THE EFFECT OF SEROTONERGIC LESIONS IN THE MEDIAL PREFRONTAL CORTEX ON PSYCHOTOMIMETIC DRUG-INDUCED LOCOMOTOR HYPERACTIVITY AND PREPULSE INHIBITION IN RATS

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ABSTRACT:

While dysfunction of the prefrontal cortex has been repeatedly implicated in the pathophysiology of schizophrenia, the role of serotonin in this brain region in schizophrenia is unclear. We therefore examined the effects of local serotonin depletion in the medial prefrontal cortex on psychotomimetic drug-induced locomotor hyperactivity and prepulse inhibition, two animal models of aspects of schizophrenia. Pentobarbital-anaesthetised (60 mg/kg, i.p.) male Sprague-Dawley rats were stereotactically micro-injected with 0.5 µl of a 5 µg/µl solution of the serotonin neurotoxin 5,7-dihydroxytryptamine into the medial prefrontal cortex. Two weeks after the surgery, rats underwent behavioural testing. When compared to sham-operated controls, rats with me-

dial prefrontal cortical lesions did not show changes in either psychotomimetic drug-induced locomotor hyperactivity or prepulse inhibition. However, following the administration of the serotonin neurotoxin into the medial prefrontal cortex, the concentration of serotonin was reduced by 60%. These results suggest that serotonin depletion in the medial prefrontal cortex does not lead to dysregulation of subcortical dopaminergic activity and does not cause aberrant responses to environmental stimuli.

Keywords: schizophrenia, serotonin, medial prefrontal cortex, prepulse inhibition

Running title: Serotonin, the medial prefrontal cortex and behaviour

Abbreviations used:

5,7-DHT- 5,7-dihydroxytryptamine
5-HT- 5-hydroxytryptamine, serotonin
5-HT_{1-7, A-F}- serotonin receptor subtypes
ANOVA- analysis of variance
D₁₋₅- dopamine receptors 1-5
DRN- dorsal raphe nucleus
GABA- γ-aminobutyric acid
HPLC- high pressure liquid chromatography
i.p.- intraperitoneal
MRN: median raphe nucleus
mPFC- medial prefrontal cortex
NMDA- N-methyl-D-aspartate
PPI- prepulse inhibition
PP- prepulse intensity
PP8- prepulse of 8 dB
s.c.- subcutaneous
SEM- standard error of the mean
VTA- ventral tegmental area

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INTRODUCTION

Schizophrenia is a chronic and severe psychiatric disorder that generally occurs in late adolescence or early adulthood. Approximately 1% of the population worldwide is affected by schizophrenia, placing a heavy burden on society, both in terms of emotional suffering and economic loss [1]. Schizophrenia is the classic example of a disorder that always has psychosis as one of its features [2]. As psychotic episodes are extremely debilitating, management and treatment aim to reduce and eliminate these dramatic personality changes, consisting of irritability, confusion and paranoia associated with hallucinations and delusions. Antipsychotic drugs are used to treat nearly all forms of psychosis, including schizophrenia. It has been generally accepted that the mechanism by which antipsychotic drugs decrease hallucinations and delusions is mediated at least in part by dopamine D_2 receptor blockade [3-5]. Moreover, atypical antipsychotic drugs, such as olanzapine, display a unique neuropharmacological profile; they minimise psychoses by interacting with a number of neurotransmitter and receptor systems through binding at multiple receptor sites. Olanzapine has a high affinity for serotonin 5-HT_{2A}, dopamine, cholinergic, histamine and α 1-adrenergic receptors [6]. However, the most important mechanisms underlying the clinical properties of atypical antipsychotic drugs appear to be mediated by interactions with the serotonin 5-HT_{2A} receptor subtype [7, 8].

Serotonin is one of the major neurotransmitters in the human brain and plays a central role in the regulation of a wide range of behaviours, such as mood, eating and the stress response [9-11]. The serotonergic projections arising from the brainstem raphe nuclei form the largest and most complex efferent system in the human brain [12, 13]. The axons of dorsal raphe nucleus (DRN) neurons contribute to the majority of the serotonergic innervation in the frontal cortex, ventral hippocampus and striatal regions [14, 15], while the axons of median raphe nucleus (MRN) serotonergic neurons are more abundant in the dorsal hippocampus and the cingulate cortex [16, 17]. The hypothalamus, the substantia nigra and the nucleus accumbens receive serotonergic innervation from both nuclei [18, 19]. This organisation of the serotonergic neuronal population suggests that serotonin is involved in the regulation of different functional systems, such as the motor, limbic and somatosensory systems [13]. Thus, it is not surprising that atypical antipsychotic medications target multiple brain serotonin receptor subtypes. As it is very difficult to assess alterations of serotonergic transmission in the pathophysiology of psychiatric disorders in the living human brain, animal models are needed.

Animal models of psychiatric disorders, including schizophrenia, rely on mimicking specific aspects or symptoms associated with the disease [20-22]. The two most widely used models are locomotor hyperactivity induced by psychotomimetic drugs and prepulse inhibition.

Psychotomimetic drugs, such as amphetamine and phencyclidine, can induce abnormal behaviours in animals and mimic certain aspects of psychotic disorders in humans [20, 23-25]. Amphetamine, an indirectly acting sympathomimetic, causes increased dopamine release from presynaptic terminals [26], and hyperlocomotion induced by amphetamine is dependent upon intact subcortical dopamine activity in the nucleus accumbens [27]. In contrast, phencyclidine interferes with multiple neurotransmitter systems [28]. Phencyclidine acts as a non-competitive antagonist at the ion channel associated with the N-methyl-D-aspartate (NMDA) glutamate receptor and also indirectly facilitates dopaminergic and serotonergic transmission [29]. Similar mechanisms are also activated in humans by phencyclidine [30]. Prepulse inhibition of the acoustic startle response is an operational measure of sensorimotor gating that is disrupted in patients with schizophrenia [31, 32] and in rats treated with drugs that facilitate dopaminergic activity [33-35]. Furthermore, prepulse inhibition is reduced in rats treated systemically with serotonin releasers, such as fenfluramine, direct 5-HT_{1A} receptor agonists [36-38] and glutamate receptor antagonists, such as phencyclidine [39]. The prepulse inhibition-acoustic startle reflex model in rats offers a unique opportunity to assess attentional and information processing deficits in schizophrenia, as modulation of the startle responses is similar among mammalian species [40]. In animals, usually the whole body startle response is measured after exposure to acoustic or tactile stimuli, while in humans the eyeblink component of the startle response is measured [40].

There is a growing body of evidence that suggests that the hippocampus, amygdala and prefrontal cortex play an important role in the pathogenesis of schizophrenia. The activity of these brain regions may cause changes in subcortical dopaminergic activity and therefore lead to the inappropriate initiation of behavioural responses to external stimuli. We have previously reported that serotonergic projections into the hippocampus and amygdala are differentially involved in the regulation of psychotomimetic drug-induced locomotor hyperactivity and prepulse inhibition [41, 42]. As serotonergic projections from both raphe nuclei innervate the prefrontal cortex, in addition to the hippocampus and amygdala, the aim of the present study was to determine whether serotonergic lesions of the prefrontal cortex caused behavioural changes similar to those produced by lesions of the hippocampus and/or amygdala.

In humans, dysfunction of the prefrontal cortical areas, with which the medial prefrontal cortex of the rat is comparable, is related to psychopathology of schizophrenia and other psychiatric disorders (for a review, see [43]). A wealth of evidence from studies in animals and humans indicates that the medial prefrontal cortex (mPFC) is a key component of the cortico-limbic-striatal circuits that generate pathological emotional behaviour [44, 45]. The various subdivisions of the mPFC appear to serve separate and distinct functions. For example, ven-

tral regions of the mPFC (the prelimbic and the infralimbic cortices) have been associated with diverse emotional and cognitive processes [43, 46, 47]. The ventral mPFC is also of interest, as it has been strongly implicated in the expression of behavioural and autonomic responses to emotionally relevant stimuli [48]. As dysfunction of the prefrontal cortex has been repeatedly implicated in the pathophysiology of schizophrenia [49–52], studies in the rat have focused on elucidating the role of this region in paradigms such as locomotor activity and prepulse inhibition. Dopaminergic lesions and intra-mPFC infusion of selective dopamine receptor antagonists have been reported to disrupt prepulse inhibition [53, 54], whereas the intra-mPFC infusion of amphetamine has been shown to decrease systemic amphetamine-induced increases in locomotor activity in the open field test [55]. However, none of these studies have addressed the importance of serotonergic innervation of the mPFC in neural circuitry involved in the regulation of motor behaviour and prepulse inhibition. Therefore, the present study investigated the effects of local lesions of serotonergic projections into the mPFC on psychotomimetic drug-induced locomotor hyperactivity and prepulse inhibition.

MATERIALS AND METHODS

Experimental animals

A total of 25 male Sprague-Dawley rats (Department of Pathology, University of Melbourne), weighing 250–300 g at the time of surgery, were used in this study. The animals were housed under standard conditions in groups of two or three with free access to food and water. They were maintained on a 12 h light/dark cycle (lights on at 0700 h) at a constant temperature of 21°C. One week prior to the surgical procedure, the animals were handled each day over a five-day period. The experimental protocol and surgical procedures were approved by the Animal Experimentation Ethics Committee of the University of Melbourne, Australia.

Drugs and solutions

D-amphetamine sulphate (Sigma Chemical Co., St. Louis, MO, USA) and phencyclidine HCl (PCP, Sigma) were dissolved in a 0.9% saline solution and injected subcutaneously (s.c.) into the nape of the neck. Desipramine HCl (Sigma) was dissolved in distilled water and injected intraperitoneally (i.p.) 30 min prior to the neurotoxin microinjection. All doses are expressed as the weight of the salt and were administered in an injection volume of 1 ml/kg body weight. The serotonergic neurotoxin, 5,7-dihydroxytryptamine (5,7-DHT) (Sigma), was dissolved in 0.1% ascorbic acid (BDH Chemicals, Kilsyth, VIC, Australia) in saline to prevent oxidation of the neurotoxin. Carprofen (50 mg/ml, Heriot AgVet, Rowville, VIC, Australia) was diluted in 0.9% saline to a dose of 5 mg/kg and injected s.c. immediately after the surgical procedure.

Surgical procedure

The rats were pretreated with 20 mg/kg desipramine, 30 min prior to surgery, to prevent the destruction of noradrenergic neurons by 5,7-DHT [56]. The rats were subsequently anaesthetised with sodium pentobarbitone (60 mg/kg i.p., Rhone Merieux, QLD, Australia). The rats were mounted in a Kopf stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA) with the incisor bar set at –3.3 mm [57]. The skull surface was exposed, and a small hole was drilled. A 25 gauge stainless-steel cannula, which was attached to a 10 µl glass syringe and connected via polyethylene tubing mounted in an infusion pump (UltraMicro-Pump, World Precision Instruments, Sarasota, FL, USA), was lowered into the mPFC. With bregma set to zero and the stereotaxic arm at 0°, the coordinates were as follows: mPFC lesions (n=13 for behavioural experiments, n=2 for histology): 3.2 mm anterior, 0.7 mm lateral and 4.5 mm ventral to bregma. A volume of 0.5 µl of 5,7-DHT (5 µg/µl) was infused over a period of 2 min on each side. Sham-operated controls (n=10) underwent the same surgical procedure and received an equal volume of vehicle solution. The injection volumes and rate of infusion were selected to minimise non-specific damage at the site of injection. Movement of the meniscus in the cannula was monitored to ensure successful infusion. After infusion, the cannula was left in place for a further 2 min to avoid backflow of the solution up the injection path. After lesioning, the skin was closed with silk-2 sutures (Cynamid, Baulkham Hills, NSW, Australia), and the animals were administered 5 mg/kg of carprofen, a non-steroidal, anti-inflammatory analgesic, to reduce post-operative inflammation and discomfort. The rats were placed on a heated pad until they recovered from the anaesthesia. After the surgery, the rats were allowed to recover for two weeks, during which they were handled regularly and health checks were made two to three times a week.

Experimental design and apparatus

Behavioural tests were performed starting two weeks after the surgery, and each session included random numbers of 5,7-DHT-lesioned rats and sham-operated rats. Locomotor activity was monitored using eight automated photocell cages (31 x 43 x 43 cm, h x w x l, ENV-520, MED Associates, St. Albans, VT, USA). The position of the rat at any time was detected with sixteen evenly spaced infrared sources and sensors on each of the four sides of the monitor. The addition of a photobeam array above the subject added a second plane of detection to the system to detect rearing and vertical counts. This infrared beam array thus defined an X, Y and Z coordinate map for the system. The sensors detected the presence or absence of the infrared beam at these coordinates. Every 50 msec, the software checked for the presence or absence of the infrared beam at each sensor, allowing for the very precise tracking of the movement of a subject. Several types of behavioural responses were recorded, including distance moved, ambulation, stereotypy and rearing. Ambulatory counts con-

sisted of consecutive interruptions of at least four beams within a period of 500 ms. Small, repetitive beam breaks within a virtual box of 4 x 4 beams around the rat were recorded as stereotypic counts. Recordings of photocell beam interruptions by the rat were taken every 5 min and stored by the computer software. Three locomotor activity tests were done after treatment with saline, 0.5 mg/kg of amphetamine or 2.5 mg/kg of phencyclidine administered in a random order. These locomotor activity tests were done with three to four day intervals to prevent habituation due to repeated testing and to allow for clearance of the drugs. Prior to any drug manipulation, the rats were placed in the locomotor photocell cages for 30 min to establish baseline locomotor activity and allow for habituation to the test environment. After 30 min of spontaneous baseline activity, the rats were injected and locomotor activity was recorded over a further 90 min, generating a total session time of two hours. For the purpose of this paper, locomotor activity data were expressed as cumulative data from 30 min periods and presented as a time course of distance moved during the 30 min before injection and 90 min after injection.

After locomotor activity experiments, rats were tested for prepulse inhibition. This was done using six automated startle chambers (SR-LAB, San Diego Instruments, San Diego, CA, USA) consisting of clear Plexiglas cylinders, 9 cm in diameter, resting on a platform inside a ventilated, sound-attenuated and illuminated chamber. A speaker mounted 24 cm above the cylinder produced both continuous background noise at 70 dB and the various acoustic stimuli. Whole-body startle responses of the animal in response to acoustic stimuli caused vibrations of the Plexiglas cylinder, which were then converted into quantitative responses by a piezoelectric accelerometer unit attached beneath the platform. The percent prepulse inhibition was calculated as $100 \times \{[\text{pulse-alone trials} - (\text{prepulse} + \text{pulse trials})] / (\text{pulse-alone trials})\}$ [31]. At least one day before the prepulse inhibition testing, rats underwent a pretest session where they were exposed to the testing cylinders and the testing protocol for the first time. This session was conducted to allow rats to habituate to the testing environment. Each rat was placed into the chamber for a 5 min acclimation period with a 70 dB background noise level that continued throughout the session. A single prepulse inhibition session lasted for about 45 min and consisted of high- and low-intensity stimulus combinations with a continuous background noise of 70 dB. The session started and ended with a block of ten pulse-alone trials of 115 dB. These blocks, together with twenty pseudo-randomly presented pulse-alone trials during the prepulse inhibition protocol, were used to calculate the basal startle reactivity and startle habituation. Prepulses were presented for 20 ms and differed in intensity. Prepulse inhibition was assessed by the random presentation of 115 dB pulses, ten each of prepulse-2, -4, -8, 12 and -16 and ten 'no-stimulus' trials. For example, prepulse-8 (PP8) is a 20-ms prepulse of 8 dB above the background noise, i.e., 78 dB, followed 100 ms

later by a 40-ms 115 dB pulse [58]. The interval between trials varied (10 - 37 s) to prevent conditioning of the responses. A microcomputer and an interface assembly that controlled the delivery of acoustic stimuli digitised and recorded the readings.

Tissue preparation for histology and high pressure liquid chromatography (HPLC)

At the end of the experiments, rats were killed by decapitation and the brains were removed from the skull. The brains were placed on a cold plate. First, the frontal cortex was dissected bilaterally [59], and then the mPFC was dissected out. For the histological assessment of the location of the injection sites, 20- μ m-thick sections of the medial prefrontal cortex of two mPFC-lesioned rats were cut on a cryostat and mounted onto gelatin-coated glass slides. The sections were then stained with cresyl violet (ProSciTech, Thuringowa, QLD, Australia) and examined microscopically to verify the location of the tips of the infusion cannulas.

The HPLC measurements of the tissue serotonin (5-HT) concentration were carried out in 23 animals. The dissected structures were weighed and stored in Eppendorf tubes at -80°C until the biochemical assays were performed. The tissue samples were homogenised in 500 μ l of 0.1 M perchloric acid by ultrasonication and centrifuged at 15,500 g for 5 min. A 50 μ l aliquot of the supernatant was injected into a high pressure liquid chromatography (HPLC) system to determine the content of 5-HT (ng/mg tissue of wet weight). The HPLC system consisted of a Waters Model 510 Solvent delivery system, a Waters U6K injector, an Alphasbond C18 125A 10 U 150* 3.9 mm column and a Column & Spectra-Physics 970 D-A1 fluorescence spectrometer. The output signal from the fluorescence detector was analysed with the chromatography software package, 810 Baseline, version 3.31. The mobile phase used consisted of 9.8 g/l KH_2PO_4 , 1.0 g/l Na_2EDTA , 5% acetonitrile and 1 ml/l triethylamine. The pH of the mobile phase solution was adjusted to 3.0 with 1 M HCl. Subsequently, the solution was filtered and degassed and delivered to the HPLC at a flow rate of 1 ml/min. Prior to sample testing, the following standards for 5-HT were run through the system: 12.5 ng/ml, 25 ng/ml, 50 ng/ml, 100 ng/ml and 200 ng/ml. Calibration curves were constructed, and the level of 5-HT in tissue samples was calculated relative to these standards. Each run lasted 8 min and the retention time for serotonin was 2.6 min.

Statistical analysis

Data were expressed as the mean $\pm$ the standard error of the mean (SEM). All of the statistical analyses were performed using the statistical software package SYSTAT 9.0 (SPSS Inc., Chicago, IL, USA). All of the data were analysed using an analysis of variance (ANOVA) with repeated measures where appropriate. In the locomotor activity experiments, data were summed in 30-min blocks, and these blocks were used to assess the main effects of the lesion type (group), the treatment with amphetamine or phency-

clidine (time) and the interactions between these factors. In this analysis, the time effect was a repeated-measures factor. The baseline and the drug-induced locomotor activity were part of the data set analysed. In the prepulse inhibition experiments, the factors were group and habituation (four blocks of ten startle responses) or group and prepulse (five different prepulse intensities), where habituation and prepulse were repeated-measures factors. After calculating ANOVAs for all of the surgery groups, subsequent pairwise ANOVAs were performed where needed. A 'p-value' of $p < 0.05$ was considered to be statistically significant. For HPLC measurements, a one-way ANOVA was used, followed by the Bonferroni-corrected t-test comparison.

RESULTS

Histology: injection sites

Inspection of cresyl violet-stained brain sections from two animals revealed that the tip of the infusion cannula was situated within the boundaries of the mPFC, as delineated by the Paxinos and Watson rat brain atlas [57].

HPLC: 5-HT depletion

The behavioural data of four mPFC-lesioned rats with partial depletions of 5-HT (<50%), as measured by HPLC, were excluded from the study. The final group size for the analysis was $n=10$ for the sham-operated group and $n=9$ for the mPFC-lesioned group. In the mPFC-lesioned rats, the local injection of 5,7 DHT caused a marked reduction of the 5-HT concentration in the mPFC. After the microinjection of 5,7-DHT into the mPFC, the concentration of 5-HT was reduced by 60% (Figure 1). An ANOVA revealed a significant reduction of the 5-HT concentration in the mPFC-lesioned rats compared to the controls ($F_{1,17}=92.3$, $p < 0.001$).

Figure 1

5-HT content in the mPFC after sham surgery or 5,7 DHT microinjection into the mPFC. The data are expressed as the average 5-HT concentration (ng/mg of tissue wet weight) $\pm$ SEM. *** $p < 0.001$ for the difference in the 5-HT concentration between the mPFC-lesioned rats and the sham-operated control rats as indicated by ANOVA.

Figure 2

Time course of the effects of a subcutaneous injection of saline, 0.5 mg/kg of amphetamine or 2.5 mg/kg of phencyclidine on locomotor activity in sham-operated rats and rats with 5,7 DHT-induced mPFC lesions. Locomotor hyperactivity is expressed as the distance moved (cm) $\pm$ SEM for sham-operated ($n=10$, $\bullet$) and mPFC-lesioned rats ($n=9$, $\circ$). There were no significant differences between the groups.

Figure 3
Effect of sham surgery (n=10) or 5,7-DHT lesions of the mPFC (n=9) on startle amplitude, startle habituation and prepulse inhibition. The top panel illustrates the basal startle reactivity and the startle habituation. The data are expressed as mean startle amplitudes $\pm$ SEM for each of the four blocks of ten 115 dB pulses. The bottom panel illustrates the prepulse inhibition of the acoustic startle response. The prepulse inhibition is expressed as the % inhibition $\pm$ SEM at different prepulse intensities. There were no significant differences between the groups as indicated by ANOVA.

The effects of the microinjection of 5,7-DHT on amphetamine- and phencyclidine-induced locomotor hyperactivity

The locomotor hyperactivity caused by treatment with amphetamine or phencyclidine was not significantly different between sham-operated rats and mPFC-lesioned rats (Figure 2). After treatment with either amphetamine or phencyclidine, there was an expected main effect of time ($F_{2,34}=10.4$, $p<0.001$ and $F_{2,34}=5.4$, $p=0.01$, respectively), reflecting the increases in activity caused by these treatments. The lack of a main group effect or a time $\times$ group interaction suggested that the time course of the effects of either amphetamine or phencyclidine was not altered after mPFC-lesions. Lesioned animals tended to show increased phencyclidine responses (Figure 2, bottom panel); however, this was seen in only two out of nine rats. The analysis of the 5-HT concentrations in these two rats did not reveal any differences in the level of 5-HT depletion in comparison

with the other rats. After a saline injection, the locomotor activity levels were very low, and there was no significant difference between the lesioned group and the sham-operated group (Figure 2).

The effects of the microinjection of 5,7-DHT on the startle response, habituation and prepulse inhibition

The startle amplitude in the pulse-alone trials and the habituation of the rats were not different between the mPFC-lesioned rats compared to the sham-operated controls (Figure 3). An ANOVA revealed that there was no significant main effect of group or of the habituation $\times$ group interaction. Figure 4 appeared to suggest that the mPFC-lesioned rats showed an increase in prepulse inhibition at PP2 and PP4 compared to the sham-operated controls; however, an ANOVA indicated that there was no significant main effect of group or of the prepulse $\times$ group interaction.

DISCUSSION

The behavioural assessment of rats with serotonergic lesions of the mPFC, using the locomotor hyperactivity and prepulse inhibition paradigms, revealed that there were no differences between the lesioned and control groups. The present findings suggest that normal regulation of locomotor activity and prepulse inhibition is independent of serotonin release from terminals in the mPFC.

Serotonin in the mPFC

and psychotomimetic drug action

As previously reported [41], it is likely that serotonin release from terminals in the dorsal hippocampus has an inhibitory effect on glutamatergic projections to the core of the nucleus accumbens. Disruption of this inhibition may lead to increased glutamatergic transmission in the nucleus accumbens and enhancement of phencyclidine-induced hyperlocomotion. In addition, enhancement of glutamatergic transmission has been shown to have an opposite effect on amphetamine-induced hyperlocomotion [41].

It has been shown that phencyclidine enhances glutamate release in the prefrontal cortex to compensate for the blockade of NMDA receptors, which leads to the overstimulation of postsynaptic non-NMDA glutamate receptors [60, 61]. Additionally, the acute administration of phencyclidine promotes dopamine release in the prefrontal cortex [62]. It has been reported that group II metabotropic glutamate receptor agonists and non-NMDA receptor antagonists diminish phencyclidine-induced hyperlocomotion by preventing the responses of pyramidal cells of the rat mPFC [60, 61]. We suggest that serotonin depletion in the mPFC does not influence phencyclidine-induced dopamine or glutamate release in this brain region. Furthermore, our results suggest that glutamatergic transmission in the nucleus accumbens is not altered after the manipulation of serotonin release in the mPFC. We postulate that the effect of en-

hanced glutamatergic transmission on the amphetamine response depends on the balance of NMDA and non-NMDA receptor activation interacting with dopamine D₁ and D₂ receptors. Both NMDA and non-NMDA receptors in the nucleus accumbens are located at the presynaptic level on glutamatergic and dopaminergic terminals arising from the cortex, the hippocampus and the midbrain, respectively (for a review see [63]). Our results suggest that serotonin depletion in the mPFC does not influence either dopaminergic or glutamatergic transmission within the nucleus accumbens.

Serotonin in the mPFC and prepulse inhibition

Prepulse inhibition is thought to be mediated by a prefrontocortico-limbic-striato-pallidal circuit in which the mPFC plays an important role [64]. Manipulations that decrease dopamine levels in the mPFC disrupt prepulse inhibition [53, 54], presumably by disinhibition of the descending glutamatergic projections [64]. The mPFC sends direct glutamatergic projections to the nucleus accumbens and the ventral tegmental area (VTA) [65], from which dopaminergic projections ascend to the nucleus accumbens. Stimulation of the mPFC increases dopamine release in the nucleus accumbens, probably via the VTA [66, 67]. It is therefore possible that disinhibition of the mPFC glutamatergic output to the VTA increases dopamine release in the nucleus accumbens and thereby reduces prepulse inhibition [68]. Our results suggest that serotonin depletion in the mPFC does not alter mPFC output neurons to either the VTA or the nucleus accumbens, thus having no effect on sensorimotor gating.

In conclusion, serotonin depletion in the mPFC does not lead to the dysregulation of subcortical dopaminergic activity and does not cause aberrant responses to environmental stimuli. It is therefore clear that the behavioural effects of raphe lesions described in our initial studies [69, 70] are not mediated by serotonin depletion in the mPFC.

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