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ARTICLE

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Sleep deprivation disrupts prepulse inhibition of the startle reflex: reversal by antipsychotic drugs

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Abstract

Sleep deprivation (SD) is known to induce perceptual impairments, ranging from perceptual distortion to hallucinatory states. Although this phenomenon has been extensively described in the literature, its neurobiological underpinnings remain elusive. In rodents, SD induces a series of behavioural patterns that might be reflective of psychosis and mania, such as hyperlocomotion and sensitization to psychotogenic drugs. Notably, such changes are accompanied by transitory alterations of dopaminergic signalling. Based on the hypothesis that both psychotic and manic disorders reflect gating impairments, the present study was aimed at the assessment of the impact of SD on the behavioural model of prepulse inhibition (PPI) of the startle reflex, a reliable paradigm for the study of informational filtering. Rats subjected to SD (24 h, 48 h, 72 h) exhibited a time-dependent increase in startle reflex and a dramatic deficit in PPI. Both alterations were reversed 24 h after termination of the SD period. Interestingly, PPI disruption was efficiently prevented by haloperidol (0.1 mg/kg i.p.) clozapine (5 mg/kg i.p.) and risperidone (1 mg/kg i.p.). Conversely, neither the anxiolytic diazepam (5 mg/kg i.p.) nor the antidepressant citalopram (5 mg/kg i.p) affected the PPI disruption mediated by SD, although diazepam reversed the enhancement in startle reflex magnitude induced by this manipulation. Our data suggest that SD induces gating deficits that might be relevant to the hallucinatory phenomena observed in humans, and provide a novel reliable animal model where such relationship can be studied.

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Key words: Clozapine, haloperidol, prepulse inhibition of the startle, risperidone, sleep deprivation.

Introduction

Sleep disturbances are a common symptom of psychotic and hallucinatory disorders (Benca et al., 1992; Benson and Zarcone, 1993; Keshavan et al., 1990; Monti and Monti, 2004; Onheiber et al., 1965; Stern et al., 1969). For example, schizophrenia patients exhibit an erratic sleep profile, with hyposomnia and deficits in both rapid eye movement (REM) and slow-wave sleep (Lauer et al., 1997; Monti and Monti, 2004; Neylan et al., 1992; Tandon et al., 1992). The intensity of such alterations is related to the severity of psychotic symptoms and is attenuated by antipsychotic therapy (Keshavan et al., 1995; Monti and Monti, 2004; Tandon et al., 1992; Taylor et al., 1992; Thaker et al., 1990; van Kammen et al., 1988). Mounting evidence suggests that alterations of sleep architecture might precipitate the neurobiological imbalances underlying psychotic disorders. In particular, sleep deprivation (SD) is conducive to several abnormalities, ranging from minor disturbances and abnormal bodily sensations to disturbances reminiscent of those observed in schizophrenia patients, including disorganized thought, depersonalization, complex acoustic and visual hallucinations, with changes in dimensional perception as well as loss of insight. Notably, this array of symptoms is typically reversed following a prolonged, restorative sleep (Tyler, 1955).

Similarly, rodents forced to prolonged SD exhibit a spectrum of manic-like and psychotic-like behavioural responses, such as hyperactivity, increased

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responsiveness to psychostimulants, irritability, aggressiveness and perseverative behaviours (Gessa et al., 1995). This evidence suggests that the neurobiological alterations induced by SD might partially mimic the pathogenesis of psychotic and hallucinatory states. Current views posit that such phenomena may result from impairments of gating function, which would lead to an altered sensitivity to sensory stimuli, perceptual overload and cognitive fragmentation (Braff et al., 2001).

The best validated paradigm to evaluate and measure sensorimotor gating is the prepulse inhibition (PPI) of the acoustic startle reflex (ASR), consisting in the reduction of the ASR that occurs when the eliciting stimulus is immediately preceded by a non-startling prestimulus (Graham, 1975). PPI is typically impaired in several neuropsychiatric disorders characterized by attentional or somatosensory deficits (Braff et al., 2001), such as psychotic disorders (Braff et al., 1999) and mania (Perry et al., 2001; Saccuzzo and Braff, 1986). Alterations in PPI can also be induced in animals by psychotomimetic drugs and selectively reversed by antipsychotic agents (Braff et al., 2001), lending further support to the validity of PPI as a model of psychosis. In light of these premises, we designed the present study to characterize the effects of SD on startle reflex and PPI in rats.

Specifically, throughout this study rats were sleep-deprived with the platform method (Jouvet et al., 1964). In this paradigm, the muscle atonia which accompanies REM sleep, causes the animal to fall into the water and wake up. Thus, this procedure produces a complete reduction of REM sleep (Kovalzon and Tsibulsky, 1984).

Method

Animals

A total of 138 male Sprague–Dawley albino rats [Harlan, S. Pietro al Natsione (UD), Italy] weighing between 200 g and 300 g served as subjects in the present study. Rats were housed four per cage in the animal care quarters, maintained at a temperature of 22 ± 2 °C on a reversed 12-h light–dark cycle (lights on 19:00 hours). Food and water were available ad libitum, and each rat was handled for 5 min on each of the 5 d prior to experiment to minimize stress effects. All experimental procedures were approved by the ethical committee of the University of Cagliari and carried out in strict accordance with the Economic Community (EC) guidelines for the care and use of experimental animals (86/609/European EC).

Drugs and chemicals

The following drugs were used in the study: haloperidol (Hal), clozapine (Clo), risperidone (Ris), diazepam (Diaz) and citalopram (Cit). All drugs were purchased from Sigma Aldrich (Milan, Italy). Hal was dissolved in 10% acetic acid buffered (to pH 7.0) with sodium hydroxide (NaOH) and diluted with saline, while Clo was dissolved in a single drop of 1 N hydrogen chloride (HCl) and diluted with saline. The pH was adjusted to 7 using sodium bicarbonate ($NaHCO_3$). Ris and Diaz were dissolved in 0.9% saline solution, with 0.3% Tween-80. Citalopram hydrobromide and nicotine were dissolved in 0.9% saline solution. All drugs were weighed out as salts and administered i.p. in an injection volume of 2 ml/kg.

Apparatus

The apparatus for the detection of the startle reflexes (Med Associates, St Albans, VT, USA) consisted of four standard cages placed in sound-attenuated chambers with fan ventilation. The cage was a Plexiglas cylinder of 9 cm diameter, mounted on a piezoelectric accelerometric platform connected to an analogue digital converter. Background noise and acoustic bursts were conveyed by two separate speakers, placed close to the startle cage so as to produce a variation of sound within 1 dB across it. Both speakers and startle cages were connected to a main personal computer (PC), which detected and analysed all chamber variables by means of custom software. Acoustic stimuli were monitored and balanced before each testing session through a digital sound level meter (Extech Instruments, Waltham, MA, USA), while the mechanical response of each cage was set and equalized in all chambers via a 10-Hz spinner calibrator provided by Med Associates.

Procedure

Three days before the experiment, all rats went through a brief baseline startle session. Rats were exposed to a background noise of 70 dB, and after an acclimatization period of 5 min, they were presented with a randomized sequence of 12–40 ms bursts of 115 dB, interposed with three trials in which an 82-dB prestimulus preceded the same pulse by 100 ms.

Rats exhibiting very high or very low baseline startle values (>2 S.D. above or below group mean values) were excluded from the study. Subsequently, treatment groups were established so that the average startle response and percent PPI of each group were equivalent in all groups.

For SD, rats were kept on a small Plexiglas platform (7 cm in diameter) within a deep tank filled with water. Each platform was surrounded by water up to 1 cm, beneath the surface. Food and water were freely available by placing chow pellets and water bottles on a grid located on the top of the tank. During the whole SD study, the temperatures of the experimental room and the water inside the tank were maintained at 23 ± 1 °C. Control rats were placed in the experimental room, either in their home cages or on water tanks equivalent to those used for SD, but with a 12 cm-diameter platform, which allowed them to reach REM sleep without falling into the water.

At the end of the SD period, rats were immediately dried out and then placed in a startle cage for a 5-min acclimatization period with a 70 dB white-noise background, which continued for the remainder of the session. Each session consisted of three consecutive sequences of trials (periods). Unlike the first and the third periods, during which rats were presented with only five pulse-alone trials of 115 dB, the second period consisted of a pseudo-random sequence of 50 trials, including 12 pulse-alone trials; 30 trials of pulse preceded by prepulses of 73 dB, 76 dB, or 82 dB (10 for each level of prepulse loudness); and eight no-stimulus trials, where only the background noise was delivered. Inter-trial intervals (ITI) were selected randomly between 10 s and 15 s. Each startle session lasted about 30 min. The study consisted of five experiments, summarized in Table 1 with the time-intervals for each treatment in all the experiments.

Table 1. Startle magnitudes in rats subjected to sleep deprivation for 72 h, in comparison to controls placed in water tanks with large platforms and in their home cages

Experimental condition	Startle amplitude
Sleep deprivation	752 ± 36
Large platform	586 ± 35*
Home cage	641 ± 43

Values represent mean $\pm$ S.E.M. for each treatment.
* $p < 0.05$ in comparison to sleep-deprived rats. (For further details, see text.)

Experiment description

This study was articulated in four series of experiments. In the first experiment ($n = 45$ rats, 15 rats/group) we evaluated if SD could affect startle and PPI parameters. Thus, 45 rats were tested and then divided into three equivalent groups (15 rats/group). The first group was subjected to SD with the narrow-platform technique. Rats in the second group were kept in identical SD cages, but with larger platforms, which allowed them to sleep. The third group included home-caged rats in the housing room, where light and temperature were kept in identical conditions as the experimental room. The experiment lasted 72 h, since this duration has been shown to produce the most remarkable behavioural changes in rats (Fratta et al., 1987).

Following the discovery that SD enhances startle reaction and disrupts PPI, we tested whether this effect could depend on the stress induced by soaking in water. A group of home-caged, single-housed rats ($n = 8$) were placed directly inside the water in SD tanks for six times at variable intervals over 72 h (the average number of lapses into water during a SD session, as assessed during preliminary observations). Rats were removed from the tanks and relocated in their home cages (without bedding) only after they climbed back on top of the narrow platforms. The last soaking episode always occurred 1 h before PPI testing. Rats were dried only immediately before PPI session, but not throughout the 72-h soaking procedure. As controls, we used rats housed singly in home cages deprived of bedding for 72 h ($n = 10$).

In a third experiment, we studied whether the SD-induced PPI alteration was time-dependent and reversible. Then, 15 rats were tested at the beginning of SD and every 24 h for the following 3 d. After the last testing (at 72 h), rats were immediately returned to their home cages and re-tested after 24 h.

The following series of three experiments ($n = 60$, 10 animals/group) was carried out to verify whether SD-induced PPI disruption could be reversed by the antipsychotic agents Hal (0.1 mg/kg i.p), Clo (5 mg/kg i.p.) and Ris (1 mg/kg i.p.), in comparison to their vehicles. All antipsychotic compounds (or their vehicle) were injected 1 h before the end of SD (71 h).

In the last phase of the study ($n = 30$, 7–8 animals/group) we verified whether SD-mediated PPI deficits by SD could also be related to anxiety or mood disturbances. Hence, rats received an injection of the anxiolytic drug Diaz (5 mg/kg i.p.), the potent antidepressant Cit (5 mg/kg i.p.) or their vehicles 30 min before the conclusion of SD.

Rats used in the first two experiments were naive to any previous treatment or environmental manipulation. To minimize the number of the rats used, control rats in the first experiment were re-used for the fourth series of experiments, after 10–14 d.

Data analysis

For each animal, the mean startle amplitudes for the first and the second halves of the second period of the session (blocks, six pulse-alone trials each) were analysed with a two-way or three-way analysis of variance (ANOVA), with pretreatment (where present) and treatment as between-subjects factors and blocks as repeated measures. The percent PPI was calculated with the following formula:

$$100 - \left(\frac{\text{MSA for prepulse-pulse trials}}{\text{MSA for pulse-alone trials}}\right)\Big/100,$$

where MSA = mean startle amplitude, and analysed in multifactor ANOVAs (with specific design and comparisons noted below for each experiment) with the different combinations of injections for pretreatment and treatment as between-subjects factors and trial types as repeated measures. Post-hoc analyses were performed using Tukey's test. Throughout the study, no significant interaction between prepulse levels and pharmacological treatment has been found: thus, the PPI values have been collapsed to represent average PPI. Alpha was set at 0.05.

Results

Effects of SD

The first experiment evaluated rats before and after 72 h of platform SD, in comparison with two control groups: home-caged rats and animals placed for the same duration of time inside the deprivation tanks on large platforms (where they were able to sleep). The analysis of startle amplitude was performed by one-way ANOVA (Table 1). A main effect was detected [$F(2,42) = 4.84$, $p < 0.05$]. Of note, Tukey's test revealed that this effect was due to a significant difference between sleep-deprived rats and control rats on the large platforms ($p < 0.05$). The difference between home-caged rats and sleep-deprived rats, however, was not fully significant ($p < 0.10$).

A two-way, repeated-measure ANOVA was carried out to test PPI values. The analysis confirmed main effects for both the environmental manipulations [$F(2,42) = 21.47$, $p < 0.001$] and the prepulse levels [$F(2,84) = 20.26$, $p < 0.001$], but did not detect any interaction between the two factors [$F(4,84) = 0.71$, n.s.]. Post-hoc comparisons revealed that SD produced a significant deficit in PPI in comparison to both control groups ($p < 0.001$ for both comparisons, Tukey's test) (Figure 1).

In the second experiment, we tested the effects of repeated soaking over 72 h on startle and PPI. As shown in Figure 2, soaked rats displayed a lower startle amplitude than controls (Figure 2a) [$F(1,16) = 4.55$, $p < 0.05$]. PPI analysis, performed by two-way ANOVA (with treatment and PPI levels as factors) found no significant difference between rats subjected to repeated soaking and controls [$F(1,16) = 0.46$, n.s.] (Figure 2b). Although a significant effect was found for prepulse levels [$F(2,32) = 13.51$, $p < 0.001$], the analysis revealed no significant treatment × prepulse level interaction [$F(2,32) = 1.72$, n.s.].

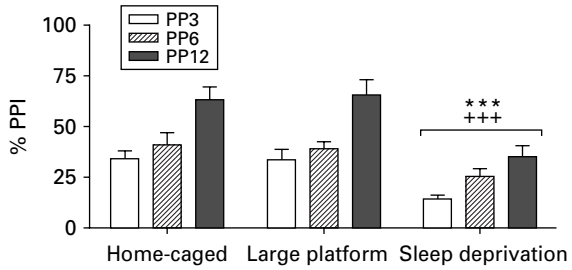

Figure 1. Effects of sleep deprivation on prepulse inhibition (PPI), compared to controls placed in water tanks with large platforms and in their home cages. Values represent mean ± S.E.M. for each treatment. Prepulses (PP3, PP6, PP12) are indicated by the intensity corresponding to decibels above background noise. *** $p < 0.001$ compared to home-caged rats; $^{+++}$ $p < 0.001$ compared to rats placed in water tanks with a large platform. (For further details, see text.)

The third experiment was aimed at assessing the effects of SD on startle reflex and PPI, at different time-intervals during SD (0, 24, 48, 72 h), as well as 24 h after termination of the procedure. Startle magnitudes were evaluated using a one-way ANOVA, with time as factor. As shown in Figure 3a, statistical analysis revealed that rats exhibited a significant, time-dependent increase of startle reflex [$F(4,70) = 9.21$, $p < 0.001$; $p < 0.05$ for comparison between 0 h and 48 h; $p < 0.01$ for comparison between 0 h and 72 h; Tukey's test], which was reversed after 24 h from the end of SD ($p < 0.01$ for comparison between 72 h and 96 h, Tukey's test). The subsequent statistical analysis on PPI values, performed via a two-way ANOVA – with time and prepulse levels as factors – detected that SD reduced PPI [main effect: $F(4,70) = 10.69$, $p < 0.001$]. Post-hoc analysis confirmed that 72 h SD produced a significant PPI deficit ($p < 0.001$ in comparison with baseline values, Tukey's test). (Figure 3b) while rats exhibited PPI values similar to the baseline after 24 h (n.s. in comparison with baseline values). Finally, a main effect was also found for prepulse levels [$F(2,140) = 21.47$, $p < 0.001$], but no interaction between the two factors was present [$F(8,140) = 0.64$, n.s.].

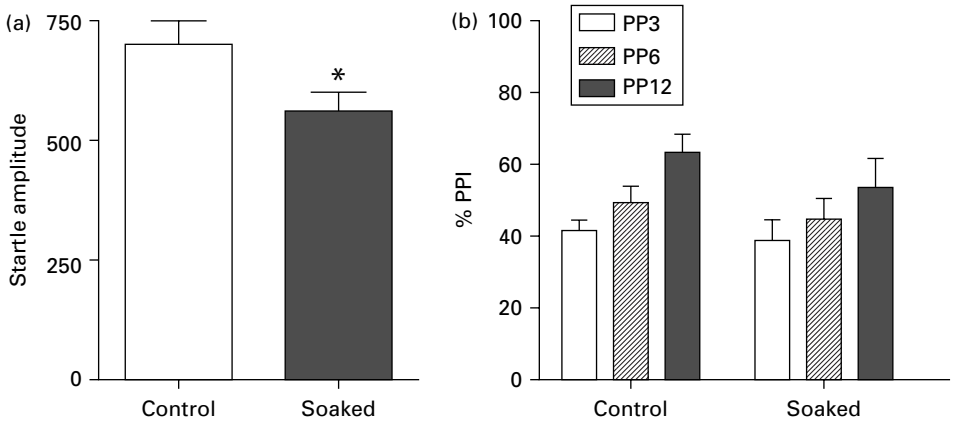

Figure 2. Effects of repeated soaking on (a) startle amplitude and (b) prepulse inhibition (PPI), compared to home-caged controls. Values represent mean ± S.E.M. for each treatment. Prepulses (PP3, PP6, PP12) are indicated by the intensity corresponding to decibels above background noise. * $p < 0.05$ compared to control rats. (For further details, see text.)

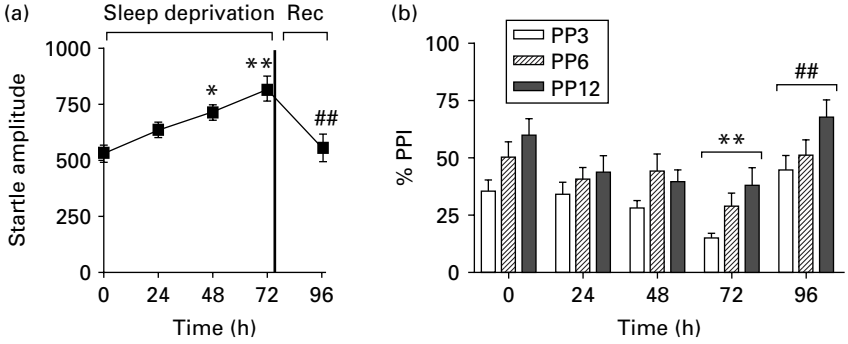

Figure 3. Time-dependent effects of sleep deprivation (SD) on (a) startle and (b) prepulse inhibition (PPI). Values represent mean ± S.E.M. for each treatment. Prepulses (PP3, PP6, PP12) are indicated by the intensity corresponding to decibels above background noise. * $p < 0.05$, ** $p < 0.01$ in comparison to baseline values immediately before the beginning of SD (0 h); ## $p < 0.01$ in comparison to values relative to 72 h of SD. Rec, recovery. (For further details, see text.)

Effects of antipsychotic treatments on SD-mediated PPI deficit

We addressed the next series of experiments to the assessment of the ability of three benchmark antipsychotics, Hal (0.1 mg/kg i.p.), Clo (5 mg/kg i.p.) and Ris (5 mg/kg i.p.), in comparison to their respective vehicles, to counter the PPI disruption produced by 72 h SD. Startle amplitudes were analysed by a one-way ANOVA, followed by Tukey's test (Table 2).

Hal did not significantly reverse the increase in startle, although ANOVA showed a statistical trend [$F(1, 18) = 2.94$, $p < 0.01$]. Conversely, it did reverse the PPI deficit [$F(1, 18) = 8.75$, $p < 0.01$] (Figure 4a). Clo antagonized the effects of SD on both startle amplitude [$F(1, 18) = 41.26$, $p < 0.001$] and PPI [$F(1, 18) = 29.43$, $p < 0.01$] (Figure 4b). Ris induced similar effects (Startle [$F(1, 18) = 10.24$, $p < 0.01$]; PPI [$F(1, 18) = 6.42$, $p < 0.05$]) (Figure 4c). For all three experiments, ANOVA detected a main effect for prepulse levels (Hal [$F(2, 36) = 7.40$, $p < 0.01$]; Clo [$F(2, 36) = 4.40$, $p < 0.05$]; Ris [$F(2, 36) = 3.92$, $p < 0.05$]). However, no interactions between treatment and prepulse levels were identified (data not shown).

Effects of Diaz and Cit on SD-mediated PPI deficit

Since SD has been shown to induce a number of disturbances of mood and anxiety, the fourth experiment was aimed at evaluating the specific predictive value of SD-induced PPI impairment as a model of gating impairment relevant to psychotic and manic phenomena. To this end, we tested whether either the anxiolytic Diaz (5 mg/kg i.p.) or the antidepressant Cit (5 mg/kg i.p.) could reverse the changes induced by SD, compared to their vehicles. Startle magnitudes were evaluated with the same statistical design as in

Table 2. Effects of antipsychotic drugs on startle amplitudes of sleep-deprived rats

Treatment	Startle amplitude
Vehicle	688 ± 54
Haloperidol (0.1 mg/kg i.p.)	552 ± 57
Vehicle	774 ± 53
Clozapine (5 mg/kg i.p.)	363 ± 34***
Vehicle	801 ± 66
Risperidone (1 mg/kg i.p.)	529 ± 52*

Values represent mean ± S.E.M. for each treatment.
* $p < 0.05$, *** $p < 0.001$ in comparison to vehicle-treated rats. (For further details, see text.)

Table 3. Effects of diazepam and citalopram on startle amplitudes of sleep-deprived rats

Treatment	Startle amplitude
Vehicle	840 ± 91
Diazepam (5 mg/kg i.p.)	535 ± 74*
Vehicle	924 ± 76
Citalopram (5 mg/kg i.p.)	823 ± 73

Values represent mean ± S.E.M. for each treatment. (For further details, see text.)
* $p < 0.05$ in comparison to vehicle-treated rats. (For further details, see text.)

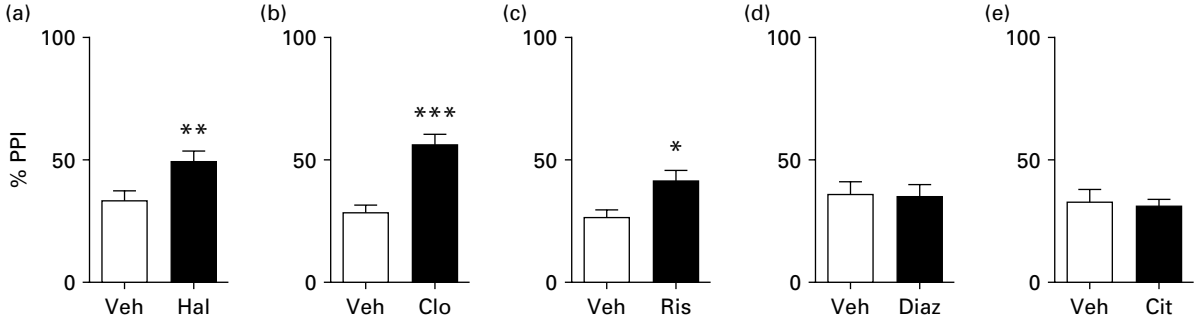

Figure 4. Effects of (a) haloperidol (Hal, 0.1 mg/kg i.p.); (b) clozapine (Clo, 0.1 mg/kg i.p.); (c) risperidone (Ris, 1 mg/kg i.p.); (d) diazepam (Diaz, 5 mg/kg i.p.); (e) citalopram (Cit, 5 mg/kg i.p.) on the prepulse inhibition (PPI) disruption induced by sleep deprivation (72 h), in comparison to their respective vehicles (Veh). PPI data represent the average of PPI produced by the three different prepulse intensities. Values represent mean ± S.E.M. for each treatment. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ in comparison to Veh. (For further details, see text.)

the previous experiment. ANOVA showed that Diaz significantly reduced startle reflex [$F(1, 13) = 6.77$, $p < 0.05$] (Table 3). A subsequent ANOVA to test PPI values yielded a significant effect for prepulse level [$F(2, 26) = 9.95$, $p < 0.01$], but not for either treatment [$F(2, 26) = 0.01$, n.s.] or treatment × prepulse level interaction [$F(2, 26) = 0.30$, n.s.] (Figure 4d).

A parallel analysis for Cit revealed that this antidepressant did not alter either startle magnitude [$F(1, 13) = 0.11$, n.s.] or PPI [$F(1, 13) = 0.11$, n.s.] in SD-subjected rats. Of interest, no fully significant effect was found for prepulse levels [$F(2, 26) = 2.57$, $p < 0.10$] or treatment × prepulse level interaction [$F(2, 26) = 3.16$, $p < 0.10$] (Figure 4e).

Discussion

The present study shows that, in rats, SD leads to a progressive, time-dependent increase in ASR and PPI deficit. Specifically, the enhancement of startle response is already significant at 48 h SD, while disruption of the gating functions reaches full significance after 72 h of the same procedure. Both impairments are completely reversed 24 h after SD discontinuation. Furthermore, our experiments strongly suggest that these deficits are specifically dependent on SD, and do not reflect the environmental stress associated with the manipulation used in the experiment, as indicated by the phenomenological dissociation between the effects of repeated soaking and SD in analogous experimental conditions.

These findings indicate that REM SD leads to a progressive reduction of informational filtering functions. This decrement, signified by the PPI reduction, is theorized to initiate hallucinatory phenomena by saturating the physiological capability of the brain to process external and internal information. This possibility is consistent with previous evidence showing that SD induces hallucinations, perceptual distortions and psychotic-like reactions in humans (Tyler, 1955).

While impairments in sleep architecture may contribute to the pathophysiological processes of psychosis, the relationship between sleep disturbances and psychotic symptoms has been shown to be bidirectional. Schizophrenia patients display an erratic polysomnographic profile, with deficits in REM and non-REM phases, which become particularly remarkable during exacerbations and relapses of the syndrome (Benca et al., 1992; Lauer et al., 1997; Monti and Monti, 2004; Tandon et al., 1992). In particular, REM parameters are correlated to the severity of all major clusters of schizophrenia, and antipsychotics prolong REM latency in schizophrenia patients (Benson and Zarcone, 1993; Monti and Monti, 2004; Taylor et al., 1992; Thaker et al., 1990).

The role of REM sleep in the modulation of gating mechanisms is poorly understood. Although PPI is not affected by either brainstem lesions producing REM sleep (Wu et al., 1990) sensory gating is abnormal during this stage (van Luijtelaar et al., 1998). An intriguing possibility is that intrusion or leakage of REM sleep events into waking may contribute to the gating impairments following prolonged SD. Accordingly, a similar process has been shown to underlie preattentional and attentional disorders in schizophrenia (Zarcone et al., 1969), as well as the psychotic manifestations in narcolepsy (Walterfang et al., 2005).

Both gating functions and REM sleep are regulated by the pedunculopontine nucleus (PPN). Indeed, physiological modifications of REM sleep have been indicated to alter gating through modifications in the PPN cholinergic system (Kobayashi et al., 2004). Furthermore, alterations in quality and duration of REM sleep in schizophrenia have been shown to reflect changes in responsiveness of PPN neurons (Rye, 1997).

The present study has shown that the effects of SD on sensorimotor gating have been completely suppressed by pretreatment with three benchmark antipsychotic drugs, such as Hal, Clo and Ris. Of note, Clo induced a remarkable reduction of startle amplitude, which may partially account for the effects in PPI. Nevertheless, this possibility is tempered by previous findings from our group, showing that the reductions in startle magnitude induced by Clo are never paralleled by significant changes in baseline PPI in our experimental conditions (Bortolato et al., 2005; Frau et al., 2007).

Since the main mechanism of action shared by these drugs is the blockade of D_2 dopamine receptors, our results suggest that these receptors may be directly involved in the SD-induced disruption of sensorimotor gating. SD induces a significant up-regulation of D_2 receptors in the nucleus accumbens and caudate putamen, in a fashion similar to that observed in schizophrenia patients (Abi-Dargham et al., 2000; Farde et al., 1990; Nunes Junior et al., 1994). Notably, both brain regions have been directly implicated in the dopaminergic regulation of PPI (Swerdlow et al., 2001) and in psychotic symptoms. Interestingly, SD has also been shown to enhance the responsiveness of rats to dopaminergic agonists, such as apomorphine (Tufik, 1981; Tufik et al., 1978), which are known to produce a dramatic deficit of sensorimotor gating and PPI (Mansbach et al., 1988). Interestingly, apomorphine and selective D_2 receptor agonists reduce REM sleep (Cianchetti et al., 1980; Monti et al., 1988), and dopamine transmission is generally believed to govern the balance between wakefulness and sleepiness (Wisor et al., 2001).

Other non-dopaminergic alterations may also be partially responsible for the gating deficits induced by SD. For example, this manipulation induces alterations of serotonergic signalling (Salomon et al., 1994) and glutamate *N*-methyl-D-aspartate (NMDA) receptor expression (McDermott et al., 2006), which may in turn lead to deficits in gating and PPI.

Besides its specific action on SD the platform method causes heavy stress to the rat, due to several factors such as isolation, falling into the water, soaking and others. Indeed, anxiety and stress are known to magnify many of the behavioural effects of SD (Tyler, 1955). In the present study, SD also produces an increase of startle reflex in a fashion responsive to the potent anxiolytic Diaz, suggesting the ability of SD to increase emotional reactivity (Ogilvie and Broughton, 1976). However, Diaz did not affect PPI parameters. This interesting premise supports the possibility that anxiogenic and psychotomimetic effects of SD reflect distinct neurobiological mechanisms.

Notably, neither startle increases nor gating deficits were reversed by the potent antidepressant Cit, lending support to the specificity of the neurobiological substrates underpinning both alterations.

PPI deficits become significant after 72 h of SD, in concomitance with other manifestations, such as hyperactivity, irritability, aggressiveness, hypersexuality and stereotyped behaviour (Fratta et al., 1987). Our study confirms previous studies interpreting this behavioural spectrum as an animal model of mania (Gessa et al., 1995), since the latter is also associated with gating deficits (Franks et al., 1983). Based on our results, SD-induced PPI disruption may also be a novel paradigm for the study of the connections between sleep and integrity of reflex and cognitive mechanisms. Finally, it could also be proposed as an

animal model of psychosis, by virtue of its face, construct and predictive validity – shown by its sensitivity to antipsychotics, but not other categories of psychotropic drugs. Nevertheless, future studies are certainly warranted to assess the heuristic value, the significance and the relevance of this paradigm to psychotic phenomena.

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None.

Statement of Interest

None.

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