Effects of the sleep-wake rhythm modulating hormone melatonin on absence seizures in the EEG of rats

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INTRODUCTION
The effects of systemic administration of the pineal hormone melatonin (MT) on the absence form of epilepsy in rats of the WAG/Rij strain were studied. Rats of this strain were chosen not only because spike-wave discharges (SWDs) are clearly present in their electroencephalographic activity but at the same time rats show small clinical phenomena during the presence of these SWDs.1 Other reasons for using WAG/Rij rats is that the physiological and pharmacological profiles are close to those of humans, which is important for studying the possibility of medical use of MT in the case of absence epilepsy. Absence epilepsy is quite widely spread in children and young people, especially in girls. It is characterised by brief episodes of a ‘loss of consciousness’, comparable to sleep, which is electrophysiographically presented by 3-3.5 Hz SWDs. As the scientific definition of consciousness is still elusive, one has to note that the ‘loss of consciousness’ is a rather operational term, i.e. during the absence episodes the patients lose ability to respond to sensory stimuli and they have almost no recall of the events occurring during these episodes. In their classical description SWDs arise abruptly and uniformly from a normal background EEG. Absences usually appear at times of transition to or from sleep, in quiet wakefulness and in light non-REM sleep. Their nature is generally believed to be biochemical with a genetic predisposition. We prefer the theory that claims that SWDs are transformed sleep spindles which are generated in thalamic, corticothalamic and thalamocortical circuits.2 MT is a pineal hormone. Its secretion is regulated by circadian rhythms that also regulate the rhythm of hormone production by the action of hypothalamic structures. MT production and secretion depends on degree of illumination, and an extra quantity of light decreases it. MT in humans is produced for 70% during the dark period of the cycle. The rate of MT synthesis increases from 8 p.m. and has a peak at 3 a.m. and later its concentration decreases. Donor of MT is the amino acid tryptophan. It is involved in the production of serotonin, which is developed into MT under the influence of N-acetyltransferase. MT is produced in the pineal gland and excreted to the liquor, from which is accumulated in the hypothalamus.

MT has a range of therapeutic actions and almost no contra-indications. It normalises night sleep and synchronises circadian rhythms. MT is a strong antioxidant, stronger than the glutamine, vitamins E and C. Studies on laboratory animals have shown that pharmacological properties of opioid peptides such as analgesia, sedation, catatonia, thermoregulation, endocrine regulation and various behavioural effects are at least partially mediated via the action of MT. It has also been shown that MT has anticonvulsant and angioprotective effects in rats of Krushinskogo-Molodkina strain (KM).3 KM rats are genetically predisposed to audiogenic seizures. MT also shows anticonvulsant effects in various types of kindled rats4,5 and in seizures induced by excitatory acids in mice.6 It was also proposed that melatonin mediates the antiepileptic action of drugs effective for absence epilepsy, and that the pineal gland is implicated in the pathogenesis of this form of childhood epilepsy.7 The aim of this preliminary study was to evaluate whether melatonin was effective in suppressing SWDs in the WAG/Rij model for absence epilepsy, in order to clear up the complete psychoactive profile of MT.

METHODS
Experiments were carried out on eight rats of the WAG/Rij strain. The rats were divided into two groups, a control group and an experimental group. Rats of the control group did not get any MT; rats of the experimental group received a single dose of 250 mg/kg i.p. MT. After a pre-injection baseline period, rats were injected. After a 15-30 minute break, the EEG was recorded for two hours. Records were made using standard “monopolar” disposition of electrodes on the brain cortex of the rat. Number and duration of the SWDs were determined according to criteria elaborated elsewhere.1

RESULTS
Data are presented in Table 1. The number of SWDs was firmly reduced in the first hour after injection, in the second hour they had completely disappeared. Also the mean duration was reduced. There were no changes in the intraspike frequency of the SWDs.
TABLE 1. Number of SWDs in the first and second hour after injection of 250 mg/kg melatonin.

<table>
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<th>Rat number</th>
<th>Drug</th>
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DISCUSSION

The results clearly show that a high dose of MT suppresses SWD characterising absence epilepsy in rats. There were no obvious behavioural effects; however, the behaviour was not quantitatively studied, nor putative effects on body temperature were studied. As a possible mechanism of the influence of MT can be considered its interaction with Ca²⁺ channels. This must be proven by future studies. Another possible mechanism can be its interaction with the opioid system, since SWDs are quite sensitive for kappa receptor agonists. Finally, an interaction with the dopaminergic system has been proposed for the action of melatonin on excitability of the nervous system. DA agonists suppress and DA antagonists enhance SWDs. These preliminary studies warrant further dose response studies towards the role of melatonin in absence epilepsy.

REFERENCES