure 4, the application of three currents of 5-HT produced a significantly smaller inhibition of firing of the hippocampus CA3 pyramidal neurons in the pretreated LSD rats ($n=11$ neurons) when compared to the controls ($n=12$ neurons), as was the case in the experiments whereby LSD was ejected directly from the micropipette in the previous experiments. There were both significant current and treatment effects ($F_{2,35}=5.74$, $p=0.008$ and $F_{1,35}=11.95$, $p=0.002$, respectively), but no treatment $\times$ current effect ($F_{2,35}=0.03$, $p=0.97$).

Discussion

The results of the present experiments indicate that the responsiveness of OFC neurons to 5-HT was enhanced by both direct application of LSD as well as by repeated systemic administration of this drug (Figures 1, 3). In contrast, the responsiveness of CA3 pyramidal neurons to 5-HT in the hippocampus was attenuated by both direct application of LSD and its systemic administration (Figures 2, 4).

Under the conditions used in the present experiments, the inhibitory action of 5-HT on the firing rate of CA3 pyramidal neurons is primarily mediated by 5-HT_{1A} receptors. This assertion is based on the blockade of this effect of 5-HT by the selective 5-HT_{1A} antagonists BMY-7378, WAY-100,135 and WAY-100,635

produced by 5-HT in the LSD-treated rat. (c) Graph showing the degree of inhibition of OFC neurons produced by the same microiontophoretic currents of 5-HT in the controls (○) and in the LSD-treated rats (●). * $p<0.05$ using a post-hoc Tukey test for the comparison of the treatment factor.

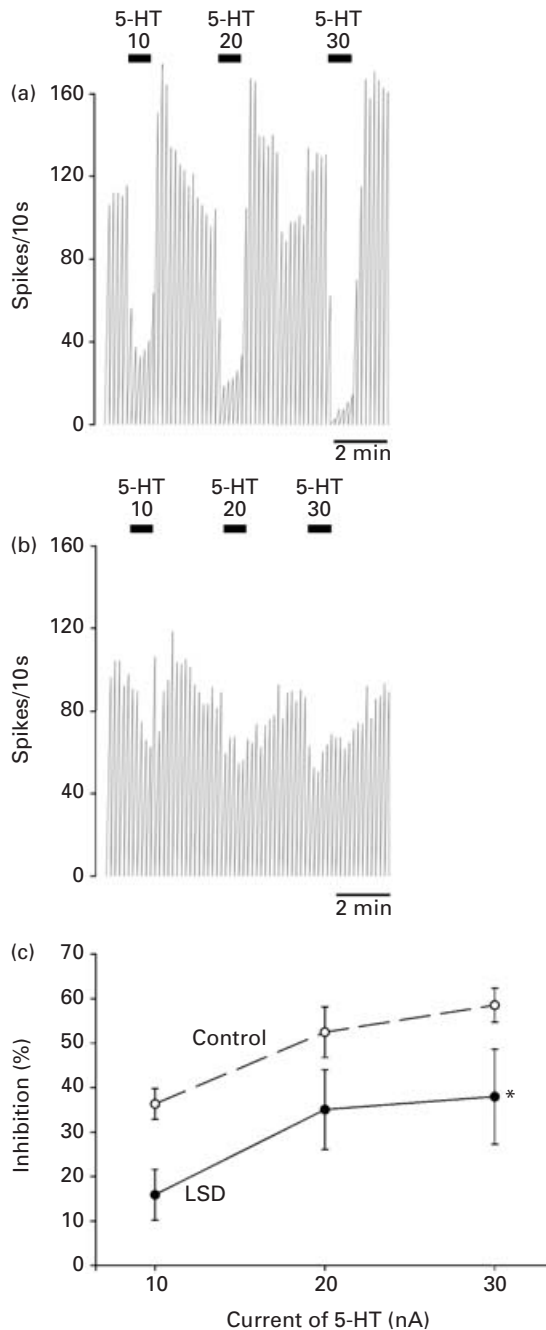


Figure 4. Integrated firing rate histograms of a hippocampus CA3 pyramidal neuron recorded in (a) a saline-treated rat and (b) a LSD-treated rat with the same micropipette on the same day, showing their responsiveness to 5-HT applied directly through the recording microiontophoretic electrode. The bars above the traces represent the periods of application of 5-HT and the numbers above these rectangles indicate the currents used (in nA) to eject 5-HT (as positive ions). These neurons were not activated by quisqualate and were firing spontaneously. Time base applies to both traces. Note the smaller degree of inhibition of firing produced by 5-HT in the LSD-treated rat. (c) Graph showing the degree of inhibition

(Haddjeri et al., 1999). Furthermore, this inhibitory action of 5-HT is abolished by a pretreatment with pertussis toxin, which is known to inactivate $G_{i/o}$ proteins coupled to 5-HT_{1A} receptors in that brain structure (Andrade et al., 1986; Blier et al., 1993). Consequently, it can be tentatively concluded that LSD interfered with the 5-HT_{1A} receptor on the CA3 pyramidal neurons. The most likely mechanism for this immediate action of LSD could be a partial agonism at the 5-HT_{1A} receptor. Indeed, several exogenous 5-HT_{1A} agonists have been shown to attenuate the responsiveness of these neurons to 5-HT through their partial agonistic activity. These include: gepirone, tandospirone, ipsapirone, flesinoxan and 8-OH-DPAT (Andrade and Nicoll, 1987; Blier and de Montigny, 1987; Haddjeri et al., 1999). However, given that repeated administration of LSD followed by a washout period also attenuated the responsiveness of the CA3 pyramidal neurons in the hippocampus, it appears that the interaction of this drug with this 5-HT_{1A} receptor is more complex than just a simple partial agonistic interaction at the binding site of the receptor. This is also suggested by the recent observations of Nichols and Sanders-Bush (2002) on multiple gene expression. It is noteworthy that only ejecting currents of a 5-HT_{1A} agonist producing a profound suppression of firing rate can reveal the low intrinsic activity of an exogenous 5-HT agonist (Blier and de Montigny, 1987, 1990). Furthermore, even administration of partial 5-HT_{1A} agonists for 14 d does not result in an attenuation of the responsiveness of these neurons to 5-HT, even if the animals are tested in the presence of the drug or following a washout period (Blier and de Montigny, 1987).

In contrast, using the same experimental conditions as those utilized in the hippocampus, LSD augmented the inhibitory action of 5-HT in the OFC, possibly through an interaction at the 5-HT₂ receptors in that structure because this drug has a high affinity for this receptor family (Titeler et al., 1988). Furthermore, Aghajanian and Marek (1999) have proposed that an effect of hallucinogens upon glutamatergic transmission through 5-HT_{2A} receptor activation in the cerebral cortex may be responsible for the higher level cognitive, perceptual and affective distortions produced by these drugs. A 5-HT₂ receptor is believed to primarily mediate the action of 5-HT in the rat OFC in the present experimental conditions for the following

of hippocampus CA3 pyramidal neurons produced by the same microiontophoretic currents of 5-HT in the controls (○) and in the LSD-treated rats (●). * $p < 0.05$ using a post-hoc Tukey test for the comparison of the treatment factor.

reason. Although these neurons are inhibited by 5-HT_{1A} and 5-HT₂ agonists, their responsiveness to 5-HT and to the 5-HT₂ agonists DOI and m-CPP remains unaltered following long-term treatment with an SRI, whereas their response to the 5-HT_{1A} agonist 8-OH-DPAT is decreased in the same animals (El Mansari and Blier, 1997b). In addition, the inhibitory action of 5-HT in this preparation is probably not mediated through excitatory 5-HT₂ receptors on GABA interneurons because the GABA_A receptor antagonist bicuculline, while blocking the inhibitory effect of GABA_A on OFC neurons, does not alter the suppression of firing produced by DOI and m-CPP (Bergqvist et al., 1999b). This 5-HT₂ response, however, does not present a typical profile because the inhibitory action of 5-HT, DOI and m-CPP could not be effectively blocked in the OFC by classical 5-HT₂ antagonists, although the same approach yielded clear results in the medial prefrontal cortex (Bergqvist et al., 1999b). Even the use of the 5-HT_{2A} antagonist MDL-100,907 in 5-HT_{2C} knockout mice did not provide a clear answer to that question (Rueter et al., 2000). It is hoped that with the availability of 5-HT_{2A} knockout mice (Fiorica-Howells et al., 2002), a definite characterization of that receptor will be reached. Nevertheless, this alteration of the responsiveness to 5-HT in the OFC may be germane to the putative anti-OCD effect of certain hallucinogens because it has been postulated that the anti-OCD effect of SRIs is due to an enhanced 5-HT release in the OFC (Bergqvist et al., 1999a). This would result from the desensitization of the terminal 5-HT_{1D} autoreceptor taking several weeks to develop during sustained SSRI administration, consistent with the longer delay necessary to obtain an optimal anti-OCD effect than an antidepressant action with these drugs. Nevertheless, the mechanisms by which LSD alters the responsiveness to 5-HT remains to be established, and may be far more complex than an interaction with 5-HT₂ receptors.

The enhancement of the response of OFC neurons to 5-HT may have an important heuristic value. Indeed, even if the anti-OCD effect of some hallucinogens were eventually confirmed in a controlled study (see Delgado and Moreno, 1998), it is not feasible to consider giving such drugs to patients on a routine basis, at least at doses producing hallucinations. However, the use of non-hallucinogenic 5-HT₂ receptor agonists could represent a novel therapeutic avenue for the treatment of OCD. Given their direct activation of the post-synaptic 5-HT₂ receptor, and the previous observations that these receptors do not adapt following sustained activation as a result of SRI treatment (El Mansari and Blier, 1997b), it is thus conceivable that

such agents may have a rapid onset of action in contrast to the SRIs which take several weeks to act. This concept, however, relies on the possibility that 5-HT₂ agonists are not necessarily hallucinogens. Although the 5-HT_{2A} receptor has recently been shown to be a crucial mediator of hallucinosis, in part because of the reduced sensitivity of 5-HT_{2A} knockout mice to hallucinogens (Gingrich and Hen, 2001), such a potential anti-OCD agent may not necessarily produce such effects if it is endowed with some other property. For instance, lisuride is an agonist at 5-HT_{2A} sites, yet this agent does not produce hallucinations in individuals taking it for its anti-parkinsonian action or for other indications (Burris et al., 1991; Hayashi et al., 1998; Kaeli et al., 2001). Similarly, the preferential 5-HT_{2C} agonist ORG-12962 is also devoid of hallucinogenic properties and has already been shown to attenuate performance anxiety in healthy volunteers (Connell et al., 1999). It will thus be interesting to test such ligands in the model used in the present study both in normal animals and in mutant mice lacking 5-HT_{2A} or 5-HT_{2C} receptors, obviously before assessing the effects of such agents in OCD patients.

In conclusion, the use of the hallucinogenic agent LSD has yielded intriguing interactions between this drug and the response to 5-HT in two brain structures. In the first, the hippocampus, a cerebral region involved in depression, LSD attenuated the inhibitory action of 5-HT both after acute exposure of these neurons to the drug and after a 4-d treatment followed by a washout period. Interestingly, this attenuation of 5-HT receptor responsiveness is the opposite of the common enhancing action of various classes of antidepressant treatments on 5-HT_{1A} neurotransmission in this region (Haddjeri et al., 1998). In contrast, in the OFC, a brain structure involved in OCD, LSD increased neuronal responsiveness to 5-HT. The latter observation may have theoretical implications for the pharmacotherapy of OCD.

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