

Electroretinographic modifications induced by agomelatine: a novel avenue to the understanding of the claimed antidepressant effect of the drug?

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Background: Agomelatine, the first melatonergic antidepressant, has been postulated to enhance the dopaminergic activity at the central nervous system by 5-hydroxytryptamine receptor type 2C (5-HT_{2C}) antagonism, yet the impact of melatonergic agonism on this pathway is unclear. Previous studies employing simplified, yet reliable, proxy (retinal) measures of the central nervous system dopaminergic activity, namely the standard electroretinogram (ERG) technique, suggested a reduction of the dopaminergic activity of the main ERG parameter, the b-wave, by pure melatonin, notably a hormone devoid of any antidepressant activity. Therefore, the antidepressant effects of the melatonergic antidepressant drug agomelatine should be reflected by a differential b-wave trend at ERG versus the effect exerted by pure melatonin, which was eventually found to be due to a contrasting effect on central dopaminergic transmission between the two drugs.

Objective and methods: The aim of the present preliminary ERG study carried out on healthy volunteers (n=23) receiving agomelatine was to explore the impact of this antidepressant drug on b-wave amplitude and latency of cones in daylight conditions using standard ERG.

Results: As postulated, agomelatine induced an enhancement of retinal dopaminergic activity, in contrast to what has been previously documented for melatonin.

Conclusion: Given the limits of this explorative study, especially the lack of a control group and that of a luminance response function to measure retinal sensitivity, further studies in clinical samples are recommended to allow more tenable conclusions about the potential role of ERG in discriminating between 5-HT antagonism and melatonergic (MT) agonism in relationship to the claimed antidepressant effect of agomelatine.

Keywords: electroretinogram, ERG, dopamine, 5-HT_{2C}

Introduction

Currently, virtually any psychiatric diagnosis is made through a combination of patient interviews, checklists, or self-report questionnaires, which rely on the symptoms coded in the *Diagnostic and Statistical Manual of Mental Disorders*, either the fourth edition¹ or the recently introduced fifth edition.² Yet, considerable debate exists about the actual validity of this sole symptom-based approach, thus sustaining the interest in objective biomarkers toward a better understanding of psychiatric disorders, including major depressive disorder (MDD), and their pharmacological response.³ Furthermore, a number of issues, including heterogeneous patients' variables, high medical and psychiatric comorbidity rates, medications/triggers, inconsistency in specimen collection, storage and measurement protocols, and complexity of neuropsychiatric biological determinants of disorders, hinder the search for reliable biomarkers.^{4,5} Ideally, a hassle-free biomarker reflecting the

central nervous system (CNS) functioning should provide a simplified, yet reliable, proxy measure of the activity of those neurotransmitters that are supposed to be involved in major psychiatric disturbances, to be flexibly applied both to clinical and healthy samples. Among other approaches, the electroretinogram (ERG) represents a relatively noninvasive, short, and cost-effective method developed to investigate the origin of a visual loss due to a retinal disease or injury, possibly representing a proxy of global CNS activity of dopamine,⁶ a core monoamine in depression, directly or indirectly modulated by a number of antidepressant drugs with different pharmacodynamics.⁷ Specifically, since the retina is part of the CNS due to its embryonic origin, the ERG has been used to investigate not only MDD, but also seasonal affective disorder, schizophrenia and bipolar disorder, autism spectrum disorders, and drug addiction,⁸ both in clinical and healthy samples exposed to different pharmacological agents,^{8–17} as well as in animal samples.^{6,18} Of note, dopamine modulates different retinal functions, including counterbalancing of the synthesis of melatonin as measured with the ERG.^{19–21} Melanergic activity is also often impaired in the course of depressive episodes with prominent circadian rhythm disturbances, even if there is no antidepressant effect firmly documented for the hormone melatonin, neither for its analogue, ramelteon.^{22–25} This seems quite puzzling considering that the recently released pro-melanergic antidepressant agomelatine has been approved in Europe for the treatment of MDD, though not in the US.^{26,27} A potential explanation for the claimed antidepressant effect of agomelatine should nonetheless be represented by its 5-hydroxytryptamine receptor type 2B (5-HT_{2B}) and 5-HT_{2C} serotonergic antagonism,²⁸ which may also promote the dopaminergic firing at the ventral tegmental area, frontal cortex, hypothalamus, hippocampus, medulla and pons, and also the retina, which is part of the CNS as well,²⁹ via enhancement of norepinephrine activity at the locus coeruleus.³⁰ Yet, while there is no question about the impact of melanergic modulation on circadian rhythms relevant for mood as well as other core functions, the discrimination of the most plausible antidepressant effect of agomelatine between 5-HT antagonism versus melanergic receptor type 1 (MT₁) and type 2 (MT₂) agonism remains elusive, at least with regard to just the simplified paradigm of dopaminergic modulation. Additionally, agomelatine has been proposed to indirectly modulate even the release of glutamate from prefrontal and frontal cortex and hippocampus,^{31,32} which further hinders the identification of a sole putative neurobiological pathway accounting for the claimed antidepressant effect of the drug.

Therefore, the aim of this preliminary study carried out on healthy volunteers was to assess the impact of agomelatine on retinal dopaminergic activity measured using standard ERG recording, to provide a dissertation on the potential clinical implications of a differential neuropsychopharmacological ERG trend eventually observed for agomelatine versus the trend already documented for melatonin.

Methods

The flash ERG: essential neuropsychopharmacological foundations

The light reaches the photoreceptors (either cones or rods) hosted at the outer segment of the retina after crossing the anterior segment of the eye, then is absorbed by the photopigment of the photoreceptors, which ignites the phototransduction process. In dark conditions, photoreceptors rest in a depolarized state, while the photon absorption leads to their hyperpolarization followed by the depolarization of the ON bipolar cells. Subsequently, the electric signal spreads to the ganglion cells, the axons of which reach the brain, mainly converging at the visual cortex. The retina also includes horizontal cells and amacrine cells, which are interneurons joining photoreceptors and bipolar cells, as well as the Müller cells acting as glia.⁸

Since dopamine represents a core retinal neurotransmitter involved in signal transduction, the ERG should be a convenient technique by which to assess such dopaminergic activity both in light- and dark-adapted conditions,³³ essentially by measurement of the “implicit time” and “amplitude” parameters of the b-wave,³⁴ a trace component of the ERG primarily determined by the bipolar cells.^{35–37} Any variation of the intensity or chromatic characteristic of the light stimulus could also be assessed by the ERG, either for rods, cones, or mixed rod/cone photoreceptors functioning, thus allowing an objective quantitative measure of the retinal sensitivity to light.³⁴ Dopamine released by the amacrine and interplexiform cells³⁸ interacts with the D₁-like receptors (namely, D₁ and D₅ subtypes) at the horizontal, bipolar, amacrine, and ganglion cells, and with the D₂-like (D₂, D₃, and D₄) receptors located at the retinal pigment epithelium cells, photoreceptors, and Müller glial cells,^{39–43} all of which are involved in the modulation of a number of retinal functions, including melatonin release.²⁰ Also, the daily synthesis and release of retinal dopamine, which is primarily influenced by lighting condition, follows a 24-hour rhythm,⁴⁴ being influenced by the interaction between the amacrine and interplexiform dopaminergic neurons and photoreceptors. Enhancement of dopamine activity via activation of D₂-like receptors (namely D₄ ones) located on photoreceptors inhibits the synthesis of melatonin, leading to subsequent inhibition of

serotonergic N-acetyltransferase activity.^{45,46} In mammals, the D4 receptor accounts for the effects of the ligands on the whole D2 receptor family,⁴² either at the rods, cones, or retinal pigment epithelium,⁴⁷ which, in turn, ultimately account for the impact of dopamine in the regulation of melatonin biosynthesis in vertebrate retina.⁴⁸ Substance P and dynorphin, which are expressed in D1 receptor-containing neurons, as well as preproenkephalin in D2 receptor-containing neurons, have also been used as monitors of dopaminergic activity in the CNS,⁴⁹ whereas there have been conflicting reports as to whether D1-like receptors are capable of increasing or decreasing the potassium efflux: D1-like agonists increase potassium current from chick retinal cells via an adenosine monophosphate (AMP)-independent mechanism, but inhibit this efflux in rat striatal neurons;⁵⁰ as such, a conclusive understanding of the actual effect of D1 (and possibly D5) stimulation or inhibition at the retina likewise remains elusive.⁵¹ Melatonin suppresses the retinal release of dopamine via activation of its own melatonergic receptors (primarily MT1, but also MT2 and MT3 subtypes), widely distributed in the CNS,⁵² including the retinal amacrine and interplexiform dopaminergic neurons.^{53,54}

As mentioned previously, the b-wave response of the ERG is influenced both by dopaminergic and melatonergic modulation. Specifically, in daylight conditions, the b-wave response seems linked to cone dominance, possibly related to a shift toward a relative dominance of dopaminergic tone. On the contrary, under scotopic conditions, the b-wave response could be influenced by a relative dominance of rod tone,⁵⁵ when the presence of circulating melatonin could account for rod dominance.⁵⁶

ERG studies carried out on healthy volunteers receiving melatonin, performed during conditions usually characterized by the absence of the hormone itself, showed a decline of cone response, either recorded as a decrease of the b-wave amplitude at 10 mg/day,⁵⁷ or as a significant reduction of cones' ERG maximal response associated to a prolonged implicit time with 15 mg/day melatonin.⁵⁸ Concordant results were recently documented in animal samples exposed to high doses of melatonin during the day (90 mg/day in anaesthetized beagle dogs), showing a decrease of the photopic amplitude of both a- and b-waves, but no impact on the implicit time, which may indicate that the negative impact of melatonin on the photopic system may promote night vision.²¹

Agomelatine shares the MT1 and MT2 agonism provided by melatonin, but not the agonism on MT3 receptors, with MT3 receptors having not been documented in mammalian samples.⁵⁹ By blocking 5-HT_{2C} receptors, agomelatine promotes the CNS release of dopamine, possibly at the retina as

well. However, at the time of writing, there are no available data whatsoever about the investigation of agomelatine using the flash ERG in contrast to previous evidence for melatonin, this being the aim of this preliminary study.

Study subjects

Twenty-three healthy volunteers, both sexes, were enrolled at the Department of Neuroscience of the San Martino Hospital of Genoa, Genoa, Italy, between September 2012 and March 2013, upon approval by the local ethical committee and patient signatures on a valid informed consent form after procedures had been fully explained by the investigators (either psychiatrists or neurologists). All procedures were carried out in accordance with the Declaration of Helsinki about human experimentation.⁶⁰ No liver function monitoring was needed due to the prescription of just a single dose of agomelatine. In order to avoid any age-dependent effect affecting the b-wave amplitude,⁶¹ all subjects were aged between 22 and 35 years old. In addition, all subjects received the same single dose of agomelatine (25 mg/day), avoiding any concomitant medication to limit potential confounding biases as much as possible. Similar considerations led to the inclusion of female subjects only during the luteal phase of the menstrual cycle (objective measure of luteinizing hormone levels: range 1–20 IU/L) in order to avoid an additional confounding factor potentially affecting the b-wave amplitude.⁶² Finally, the baseline ERG assessments (with each session requiring about 1 hour for completion) were performed according to the following scheme: 1) first ERG recording at 10 am (baseline = T₀), immediately followed by oral intake of agomelatine 25 mg (one pill); 2) 1 hour's rest; 3) second ERG recording; 4) 1 (more) hour's rest; 5) third (final) ERG measurement. Finally, a pictorial description of the standard ERG has been provided in Figure 1 along with a synthetic flow of study procedures in Figure 2.

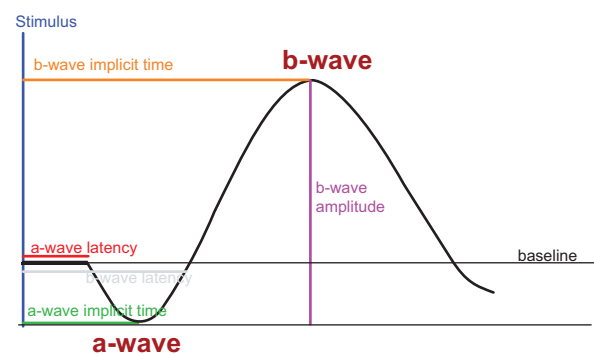


Figure 1 The a-wave of the electroretinogram reflects the activity of photoreceptors; the b-wave indicates the activity of the amacrine, horizontal, bipolar, and Müller cells. Implicit time refers to the time occurring between the initiation of the light stimulation (flash) and the peak of a- and b-waves. The a-wave amplitude was measured from baseline to a-wave trough; the b-wave amplitude was measured from a-wave trough to b-wave peak.

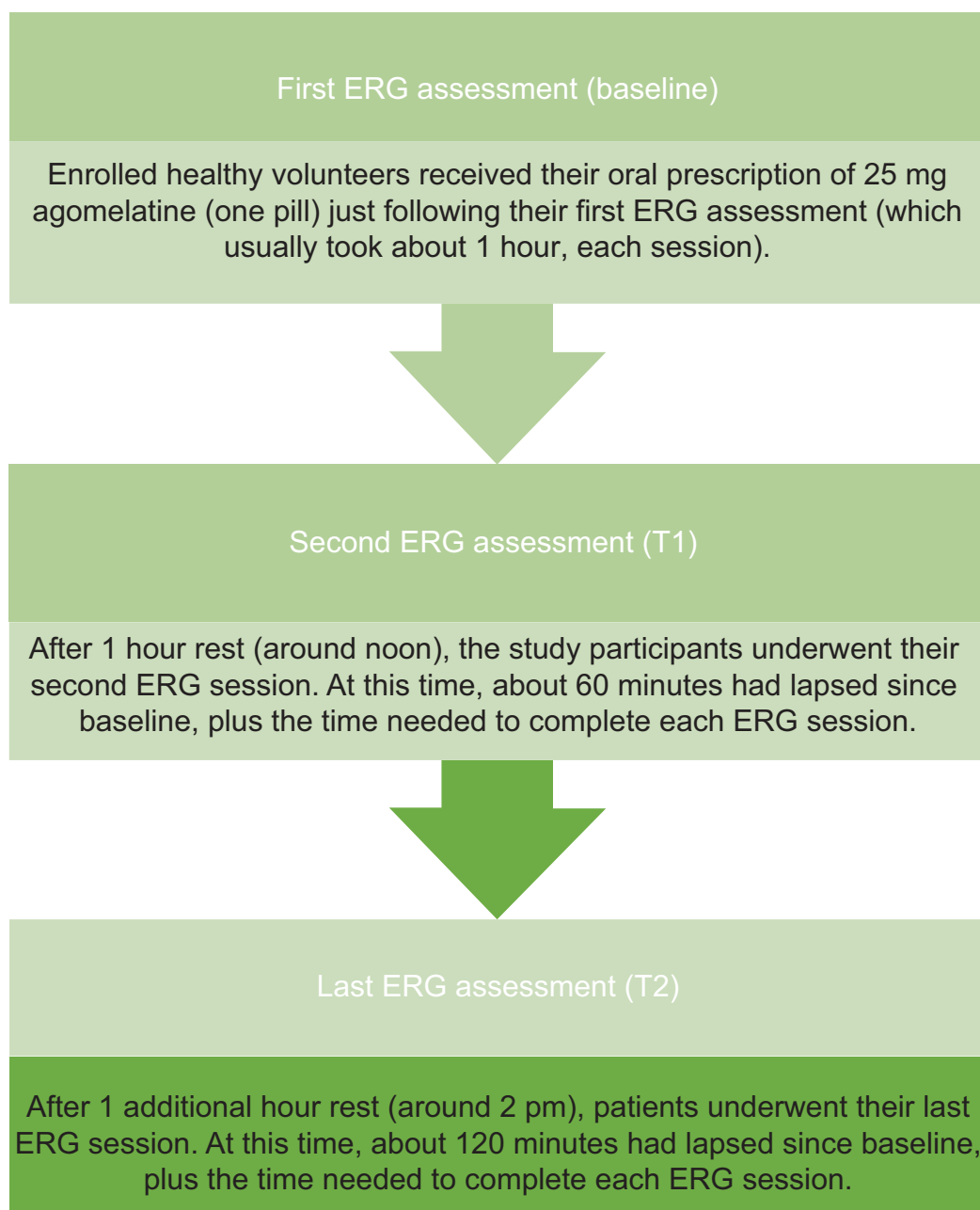


Figure 2 Flowchart of study procedures.

Abbreviation: ERG, electroretinogram.

Stimulation and recording

All subjects underwent a full-field ERG recording. The electric signal was recorded binocularly (dilated pupils) using 9 mm silver/silver chloride skin disc electrodes placed on the lower eyelid; the reference electrodes were placed close to the outer canthus of the eye and the ground electrode was placed on the forehead. The electrode impedance was maintained below 5 k Ω in order to provide consistent results independent of the response yielded by skin electrodes with lower amplitude and higher noise levels with regard to either

the corneal or conjunctival electrodes. The band-pass filter was set between 0.1 Hz and 500 Hz, and the subjects were dark-adapted for 20 minutes before recording. A full-field Ganzfeld stimulator was used throughout the study, with the subjects seated in front of the stimulator bowl fixating on a point incorporated in the stimulus dome during each session. The dark-adapted 0.01 ERG (rod response) was recorded using a dim white flash of 0.01 cdsm². The dark-adapted 3.0 ERG (combined rod–cone response) was generated by a white 3 cdsm² flash. After 10 minutes of light

adaptation, the light-adapted 3.0 ERG (single-flash cone response) was recorded, using a 3 cdsm2 stimulus with a background luminance of 30 cd/m² measured at the surface of the full-field stimulus bowl. b-wave amplitude and time to peak (implicit time) were measured (ms) for all ERGs. The a-wave was measured when detectable. The a-wave amplitude was measured from baseline to a-wave trough, while the b-wave amplitude was measured from a-wave trough to b-wave peak (μ V); the a-wave and b-wave implicit times were measured from the time of the flash to the peak of each wave.

Statistical analysis

Demographic and descriptive analyses were carried out using the IBM SPSS® software package (v 21) for Microsoft Windows® (v 7) (IBM Corporation, Armonk, NY, USA). Since data follow a nonparametric distribution, as assessed by the Shapiro–Wilk test, Friedman’s analysis of variance was used in order to compare the median scores of the ERG parameters.

Results

Twenty-three subjects (females n=8 or 35% of the sample; males n=15 or 65%) were included in the study and completed all the scheduled appointments and procedures. The average age was 26.61±3.3 years. Notably, among different measures of the b-wave parameters for both eyes (including latency and amplitude either for cones or rods, and for ERG maximal response), the only statistically significant modifications observed across the study were those related to cones’ b-wave amplitude and latency, in both eyes (Table 1). Finally, no statistically significant difference was observed for such parameters in males versus females.

Discussion

Limitations of the study

The absence of a control group, including differential doses of agomelatine, placebo, or melatonin, or depressed

controls, make the present results merely indicative at this time. Moreover, while dopamine could also affect the ERG, its effect was basically observed in terms of changes in the retinal sensitivity.⁶³ Therefore, in this study, the lack of a luminance response function to measure retinal sensitivity with the ERG prompts for caution in the interpretation of our preliminary findings. Oscillatory potentials most likely generated by the dopaminergic neurons of the amacrine (or interplexiform) cells, should also be accounted for in replication studies. Similarly, we followed the International Society for Clinical Electrophysiology of Vision (ISCEV) Standard⁶⁴ to record the ERG, which represents the minimum standard flashes to be used to investigate the retinal function (for patients with an eye disease); however, in terms of mere research purposes, assessing the dynamic of retinal functioning over a wide range of intensities should allow a more reliable assessment of the retinal sensitivity. Specifically, this latter consideration may have hampered the validity of the present preliminary protocol in the investigation of a possible impact of the ERG.

Clinical and neuropsychopharmacological implications of study results

In our sample, agomelatine induced a slight, yet statistically significant, increase of the cones’ b-wave amplitude and latency in both eyes. While it may be argued that the above mentioned change in amplitude may actually be within the normal variation of the measure, this is nonetheless in contrast to previous reports^{56–58} from comparable ERG studies involving healthy subjects receiving melatonin. While both melatonin and agomelatine act on melatonergic receptors, the presence of 5-HT_{2C} (and 5-HT_{2B}) antagonism for the antidepressant drug should be prudently hypothesized to account for the differential trend observed at ERG, eventually observed to play a role in the therapeutic effect claimed in depressed samples. Notably, a previous polysomnographic study

Table 1 Slightly, yet statistically, significant trends of increase of b-wave parameters

	LE			RE		
	Baseline value	60 minutes	120 minutes	Baseline value	60 minutes	120 minutes
Amplitude of the cones $\pm$ SD (LE $P=0.026$; RE $P=0.009$)*	49.22±18.71	52.30±18.43	55.52±20.95	45.35±18.48	48.65±17.02	51.56±17.22
Cone latency $\pm$ SD (LE $P=0.001$; RE $P=0.001$)*	33.83±2.79	34.74±3.67	36.39±3.13	33.52±2.69	34.48±3.33	36.17±3.08

Notes: Modifications that were not statistically significant are omitted (Friedman’s two-way analysis of variance by ranks). REs and LEs were analyzed separately. Amplitude values are in μ V (latency in ms). All results were obtained in daylight conditions. *Provided P -values for the nonparametric test indicated to reject the null hypothesis (of a difference observed by chance); asymptotic significance not reported; significance level set to $P=0.05$.

Abbreviations: LE, left eye; RE, right eye; SD, standard deviation.

carried out on a small sample of healthy volunteers with the same dose of agomelatine (25 mg/day) raised doubts about the actual blockade of 5-HT_{2C} receptors in humans, based on the observation that this agent failed to increase slow-wave sleep, whereas potent 5-HT_{2C} antagonists (eg, cyproheptadine 4 mg, ritanserin 5 mg, olanzapine 5 mg, or mirtazapine 30 mg) did.⁶⁵ Furthermore, in a recent animal study, neither the long-term administration of melatonin (40 mg/kg/day) nor the selective 5-HT_{2C} receptor antagonist SB 242084 (0.5 mg/kg/day) had an effect on the firing rate and burst parameters of serotonergic and dopaminergic neurons. The combination of these latter mechanisms, however, enhanced only the number of spontaneously active dopaminergic neurons at the ventral tegmental area, while leaving the firing of the serotonergic neurons unaltered at the raphe dorsal nucleus. Finally, the addition of a specific 5-HT_{2B} antagonist (LY 266097 at 0.6 mg/kg/day), which proved by itself to be devoid of effect, to the previous dual regimen increased the number of bursts per minute of dopaminergic neurons and the percentage of spikes occurring in burst, which ultimately mimics the effect of the antidepressant agomelatine.⁶⁶

Conclusion

Agomelatine may differ from melatonin not only in the absence of MT₃ agonism, but also in the presence of a dual antagonism on 5-HT_{2C} and 5-HT_{2B}, which may corroborate the claimed clinical antidepressant effect and account for the increase of the b-wave amplitude and latency of the cones (in daylight conditions). Nonetheless, along with the abovementioned limitations urging much prudence in the interpretation of our results and the acknowledgement that a decline in the central serotonin activity may itself affect the cone b-wave latency, it pays to note that the “classical” paradigm of monoamines (including dopamine) as a core pathway involved in depression has been debated, shifting more attention toward impaired circadian rhythms in depression.⁶⁷ Therefore, with the ultimate goal of shedding further light on the mechanism of action of novel antidepressants, with agomelatine being the case in point, additional, more methodologically accurate ERG studies on the matter are warranted.

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Disclosure

The authors report no conflicts of interest in this work.

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