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Melatonin secretion in migraine patients: the current state of knowledge

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ABSTRACT

Introduction. In this edition, Zduńska et al. [1] present the results of a pilot study exploring changes in melatonin serum concentration in migraine patients, and the clinical implications of these changes.

Clinical reflections. Melatonin secretion may be altered for several reasons, and migraine is one of those clinical conditions where melatonin secretion can be changed. Correlations between migraine clinical phenotype and melatonin secretion patterns may bring exciting results.

Clinical implications. Alterations in melatonin secretion in migraine has not been explained. Studies which aim at exploring the mechanism(s) of action of melatonin secretion in migraine patients may provide an insight into the pathogenesis of migraine and contribute to effective treatment options.

Key words: melatonin, light, migraine

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Migraine is a common disabling primary headache disorder, ranked in 2010 as the third most prevalent globally. In 2015, it was the leading cause of disability worldwide in both males and females under the age of 50 [2, 3]. Migraine is most often displayed as a paroxysmal headache preceded or not by aura, but it can also be a long-lasting headache and/or headache with several concomitant symptoms [4]. Recent studies have indicated the role of fluctuating excitability, plasticity, and metabolism of cortical neurons involved in the migraine cycle [5, 6]. Conduction of visual impulses via the hypothalamic region and the thalamic pulvinar nucleus to the visual cortex seems to be responsible for photic hypersensitivity in the premonitory phase of a migraine attack [7, 8].

Melatonin is an indolamine synthesised by the pinealocytes in the pineal gland under a neural system's control, including the light sensitive retina and suprachiasmatic nucleus (SCN) [9, 10]. Melatonin secretion is closely synchronized with the circadian rhythm where light evokes an inhibitory effect on its secretion, moreover, lesions located in the tracts connecting the retina with the pineal gland can disturb the secretion of melatonin [11]. The secretion of melatonin is vital for sleep regulation and its decrease with age may contribute to the worsening of sleep-quality in older people [12].

Melatonin plays a role in the pathophysiology of migraine where it demonstates antimigraine effects via several ways. Neurotransmitter changes and neural pathway modifications, such as restraining nitric oxide synthesis, inhibiting dopamine release, and antagonising glutamate-induced excitotoxicity, are reported mechanisms for melatonin's beneficial effect in migraine [13–16]. Calcitonin gene-related peptide (CGRP) vasodilating effect is responsible for migraine attacks, when melatonin significantly decreases mRNA expression of CGRP release, nitric oxide production, and nitric oxide synthase activity in migraine patients [17].

Interestingly, melatonin has a similar structure to indomethacin; therefore, it is expected to evoke an indomethacin-like analgesic effect [18]. Moreover, the release of β-endorphins, activation of melatonin receptors, and regulation of γ-aminobutyric acid receptors are several ways by which melatonin produces its analgesic effects [19]. In the urine of migraine patients, a low level of melatonin metabolites was observed; therefore, a weaker antimigraine effect of melatonin is expected in these patients [20, 21].

Several observations on melatonin's antimigraine effects have led scientists to test its beneficial results in patients with migraine, however, recent systemic review yielded conflicting

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outcomes [22]. Hence, extensive research on melatonin's antimigraine effects is yet to be conducted.

To understand melatonin's beneficial effects in migraine, it is important to confirm either disturbances in its secretion or in its metabolism. Zduńska et al. [1] conducted a pilot study which indicated alterations in melatonin secretion profiles and concentration in a migraine group compared to controls. The authors of this study observed insignificantly lower concentrations of melatonin in migraine patients as opposed to the controls, nevertheless, melatonin concentrations became significantly lower with disease duration.

Some similar studies were earlier conducted. First one in 1989 when 93 patients with migraine and 46 controls were examined identifying lower melatonin levels in women patients, notably those with concomitant depression [23]. Respectively in 1994 and in 1995 other authors confirmed this observation in studies carried out in female subjects where they found a significant difference in melatonin levels betwen women with migraine and controls [24, 25]. Importantly, in [24] the authors identified a significant decrease in melatonin levels in patients experiencing a migraine attack. The abovementioned studies were performed in small patient groups, with the next conducted in 2001 on a mostly female group; here again, a melatonin level decrease was confirmed in the migraine group [26]. In 2008 and in a relatively larger study authors observed the lack of the melatonin metabolite (6-sulphatoxymelatonin) difference in the urine of 146 patients (with the exception of 53 patients who experienced a migraine attack on urine collection day) with migraine as compared to 76 controls [21]. Finally, in 2017, a study on 55 migraine patients and 57 controls (both female-preponderant) indicated significantly lower peak melatonin level (sampling at 1 a.m.) in patients with migraine [27].

Intending to provide melatonin-based therapeutic advice for migraine patients, appreciating the contradictory results of previous trials, and the low melatonin side effect risk [22], and based on findings from the above-mentioned studies, this therapeutic approach could be considered in some special patient groups such as women in *status migrainosus* [28, 29], or these with disturbed light exposure [30, 31].

Further exploratory studies concerning the pathophysiology of migraine and melatonin's role are urgently required, as are numerous well-designed trials utilising melatonin for treatment.

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