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Effects of melatonin on prepulse inhibition, habituation and sensitization of the human startle reflex in healthy volunteers

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ABSTRACT

Prepulse inhibition of the startle reflex (PPI) is an operational measure of sensorimotor gating, which is demonstrated to be impaired in patients with schizophrenia. In addition, a disruption of the circadian rhythm together with blunted melatonin secretion is regularly found in patients with schizophrenia and it is theorized that these may contribute to their attentional deficits. The aim of this study was to assess the effects of acute melatonin on healthy human sensorimotor gating. Twenty-one healthy male volunteers were administered melatonin or placebo after which their levels of PPI were assessed. Melatonin significantly reduced startle magnitude and ratings of alertness, but did not influence PPI, nor sensitization and habituation. However, when taking baseline scores in consideration, melatonin significantly increased PPI in low scoring individuals while significantly decreasing it in high scoring individuals in low intensity prepulse trialtypes only. In addition, subjective ratings of alertness correlated with PPI. The results suggest that melatonin has only minor influences on sensorimotor gating, habituation and sensitization of the startle reflex of healthy males. The data do indicate a relationship between alertness and PPI. Further research examining the effects of melatonin on these processes in patients with schizophrenia is warranted.

1. Introduction

Deficits in attention and perceptual awareness have long been observed in schizophrenia and, as postulated by McGhie and Chapman (1961), may be due to a malfunction in the neural mechanism that filters sensory information from the environment. Following extensive clinical observation, they theorized that early filtering, or gating, of external sensory information is critical in safeguarding the brain from irrelevant stimuli, allowing processing capacities to be directed only toward the most salient input. Such inhibitory processes would be particularly important for the ability to draw and maintain attention at will, something which is since long found to be impaired in patients suffering from schizophrenia (Kraepelin, 1913; Bleuler, 1937). Sensory and sensorimotor gating deficits are assumed to lead to an over flooding of the higher brain regions, which in turn, is thought to result in cognitive disturbances and ultimately to psychosis (e.g. Perry et al., 1999). In support of this hypothesis, reduced sensorimotor gating efficiency can also methodically be demonstrated in schizophrenia. One type of operational measure that has been studied in this respect is the prepulse inhibition (PPI) of the startle reflex, which is consistently found to be impaired in patients with schizophrenia (e.g. Braff et al., 1978, 1992).

The startle reflex, which is regulated by a relatively simple neural circuit (Koch, 1999), is a universal involuntary defense mechanism to a sudden intense stimulus (usually auditory) and can be inhibited, if the startling stimulus is closely preceded by a weaker stimulus (prepulse) (Graham, 1975). Inhibition of the startle reflex, which is a form of sensorimotor gating, is thought to exist due to the still on-going processing of the information derived from the prepulse, as the two stimuli are maximum 500 ms apart, which is enough to exceed the capacity of the brain to process, or react to, both stimuli (Graham, 1975). Frequently, and in parallel to sensorimotor gating, an individual's sensitization and habituation processes are assessed. Sensitization represents the exponential increase of a response to the same and initially new stimulus, whereas habituation is the opposite, representing

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attenuation of a response to a repetitive stimulus over time. Sensitization typically takes place over the first 2–3 trials of a startle-eliciting stimulus block, followed by a gradual habituation over the remaining trials. There are inconsistent reports as to whether habituation is impaired in patients with schizophrenia; some studies report a reduced habituation in patients compared to healthy controls (Geyer and Braff, 1982; Braff et al., 1992; Ludewig et al., 2003), while others find no such impairment (Mackeprang et al., 2002; Quednow et al., 2006). The literature regarding sensitization is sparse and conflicting with one publication reporting an increased sensitization in medicated patients with schizophrenia (Meincke et al., 2004), whilst another study found a trend for a reduced sensitization in antipsychotic-naïve first episode patients (Aggernaes et al., 2010).

Some atypical antipsychotics, such as quetiapine and clozapine, have been demonstrated to improve PPI together with alleviating psychotic symptoms in some patients with schizophrenia (e.g. Kumari et al., 1999, 2000; Oranje et al., 2002; Wynn et al., 2007; Aggernaes et al., 2010), whereas others have not (e.g. Mackeprang et al., 2002; Duncan et al., 2003a, 2003b). However, the effects of atypical as well as typical antipsychotics on the disabling information-processing disturbances as well as psychopathology are unsatisfactory and all antipsychotics have adverse effects contributing to non-compliance and discontinuation of treatment. Accordingly, there is an urgent need for new medical treatments. Furthermore, following antipsychotic discontinuation, patients who also suffer from sleep disturbances are found to be at a greater risk for worsening of psychotic symptoms (Chemerinski et al., 2002; Poulin et al., 2003; Benson, 2006). Sleep deficits are frequently observed in patients with schizophrenia and are often part of the prodromal phase preceding relapse, even when the patients are on medication (Chemerinski et al., 2002). This observation has drawn growing interest in the role of sleep in the pathophysiology of schizophrenia, as reestablishing a healthy circadian rhythm together with its restorative processes is believed to improve clinical outcome. There is evidence suggesting that the cause of these disturbances in sleep architecture is due to low circulating levels of the endogenous sleep promoter melatonin, which functions as the regulator of the circadian sleep-wake cycle: several investigations have detected blunted nocturnal melatonin levels in drug-free as well as medicated patients (Fanget et al., 1989; Monteleone et al., 1992). Although antipsychotic treatment is able to treat some sleep deficits, it does not restore the disturbed melatonin production (Robinson et al., 1991; Monteleone et al., 1997; Suresh Kumar et al., 2007; Anderson and Maes, 2012). A case study by Afonso et al. (2010) found discrepant nocturnal melatonin profiles in a monozygotic twin pair discordant for schizophrenia, suggesting that the reduced melatonin secretion may be a consequence of the pathological process of the disorder and hence may not solely be genetic.

Preclinical studies have shown that melatonin receptor knockout mice exhibit reduced sensorimotor gating (Weil et al., 2006). Although a beneficial effect of melatonin on PPI is likely to be mediated by an improvement of a patient's circadian rhythm or sleep composition, it cannot be ruled out that melatonin may have a direct effect on PPI. We previously reported the effects of melatonin on another widely believed measure of sensory filtering of information, i.e. P50 suppression, in a group of healthy males (Ucar et al., 2012), and now report on its effect on PPI, habituation and sensitization in this same group of subjects. To our knowledge, there are no previous reports on the effects of exogenous (nor endogenous) melatonin on the psychophysiology of attention or PPI in humans. However, gaining an understanding of the role of melatonin and its alterations in the neural processes involving attention may be fruitful in order to identify core biological mechanisms underlying the psychopathology of psychosis. Moreover, this knowledge can form a basis for more efficient medical treatments strategies for schizophrenia and for psychotic disorders in general. Hence, the aim of the present study was to investigate the acute effect of sustained-release melatonin on PPI of the startle reflex in a group of healthy male volunteers. Based on the above described literature, we expected melatonin to improve sensorimotor gating.

2. Methods

The study was approved by the Ethics Committee of the Capital Region, Copenhagen, in regard to the ethical principles of the Declaration of Helsinki II.

2.1. Subjects

Twenty-one healthy male volunteers aged between 18 and 30 years were recruited from the capital region of Copenhagen by web advertisement. All included participants were in good physical and mental health as assessed by anamnesis. Exclusion criteria were current medication, history of neurological illness, psychiatric illness in a first degree relative, alcohol or drug abuse and receiving any experimental medication within 30 days of the study start. All volunteers were informed about the experiment in detail and provided a written informed consent before enrollment to the study. Subsequently, they were interviewed with the Schedules for Clinical Assessments in Neuropsychiatry (SCAN) to ensure absence of psychiatric illness and rendered a urine sample, which was evaluated for the content of opiates, cocaine, amphetamine and cannabis. The volunteers were also screened for hearing deficits (at frequencies of 500, 1000 and 6000 Hz and intensities of 20 and 40 dB(a)) and individuals not able to perceive tones under 20 dB(a) were excluded: none of the volunteers had to be excluded. Furthermore, in accordance to our laboratory standards, we defined non-responders as those subjects who scored less than 20 μV on average on the pulse alone trials; also on these grounds none of the subjects had to be excluded. The mean age of the included participants was 25 (S.D.: 3.0) years and their mean BMI was 23 (S.D.: 1.90). Of the 21 participants, three were tobacco smokers.

2.2. Experimental design

In a double-blind, randomized yet balanced, crossover experiment, participants were administered melatonin (4 mg Circadin® controlled-release) or placebo (folic acid also known as vitamin B9) in a white opaque capsule on two occasions separated by a minimum interval of 1 week. None of the volunteers had participated in a psychophysiological assessment before. Volunteers were instructed to fast from 11:00 PM the preceding night and to sleep a minimum of 7 h before arriving at the Center for Neuropsychiatric Schizophrenia Research, Glostrup, at 8:00 AM. To avoid acute or withdrawal effects of caffeine and nicotine, subjects were requested to refrain from smoking 1 h prior and from caffeinated drinks, 2 h prior to test start. They had also been asked not to consume alcohol the preceding day. The capsule containing either melatonin or placebo was administered at 8:30 AM. We choose the morning because we were only interested in the acute, direct effects of melatonin on our dependent variables, with as little influence as possible of endogenous levels of melatonin: the levels of endogenous melatonin are low after waking in the morning (Pacchierotti et al., 2001). At 9:00 AM participants were accompanied to a soundproof, electrically shielded experimental room and signal recording was started 90 min after administration of the capsule in order to assure maximum plasma concentration of melatonin (DeMuro et al., 2000). The subjects were subsequently tested in the Copenhagen Psychophysiological Test Battery (CPTB). Besides a PPI paradigm, the CPTB consists of a P50 suppression, selective attention and mismatch negativity paradigm. The CPTB has recently been validated in, amongst others, a large cohort of antipsychotic-naïve and first-episode patients with schizophrenia (Oranje et al., 2008; Jensen et al., 2008; Aggernaes et al., 2010). For reasons of comprehensiveness, the current manuscript will only report on PPI, sensitization and habituation of the human startle reflex. The results of melatonin on P50 suppression were published elsewhere (Ucar et al., 2012) and so will be the results of the other CPTB-tests. Subjective ratings with a visual analog scale (VAS) of alertness were assessed prior to capsule administration and prior to PPI assessment (Bond and Lader, 1974).

2.3. Assessment of PPI, habituation and sensitization

The method has been described previously (Aggernaes et al., 2010; Oranje and Glenthoj, 2013). Briefly, subjects were seated in a comfortable armchair in a room with a sound level <40 dB and situated adjacent to the control room. They were instructed to sit still, to keep their eyes fixed on a spot on the wall directly in front of them and were asked to stay awake. The assessment of PPI and habituation started with 5 min of acclimation to a background noise (70 dB(a) white noise) after which three experimental blocks of stimuli were superimposed on the background noise. Blocks 1 and 3 were used to assess habituation of the acoustic startle reflex. The two blocks were identical and consisted of eight pulse-alone trials (white noise with an intensity of 115 dB(a), and a duration of 20 ms, instant