

Melatonin for Autism Spectrum Disorder: Beyond Sleep Disturbances?

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Autism spectrum disorder (ASD) affected subjects often suffer from sleep disturbances [1]. Among these, altered time duration, night-time awakenings and anxiety before sleep are reported [2]. Day time behaviour disturbances could affect the onset of sleep problems in ASD [3]. Melatonin (N-acetyl-5-methoxy tryptamine) is a methoxyindole responsible for regulating sleep. This molecule is mainly synthesized and secreted by the pineal gland at night under normal light/dark conditions. As hormone, it carries molecular information about the 24-hours light/dark cycle (circadian rhythm) to the body structures [4]. Its signalling transduction mechanism takes place through activation of G-protein coupled receptors (MT1 and MT2 receptor subtypes) [5]. Interestingly, lower night-time melatonin and melatonin metabolite levels have been reported in ASD children. Several clinical studies demonstrated significant improvements in sleep parameters with exogenous melatonin supplementation in ASD subjects [6]. Recently, a double-blind randomized placebo-controlled study reported 3-month efficacy and safety of a novel paediatric appropriate prolonged release melatonin for insomnia in ASD children and adolescents [7]. Moreover, it is noteworthy to consider that melatonin is also a powerful anti-oxidant molecule [8]. It is able to act as scavenger of free radical species, as well as to enhance endogenous anti-oxidative system and mitochondrial metabolism [9]. Impaired biochemical processes are related to ASD, among others: oxidative stress, endoplasmic reticulum stress, decreased methylation capacity, altered ratio between anti-oxidant reduced glutathione (GSH) and oxidized one (GSSG) [10]. Melatonin supplementation in ASD could exert ameliorative effects in autistic core symptoms, through restoration of disrupted anti-oxidant pathways. Strong inflammation states and immune system dysfunctions have been associated with ASD [11]. Pro-inflammatory cytokines are aberrantly up-regulated in plasma of ASD children [12]. Melatonin acts as pleiotropic molecule also in the regulation of the immune system [13]. This hormone freely moves through blood brain barrier [14] and could restore altered neuro-immune cross-talk. Indeed, as immune-modulatory effect, melatonin is able to stimulate the production of natural killer (NK) cells and lymphocytes CD4+ cells and the inhibition of CD8+ cells [15]. To note, it has been demonstrated that NK cells are strongly decreased in ASD children, indicating a defect in the immune counter-regulatory functions [16]. Lastly, mitochondrial dysfunction is present in a significant subgroup of ASD children [17]. Melatonin is also capable of preventing mitochondrial impairment, energy failure, and apoptosis in oxidatively-damaged mitochondria [18]. Interestingly, melatonin helps in regulating hippocampal neural plasticity and in contributing to change in neuronal excitability in mouse [19]. Beyond ASD core symptoms, melatonin could also impact several ASD associated co-morbid conditions, such as anxiety, depression, pain, and

gastrointestinal dysfunctions [20]. Melatonin could take a role in regulating gut-brain signalling [21]. This aspect is very important, as the gut-brain axis plays a key role in the development of ASD [22]. Alteration of this signalling axis is associated with low-mild gut inflammation, dysbiosis, gastrointestinal symptoms, and increased intestinal permeability. Restoring gut homeostasis with melatonin could repair all these co-morbidities.

Taken together, all these data highlight a possible molecular mechanism of action for melatonin in ASD management. Experimental and clinical studies addressing molecular effects of melatonin in ASD behavioural symptoms, beyond sleep issues, could offer novel perspectives in ASD research and possible treatment options.

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