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LETTER TO EDITOR

Does agomelatine block 5-HT2$_C$ receptors in humans?

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Agomelatine is a recently licensed antidepressant with a novel pharmacological profile which includes agonist actions at melatonin M1 and M2 receptors and antagonist effects at serotonin$_{2C}$ (5-HT$_{2C}$) receptors (Millan et al. 2003; Dolder et al. 2008). However, the affinity of agomelatine for the 5-HT$_{2C}$ receptor is in the micromolar range and about 100-fold less than its affinity for melatonin receptors (Millan et al. 2003). It is, therefore, important to find out whether agomelatine causes functional blockade of 5-HT$_{2C}$ receptors in the human brain at standard clinical doses. Acute administration of drugs with 5-HT$_{2C}$ receptor antagonist properties to healthy volunteers produces reliable increases in slow wave sleep (SWS) in the polysomnogram (see Sharpley et al. 1994; Sharpley and Cowen 1995). The aim of the present study was to test the hypothesis that agomelatine would also increase SWS in humans.

We studied 15 healthy subjects (eight female, seven male; mean age 25.9 years, range 19–47 years) who were determined by clinical interview (non-patient version of the Structured Clinical Interview for DSM-IV) to have no current history of psychiatric disorder or sleep disorder and who were not taking any other medication. Each subject took matching capsules of placebo and agomelatine (25 mg) once, orally, 30 min before retiring to sleep in a double blind, balanced order, crossover design with a 7- to 14-day washout period between each sleep polysomnogram. Subjective ratings of sleep (on a five-point scale) and side effects (on a four-point scale) were elicited the morning after each sleep study.

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On each study night, polysomnograms were recorded as each participant slept at home, using the Embla A10 digital data recording system (Medcare, Broomfield, CO, USA). Participants retired and rose at their usual time, and this was kept constant for all study nights and all preceding nights. Polysomnography involved a standard montage: four electroencephalogram channels (C3/A2, C4/A1, O1/A2, O2/A1), two electro-oculogram channels, and a submentalis electromyogram. Polysomnograms were staged in 30-s epochs using the Embla diagnostic software, Somnologica Studio. This software provides measures for all aspects of sleep architecture according to standard criteria. In addition, the polysomnograms were edited by an experienced sleep physiologist blind to treatment status. The polysomnograms of two participants were excluded due to technical difficulties. However, their subjective ratings were available and were included. Differences between the pairs of sleep nights were assessed using Student's paired *t* test (two-tailed).

Agomelatine produced no change in any polysomnographic parameter including SWS (Table 1). Separate examination of sequential cycles of SWS also failed to reveal any effect of agomelatine (data not shown). Following agomelatine, participants rated their sleep quality as improved, but they also experienced more nausea (Table 1).

Our findings suggest that initiation of a standard clinical dose of agomelatine does not cause functional blockade of brain 5-HT$_{2C}$ receptors in humans as judged by increases in SWS. Previous studies in both our and other laboratories have shown that single doses of selective 5-HT$_{2C}$ receptor antagonists such as cyproheptadine (4 mg) and ritanserin (5 mg) as well as other psychopharmacological agents which possess 5-HT$_{2C}$ receptor antagonist properties such as olanzapine (5 mg) and mirtazapine (30 mg) cause approximately 50% increases in SWS (Solomon et al. 1989; Sharpley et al. 2000; Aslan et al. 2002). From the confidence limits in

Table 1 Effect of agomelatine, 25 mg orally, on polysomnogram (n=13) and subjective measures (n=15) in healthy volunteers

Selected sleep parameters[a]	Group mean ± SD	Difference of mean (SD)	95% CI	t	Two-tailed significance, p value
Sleep continuity measures					
Total sleep time					
Placebo	470.8±48.2	−0.8 (24.4)	−15.6 to 13.9	−0.119	.9
Agomelatine	470.0±50.0				
Sleep efficiency,% [b]					
Placebo	92.3±3.8	−0.1 (4.3)	−2.7 to 2.5	−0.109	.9
Agomelatine	92.2±4.9				
Wake after sleep onset					
Placebo	28.5±20.5	−2.7 (20.4)	−15.0 to 9.6	−0.476	.6
Agomelatine	25.5±26.5				
Sleep onset latency					
Placebo	11.6±6.1	3.6 (14.8)	−5.3 to 12.6	0.879	.4
Agomelatine	15.2±13.9				
NREM sleep measures					
Stage 1					
Placebo	64.7±28.9	−7.4 (21.6)	−20.5 to 5.6	−1.241	.2
Agomelatine	57.3±31.0				
Stage 2					
Placebo	181.3±48.9	4.6 (27.0)	−11.8 to 20.9	0.610	.5
Agomelatine	185.9±40.7				
Slow-wave sleep					
Placebo	119.1±21.1	−4.8 (18.7)	−16.1 to 6.5	−.928	.4
Agomelatine	114.3±24.9				
REM sleep measures					
REM latency					
Placebo	88.7±33.4	−15.9 (36.2)	−16.1 to 6.5	−1.6	.1
Agomelatine	72.8±14.0				
REM sleep					
Placebo	67.0±18.7	7.3 (26.6)	−8.7 to 23.4	.996	.3
Agomelatine	74.0±25.8				
Subjective sleep measures					
Sleep quality					
Placebo	2.4±0.7	0.8 (1.0)	0.2 to 1.4	3.055	.009
Agomelatine	3.3±0.9				
Nausea					
Placebo	0.0±0.0	0.4 (0.6)	0.05 to 0.75	2.449	.028
Agomelatine	0.4±0.6				

NREM non-rapid eye movement, *REM* rapid eye movement

[a] Sleep parameters expressed in minutes unless stated otherwise

[b] Sleep efficiency = actual sleep time/time in bed × 100

the present study, we are able to exclude an increase in SWS by agomelatine of more than 6%.

It should be noted that Quera Salva et al. (2007) found that the SWS of depressed patients treated with agomelatine increased by about 20% after 6 weeks treatment. However, this increase was not apparent after either 7 or 14 days agomelatine therapy and, therefore, seems more likely to be due to change in underlying clinical state rather than a direct pharmacological effect of agomelatine on 5-HT_{2C} receptors which would presumably be manifest soon after treatment initiation. In support of this interpretation, Leproult et al. (2005) found no effect of agomelatine (50 mg daily for 2 weeks) on SWS of older male volunteers (mean age 60 years).

In our study, agomelatine did not produce changes in the polysomnogram that would be consistent with improved sleep, for example, increased sleep efficiency. However, agomelatine is not regarded as a hypnotic agent, and improvements in sleep in depressed patients treated with agomelatine may be a consequence of amelioration of the underlying depressed state or perhaps through chronobiotic effects (Leproult et al. 2005; Dolder et al. 2008).

There are a number of possible explanations for the lack of effect of agomelatine in our SWS model, apart from its relatively low affinity for 5-HT_{2C} receptors. Agomelatine has a large first pass effect and a short half life (about 2 h) (Dolder et al. 2008). Thus, its antagonism of 5-HT_{2C} receptors might be relatively transient, making it difficult to demonstrate a robust effect on SWS; however, examining SWS in separate cycles throughout the night did not reveal any effect of agomelatine. It also possible that the melatonin agonist properties of agomelatine might have, in some way, suppressed a facilitation of SWS. While polysomnographic studies of melatonin used as a sole agent do not indicate an effect on SWS (see, for example, Attenburrow et al. 1996), it is possible that melatonin agonists could in some way interact with 5-HT_{2C} receptor antagonists to prevent increases in SWS produced by the latter. Controlled trials have shown that agomelatine is an effective antidepressant (Dolder et al. 2008) so it is important to elucidate its mode of action in humans. Other models of 5-HT_{2C} receptor antagonism, for example, attenuation of the effects of the 5-HT_{2C} receptor agonist, m-chlorophenylpiperazine, might prove useful in this respect (Seibyl et al. 1991).

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