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Neuropharmacology of light-induced locomotor activation

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ABSTRACT

Presentation of non-aversive light stimuli for several seconds was found to reliably induce locomotor activation and exploratory-like activity. Light-induced locomotor activity (LIA) can be considered a convenient simple model to study sensory-motor activation. LIA was previously shown to coincide with serotonergic and dopaminergic activation in specific cortical areas in freely moving and anesthetized animals. In the present study we explore the neuropharmacology of LIA using a receptor antagonist/agonist approach in rats. The non-selective 5-HT_2-receptor antagonist ritanserin (1.5–6 mg/kg, i.p.) dose-dependently reduced LIA. Selective antagonism of either the 5-HT_{2A}-receptor by MDL 11,939 (0.1–0.4 mg/kg, i.p.), or the 5-HT_{2C}-receptor by SDZ SER 082 (0.125–0.5 mg/kg, i.p.), alone or in combination, had no significant influence on LIA. Also the selective 5-HT_{1A}-receptor antagonist, WAY 100635 (0.4 mg/kg, i.p.) did not affect LIA. Neither did the preferential dopamine D2-receptor antagonist, haloperidol (0.025–0.1 mg/kg, i.p.) nor the D2/D3-receptor agonist, quinpirole (0.025–0.5 mg/kg, i.p.) affect the expression of LIA. However, blocking the glutamatergic NMDA-receptor with phencyclidine (PCP, 1.5–6 mg/kg, i.p.) dose-dependently reduced LIA. This effect was also observed with ketamine (10 mg/kg, i.p.). These findings suggest that serotonin and dopamine receptors abundantly expressed in the cortex do not mediate light-stimulus triggered locomotor activity. PCP and ketamine effects, however, suggest an important role of NMDA receptors in LIA.

1. Introduction

A directed response to a novel stimulus is an important basic capability of vertebrates. Disruption of this response is part of a core psychopathological domain associated with psychiatric disorders like schizophrenia or autism (Schumann et al., 2014). Serotonin (5-HT) plays a key role in sensory-motor processing in several sense modalities. Stimulus-evoked neuronal activity in the visual cortex can be modulated by iontophoretic application of 5-HT (Waterhouse et al., 1990), and enhanced levels of 5-HT in the somatosensory cortex potentiate the neuronal response to whisker stimulation (Waterhouse et al., 1996). Several 5-HT receptors were found to mediate these responses. For example, stimulation of 5-HT_{1A}-receptors in the visual cortex modulated synaptic excitation in this brain area (Edagawa et al., 1999). 5-HT_{1A}- and 5-HT_2-receptors, were shown to influence auditory evoked potentials in the EEG of awake cats (Juckel et al., 1997). Levels of extracellular 5-HT have been related to intensity-dependent auditory evoked EEG components in rats (Wutzler et al., 2008).

It was found that visual stimulation of rats with white-light of 82 lux intensity induced locomotor activity and increased extracellular 5-HT and dopamine (DA) levels in the visual cortex (Müller et al., 2007a; Müller and Huston, 2007) and 5-HT in the medial prefrontal cortex (Pum et al., 2008). The 5-HT and DA increase were also seen in anesthetized animals (Pum et al., 2008). Cocaine, which induces serotonergic and dopaminergic activation (Izenwasser et al., 1990; Müller and Homberg, 2015), potentiates LIA (Pum et al., 2011). Such presentation of a light stimulus seems not to have aversive effects, as the animals did not escape the stimulation when given an active withdrawal opportunity. Instead, they showed an exploratory orienting response towards the stimulus source (Pum et al., 2009). These observations supported earlier

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findings on the neuronal activity of serotonergic neurons, which is also related to visual stimulus processing and the effort involved in locomotor activity (Jacobs and Fornal, 2010). Thus, LIA can be considered a convenient simple model to study sensory-motor activation.

Electrophysiological findings and the temporal coincidence of the neurochemical and behavioural responses suggest that 5-HT, DA, and subsequent 5-HT- and DA-receptor activation have significant roles in the control of LIA. The cortex displays a high level of 5-HT_2-receptor expression, particularly of the 5-HT_{2A}- and 5-HT_{2C}-type (Barnes and Sharp, 1999). Here we tested the effects of the overall blockade of 5-HT_2-receptors by the non-selective antagonist ritanserin (Meert et al., 1989), which has a comparable affinity for the 5-HT_{2A}- and 5-HT_{2C}-receptors (Baxter et al., 1995). To segregate the role of each neurotransmitter receptor subtype, we examined the effects of the selective 5-HT_{2A}-receptor antagonist, MDL 11,939, and the selective 5-HT_{2C}-receptor antagonist, SDZ SER 082, respectively. These compounds were given either alone or in combination to probe possible synergistic effects. 5-HT_{1A}-receptors have also been found in high density in the cortex. Therefore, we also assessed the effects of 5-HT_{1A}-receptor antagonism with WAY 100635 (Fletcher et al., 1996). In order to address the role of dopamine D2-receptors, we examined the effects of the D2-receptor antagonist, haloperidol. Ritanserin, which was effective in blocking LIA in the present study, was shown to increase cortical DA tone (Pehek, 1996; Ruiu et al., 2000). In order to determine whether the inhibitory effect of ritanserin was mediated by D2-receptors, we tested the D2/D3-receptor agonist, quinpirole (Amato et al., 2007). Since serotonergic and dopaminergic effects in the cortex converge on glutamatergic signalling, we addressed the role of the glutamatergic system by testing the effect of the non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonists, phencyclidine (PCP) and ketamine.

2. Methods

2.1. Animals

All experiments were conducted in accordance with the Animal Protection Law of the Federal Republic of Germany and the European Communities Council Directive of 24 November 1986 (86/609/EEC), and were approved by local authorities. All efforts were made to reduce the number of animals used and to minimize discomfort.

Male Wistar rats (Charles River, Germany), weighing between 310 and 340 g, were used. They were housed four animals per cage under standard laboratory conditions, with a temperature of 22 ± 2 °C (relative humidity 55 ± 10%), a reversed light–dark rhythm (light on from 19.00 to 7.00 h) and food and water provided ad libitum. After arrival they were given at least two weeks to adapt to the reversed light–dark cycle.

2.2. Apparatus

Testing was carried out in a commercialized TruScan system arena (Coulbourn Instruments, Allentown, USA) from 9 am to 8 pm. The Truscan system is an activity-field arena measuring 40 × 40 × 39 cm. As used in this study, it mounts a photo beam sensor ring located onto elevation rods, which are separated from the station's processor and which surround the 4 sides of the arena. It senses in two dimensions (X and Y) and can measure horizontal locomotion. The sensor ring has built-in photo beams that scan the coordinates of the body centre of the subject and analyse the location of the subject by finding new coordinates with their run-time date stamps. A coordinate change is simply found as a difference in the spatial location of the subject from one beam scan to the next scan, which shows a change in location. Coordinates and their run-time dates are the basis for all measurements in the system (Coulbourn Instruments, Allentown, USA). The Truscan system arena was situated in a larger sound- and light-isolated chamber (110 × 70 × 70 cm). The animals were tested in the dark-phase activity period. The test boxes were illuminated by red light (2.6 lux). For white light stimulation, a fluorescent lamp (16 W), mounted on one of the maze walls was used. In front of the light source, Plexiglas plates were introduced to regulate stimulus intensity to 82 lux (Müller et al., 2007a; Pum et al., 2009).

2.3. Drugs

The doses used were the following: ritanserin (1.5, 3, 6 mg/kg; i.p.; injection volume 2 ml/kg; Sigma, Steinheim, Germany) or its vehicle (1% Tween 80 in saline). MDL 11,939 (0.1, 0.2, 0.4 mg/kg; i.p.; Biotrend, Köln, Germany) or its vehicle (1% Tween 80 in saline; 1 ml/kg). SDZ SER 082 (0.125, 0.25, 0.5 mg/kg; i.p.; 1 ml/kg; Biotrend, Köln, Germany), or its vehicle (1% Tween 80 in saline; 1 ml/kg). MDL 11,939 and SDZ SER 082 were also given in combination at the following doses: D1 (0.4 mg/kg MDL 11,939 + 0.5 mg/kg SDZ SER 082), D2 (0.2 mg/kg MDL 11,939 + 0.25 mg/kg SDZ SER 082) or D3 (0.1 mg/kg MDL 11,939 + 0.125 mg/kg SDZ SER 082) or their vehicle (1% Tween 80 in saline; 1 ml/kg). WAY 100635 (0.4 mg/kg, Research Biochemicals) was dissolved in saline (1 ml/kg). Haloperidol (0.025, 0.05, 0.1 mg/kg; 1 ml/kg; Sigma, Steinheim, Germany) or its vehicle (0.01% acetic acid in saline), and quinpirole (0.25, 0.5 mg/kg; 1 ml/kg, Sigma, Germany) or its vehicle (0.9% saline) were administered. Phencyclidine (1.5, 3.0, 6.0 mg/kg; 1 ml/kg, Sigma, Germany) and ketamine (10 mg/kg; 1 ml/kg, Sigma, Germany) were dissolved in saline.

2.4. Experimental procedures

Animals were habituated to the test apparatus in 20 min sessions on two consecutive days in a dimly lit room (2.6 lux). On the third day, visual stimuli (82 lux) were presented. On the test-day treatment groups were injected with one compound or mixture and placed into the open field. Behavioural measurements were started 10 min after treatments. Thus, the animals started the LIA test after a 20 min habituation period, followed by a 20 min interval of stimulus presentation (10 stimuli of 30 s duration, distributed randomly over the 20 min period) and an additional 20 min post-stimulus interval in which no light stimuli were presented. The no-light stimulus control groups did not receive any light stimulation during the second 20 min interval. Within the stimulation interval, the presentation of a stimulus required an inter-stimulus interval of at least 30 s. Horizontal locomotion was automatically measured by the TruScan system (Müller et al., 2007a; Pum et al., 2009).

2.5. Statistics

Locomotor activity data were analysed as mean ± SEM. When significant baseline differences emerged between treatment groups, LIA effects were normalized to the last 5 min baseline interval, which was set as "zero". Activity in all subsequent 5 min intervals was then calculated and statistically analysed as delta (Δ) from this interval. Figures reporting the absolute baseline values are shown in the Supplementary material. Two-way ANOVAs were conducted for each test phase for the stimulus group and the no-stimulus control group with the factors 'time' and 'treatment'. Pre-planned comparisons were calculated to compare group differences at single 5 min intervals using Bonferroni-corrected LSD tests. An alpha-level of <0.05 was considered as statistically significant.

3. Results

3.1. The non-selective 5-HT2-receptor antagonist ritanserin blocks LIA

The application of the non-selective 5-HT_2-antagonist, ritanserin, attenuated LIA. *Habituation:* In the stimulus groups there was an effect of time [$F(3, 84) = 82.452$, $p < 0.001$] and a trend towards an effect of treatment [$F(3, 28) = 2.884$, $p = 0.053$], but no significant interaction ($p > 0.05$; Fig. 1A). The analysis of the no-stimulus control groups did shown an effect of time [$F(3, 84) = 87.910$, $p < 0.001$], but no effect of treatment and no interaction ($p > 0.05$; Fig. 1B). *Stimulus:* There was a significant effect of dose [$F(3, 28) = 4.585$, $p = 0.010$] and time [$F(3, 84) = 3.687$, $p = 0.015$], as well as a significant interaction [$F(9, 84) = 2.359$, $p = 0.020$] between these factors in the light stimulus groups. Post-hoc tests revealed that LIA was attenuated in the 1.5 mg/kg ($p = 0.023$) and the 6.0 mg/kg group ($p = 0.018$) as compared to the vehicle groups. The two-way ANOVA did not show a significant main effect or interaction in the no-stimulus control groups ($p > 0.05$). *Post-stimulus:* The statistical analysis of the post-stimulus phase did not yield any significant main effects or interactions ($p > 0.05$).