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Synergistic effect of decreased opioid activity and sleep deprivation on head-twitch response in mice

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ABSTRACT

In schizophrenia, an opioidergic understimulation and a decreased sleep duration are found. The pathogenic significance of these factors is unknown. The present study assessed the influence of the combination of the factors on serotonergic 2A (5-HT(2A)) receptors that are possibly related to psychosis development. 2,5-dimethoxy-4-iodoamphetamine (DOI)-induced head-twitch response in mice was used as a model of 5-HT (2A) receptor functioning. Mice underwent sleep deprivation and/or a blockade of opioidergic receptors with naloxone. To evaluate the involvement of 5-HT(2A) receptor in effects observed, animals were pretreated with MDL 100,907, a potent and selective antagonist of 5-HT(2A) receptor. As was found, 4 h of sleep deprivation followed by administration of naloxone significantly increases the frequency of head twitches, with sleep deprivation and naloxone being ineffective alone. The action of the "sleep deprivation–opioid understimulation" combination is antagonized completely by MDL 100,907. Thus, some schizophrenia-associated factors can synergistically enhance the activity of 5-HT(2A) receptors. These results suggest the above factors being pathogenically relevant in schizophrenia.

1. Introduction

Schizophrenia has been the subject of intense research over many decades. Diverse pathological processes were revealed in disease-affected brain, and a number of hypotheses has been put forward to explain the mechanisms of schizophrenic psychosis (reviews Schöpf, 1975; Kornhuber and Weller, 1994; Kornhuber et al., 2004; Sperner-Unterweger, 2005). Meanwhile, despite all research efforts, the investigation of schizophrenia pathogenesis is just as relevant as ever.

One of the concepts of the schizophrenia pathogenesis, serotonin hypothesis, is of special interest since for years it remains viable (Geyer and Vollenweider, 2008). This hypothesis has received the substantial support by investigations with psilocybin, a hallucinogen with serotonergic agonist properties. As was shown, in healthy humans psilocybin produces schizophrenia-like effects that are effectively blocked by ketanserin (Vollenweider et al., 1998; Carter et al., 2007), a preferential 5-HT(2A)-receptor antagonist (for refs. see Willins and Meltzer, 1997).

The ketanserin inhibition of the psilocybin action (Vollenweider et al., 1998; Carter et al., 2007) and the similarity between the psilocybin-induced effects and schizophrenia (Keeler, 1965; Vollenweider et al., 1998; Carter et al., 2007) suggest that the ketanserin-sensitive 5-HT(2A)-receptors may participate in the development of psychotic symptoms in schizophrenia.

In view of this, of interest is to determine whether 5-HT(2A)-receptors may be stimulated by the processes operating in the schizophrenia-affected organism.

A notable feature of schizophrenia is a reduced level of endogenous opioid peptide, methionine–enkephalin, in brain tissue (Kleinman et al., 1985) and in cerebrospinal fluid (Wen et al., 1983).

A further trait of schizophrenia is a disturbance of night sleep, e.g. decreased time spent asleep, an increase in number of arousals to wakefulness (Tandon et al., 1992; Chouinard et al., 2004) and increased time spent awake displayed by never-medicated patients (Ganguli et al., 1987; Tandon et al., 1992; Chouinard et al., 2004) and patients that were free of psychotropic medications for a minimum 2 weeks (Yang and Winkelman, 2006).

It is not yet known from direct studies whether the above abnormalities influence 5-HT(2A) receptor functioning. Some relevant data are obtained with rat neocortical layer V pyramidal cells. In this model, methionine–enkephalin was found to suppress spontaneous excitatory postsynaptic currents (Marek and Aghajanian, 1998) which can be dependent on 5-HT(2A) receptors (Aghajanian and Marek, 1997). No data on the influence of a decrease in sleep time on 5-HT(2A) receptors have been reported nor have the effects on 5-HT(2A) receptors of a combination of the abnormalities noted above been studied.

The present study addresses the influence of the combination of the above-mentioned schizophrenia-related abnormalities on

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function of the 5-HT(2A) receptors which are possibly involved in psychosis development.

2. Materials and methods

2.1. Animals

The research protocol was approved by the local Ethics Committee. Male C57Bl/6 mice weighing 22–24 g (Rappolovo Breeding Nursery, Russian Academy of Medical Sciences) were used.

Animals were housed in group of five to six per 44×25×26 cm Plexiglas cage with sawdust-covered flooring and maintained at 22 °C on a 12/12-h light–dark cycle (lights on from 0700 to 1900 h) in a well-ventilated room. The animals were adapted to these conditions for a minimum of 3 weeks before the experiments. Animals had free access to standard food and to water until immediately before injections of drugs tested.

For use in experiments, animals were divided randomly into groups. Each animal was used only once.

2.2. Drugs

(±)-2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI) and naloxone dehydrate hydrochloride (naloxone) were purchased from Sigma-Aldrich (St. Louis, MO, USA). The drugs were dissolved in sterile saline (0.9% sodium chloride) just before administration.

R(+)-alpha-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol (MDL 100,907) was synthesized at Timpharm Ltd (Moscow, Russia) according to previously described method (Carr et al., 1992). The drug was dissolved in 0.9% saline assisted by the addition of acetic acid (Rueter et al., 2000).

All injections were administered intraperitoneally at a volume of 1.0 ml/100 g body weight. The animals of control groups received vehicle solution.

2.3. Evaluation of 5-HT(2A) receptor responsiveness

Head-twitch response to DOI was examined in the present study since it is a quantifiable and reliable measure of 5-HT(2A) receptor function (Schreiber et al., 1995; Willins and Meltzer, 1997; Vickers et al., 2001; Fantegrossi et al., 2008; Jennings et al., 2008).

On experimental days, mice were weighed, marked, and returned to the home cage. DOI, naloxone, MDL 100,907, and saline doses were then calculated and prepared for injection. For testing, mice were transferred to a 12 cm (diameter)×20 cm (height) glass cage lined with 2 cm sawdust. Mice were allowed to habituate for 30 min before administration of test agents.

Mice were videotaped over 50 min after the DOI or the control vehicle injection. Afterwards, an observer blind to treatment status of animal counted the number of the head twitches that occurred during each 5-min period. The head twitch was defined as a characteristic rotation of the head, neck and shoulders (Heal et al., 1986), differing from autogrooming or scratching.

2.4. Simulation of methionine–enkephalin deficiency

A deficiency of enkephalin was simulated by a blockade of opioid receptors. Methionine–enkephalin is mixed delta/mu opioid receptor agonist (Lord et al., 1977). In the present study, naloxone was used to simulate a deficiency of enkephalins. Naloxone is known to act as an antagonist at delta and mu opioid receptors (Lord et al., 1977), to enter the brain after systemic administration (Fishman et al., 1975), and to inhibit enkephalin-induced effects in the brain (Bloom et al., 1976; Bhargava, 1978).

2.5. Evaluation of the 5-HT(2A) receptor involvement in head-twitch behavior

For this purpose, the influence of MDL 100,907, a highly potent and selective antagonist at 5-HT(2A) receptors (Kehne et al., 1996), was determined.

2.6. Drug administrations

In preliminary experiments, mice were injected with varying doses of DOI (0.4, 0.8, 1.6, and 3.2 mg/kg, $n=6$–7), and a number of the head twitches was counted over 15 min after injection. 1.6 mg/kg was the lowest DOI dose sufficient to induce the significant ($p<0.05$) increase in head-twitch response compared with saline-treated controls. The use of this dose permitted an evaluation of both stimulatory and inhibitory effects, and the dose was used throughout the study. DOI was injected immediately at the end of sleep deprivation period.

MDL 100,907 was used at the dose of 0.3 mg/kg that was found behaviorally active in C57Bl/6 mice (Winter et al., 2005. The drug was injected 15 min prior to DOI that leads to blockade of DOI-stimulated receptors (Jennings et al., 2008).

Naloxone was injected at a dose [2 mg/kg] that was shown to inhibit brain effects of enkephalin (Michael-Titus et al., 1989). The drug was administered 15 min before DOI. This time interval was shown sufficient for intraperitoneally administered naloxone to influence brain functions (Michael-Titus et al., 1989).

2.7. Sleep deprivation

4 h of sleep deprivation was performed from 0900 to 1300 by gently handling of mice, cage tapping, and gentle cage shaking (Renegar et al., 1998). In preliminary experiments, sleep deprivation of this duration failed to affect head-twitch responses, both spontaneous and induced by DOI at the dose of 1.6 mg/kg.

2.8. Groups

The following groups of mice (10 animals each) were tested: I, control (without sleep manipulation and drug interventions); II, sleep deprivation; III, naloxone; IV, MDL 100,907; V, DOI; VI, DOI, sleep deprivation; VII, DOI, naloxone; VIII, DOI, naloxone, sleep deprivation; and IX, DOI, naloxone, sleep deprivation, MDL 100,907.

2.9. Statistical analysis

Data are expressed as means ± SD. Kolmogorov–Smirnov one-sample test was used to assess normality of the data distribution. Since the data were not distributed normally, comparisons were made with a one-way repeated-measures ANOVA on ranks, followed by a non-parametric Tukey's test. Differences with a p value of less than 0.05 were considered statistically significant.

3. Results

As is shown in Table 1, sleep deprivation, naloxone, and MDL 100,907 alone do not induce head twitches (groups II–IV do not differ from group I). Similarly, sleep deprivation and naloxone do not alter DOI-evoked response (groups VI and VII do not differ from group V).

In contrast, the combination "sleep deprivation + naloxone" (group VIII) significantly increases the number of DOI-induced head twitches ($p<0.01$) compared with controls (groups I and V) and groups with sleep deprivation and naloxone individually combined with DOI treatment (groups VI and VII, respectively). Pretreatment with MDL 100,907 (group IX) completely abolishes this response to

Table 1
Effect of understimulation of opioid receptors and sleep deprivation on head-twitch response in mice.

Group	Mean number of head twitches in different time (min) after DOI injection									
	0–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40	41–45	46–50
I, control	1.0 ± 0.47^{a}	0.9 ± 0.73^{a}	1.0 ± 0.94^{a}	0.9 ± 0.87^{a}	1.0 ± 0.82^{a}	0.8 ± 0.92^{a}	1.0 ± 0.82^{a}	1.2 ± 1.03^{a}	1.0 ± 1.05^{a}	0.8 ± 0.78^{a}
II, sleep deprivation	0.8 ± 0.63^{a}	1.0 ± 0.67^{a}	1.1 ± 0.88^{a}	1.0 ± 0.67^{a}	1.1 ± 0.74^{a}	1.1 ± 0.57^{a}	1.0 ± 1.05^{a}	1.1 ± 0.88^{a}	0.8 ± 0.63^{a}	0.7 ± 0.67^{a}
III, naloxone	0.9 ± 0.87^{a}	0.9 ± 0.74^{a}	1.1 ± 0.99^{a}	1.1 ± 0.88^{a}	1.0 ± 0.67^{a}	0.7 ± 0.82^{a}	1.1 ± 1.20^{a}	1.0 ± 1.25^{a}	0.9 ± 1.10^{a}	0.9 ± 0.99^{a}
IV, MDL 100,907	0.8 ± 0.79^{a}	1.0 ± 0.94^{a}	1.2 ± 0.92^{a}	1.0 ± 0.82^{a}	1.1 ± 0.57^{a}	1.0 ± 0.94^{a}	0.9 ± 0.88^{a}	1.0 ± 0.67^{a}	0.9 ± 0.57^{a}	0.9 ± 0.74^{a}
V, DOI	4.6 ± 1.17^{b}	14.6 ± 1.35^{c}	9.9 ± 1.20^{d}	6.6 ± 1.07^{e}	4.4 ± 0.84^{f}	3.9 ± 1.45^{g}	3.8 ± 1.14^{h}	3.1 ± 1.10^{i}	2.5 ± 0.97^{j}	2.3 ± 1.16^{k}
VI, DOI, sleep deprivation	5.1 ± 1.97^{b}	14.3 ± 1.89^{c}	9.6 ± 2.01^{d}	6.9 ± 1.66^{e}	4.9 ± 0.88^{f}	4.2 ± 1.23^{g}	3.7 ± 0.95^{h}	3.2 ± 1.14^{i}	2.4 ± 1.17^{j}	2.2 ± 1.40^{k}
VII, DOI, naloxone	4.9 ± 1.29^{b}	14.0 ± 2.67^{c}	10.0 ± 2.16^{d}	6.7 ± 1.70^{e}	4.7 ± 0.95^{f}	4.4 ± 1.43^{g}	4.0 ± 1.15^{h}	3.4 ± 0.97^{i}	2.3 ± 1.25^{j}	2.0 ± 1.25^{k}
VIII, DOI, naloxone, sleep deprivation	$8.8 \pm 1.99^{*}$	$22.8 \pm 2.39^{\#}$	$16.9 \pm 1.52^{\#}$	$10.4 \pm 1.84^{*}$	6.1 ± 1.37^{f}	5.1 ± 2.02^{g}	4.1 ± 0.99^{h}	4.5 ± 2.46^{i}	2.5 ± 1.72^{j}	2.9 ± 1.29^{k}
IX, DOI, naloxone, sleep deprivation, MDL 100,907	1.3 ± 0.67^{a}	1.5 ± 0.70^{a}	1.3 ± 1.16^{a}	1.4 ± 0.84^{a}	1.1 ± 0.88^{a}	1.1 ± 0.74^{a}	1.0 ± 0.82^{a}	1.1 ± 0.88^{a}	1.2 ± 0.92^{a}	1.0 ± 0.94^{a}

[a–k]Means followed by same letter are not significantly different, $p > 0.05$.
[*]Values are significantly different from groups V–VII in comparison at the same time points, $p < 0.05$.
[#]Value are significantly different from groups V–VII in comparison at the same time points, $p < 0.01$.

DOI indicating a critical involvement of 5-HT(2A) receptors in stimulatory effect of the combination "sleep deprivation + naloxone".

4. Discussion

The present data indicate that a decrease in sleep duration or understimulation of opioid receptors by itself has no influence on 5-HT(2A) receptor functioning. However, the combination of these events that is characteristic of schizophrenia-affected organism, markedly enhances the intensity of 5-HT(2A) receptor-mediated response. This synergistic activation of the receptors that are presumably responsible for the development of psychotic disorders may play a role in schizophrenia pathogenesis.

Conceivably, this newly described synergistic activation of 5-HT (2A) receptors can promote not only an initiation of mental abnormalities but also their perpetuation. Indeed, specific stimulation of 5-HT(2A) receptors was shown to disturb sleep (Monti and Jantos, 2006). Thus, the stimulation of the above receptors can create the possibility for its own further aggravation. In essence, schizophrenia may be initiated or influenced by a vicious circle involving the stimulation of 5-HT(2A) receptors by the combination of sleep inhibition and hypoactivity in endogenous opioid systems which leads to further sleep deprivation.

The effect of the combination might be corticosterone-mediated. Sleep deprivation is a potentially stressful experience (Rechtschaffen et al., 1983) that activates hypothalamic-pituitary-adrenocortical axis (Andersen et al., 2005). Specifically, a rise in corticosterone can take place under sleep deprivation (Peñalva et al., 2003). This hormone is found to stimulate 5-HT(2A) receptor-mediated behavior in rat (Gorzalka et al., 1999). In the present experiments, 4-h deprivation apparently fails to activate corticosterone release to a sufficient extent to stimulate the 5-HT(2A) receptors discernibly. However, the deprivation-induced corticosterone release may be strengthened by the second factor, naloxone, since enkephalins are found to inhibit the adrenocortical response to adrenocorticotropic hormone (ACTH) in rats (Guaza and Borrell, 1984). A blockade of opioid receptors by naloxone can stimulate the 5-HT(2A) receptors also through prolonging stress-induced corticosterone response (Odio and Brodish, 1990).

Whatever the mechanism of above synergistic action, the sleep duration and opioidergic tone might represent targets in the management of schizophrenia.

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