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

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A R T I C L E   I N F O

Article history:
Received 7 December 2012
Received in revised form
13 February 2014
Accepted 19 February 2014
Available online 28 February 2014

Keywords:
Sensorimotor gating
PPI
Schizophrenia
Electromyography
Orbicularis oculi muscle

A B S T R A C T

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 trials types only. In addition, subjective ratings of alertness correlated significantly decreasing it in high intensity trials types only. In addition, subjective ratings of alertness correlated significantly 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.

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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...
with its restorative processes is believed to improve clinical outcome. Of schizophrenia, as reestablishing a healthy circadian rhythm together has drawn growing interest in the role of sleep in the pathophysiology. There is evidence suggesting that the cause of these disturbances in antipsychotic treatment is able to treat some sleep de-blunted nocturnal melatonin levels in drug-free as well as medicated circadian sleep-wake cycle: several investigations have detected sleep architecture is due to low circulating levels of the endogenous (endogenous) melatonin on the psychophysiology of attention or there are no previous reports on the effects of exogenous (nor melatonin or placebo was administered at 8:30 AM. We choose the morning because 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 Assessment of Psychopathology (Simplistic test) 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 over 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.: 1.50). 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., 2003). At 9:00 AM participants were accompanied to a soundproof, electrically shielded experimental room and signal recording was started 90 min after administra- tion 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-naive 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 the P50 suppression on P50 suppression were published elsewhere (Ucar et al., 2012) and will so 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 Genthof, 2011). 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...
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