Commentary

Onset in late adolescence of schizophrenia: Could melatonin modulate this debut?

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ABSTRACT

Schizophrenia, one of the most serious and widespread mental disorders in the world, makes its debut often in late adolescence and early adulthood, which allows us to focus our attention on those brain areas that still retain plasticity during this period. Parvalbumin interneurons, GABAergic and inhibitory, in both cortical and hippocampal areas, maintain their plasticity and are particularly vulnerable to oxidative stress due to their high energy requirements. Evidence has shown that their damage favors the triggering of schizophrenia by altering the neurobehavioral development of individuals. These neurons have melatonin receptors of MT1 and MT2, and the cytoprotective role of melatonin has been reported on these neurons. However, the role of this indolamine played in adolescence in protecting parvalbumin interneurons, reducing their oxidative stress and/or preventing their disappearance, which could prevent the onset of schizophrenia, is not yet known. The importance of this activity and its implications on patient therapy require the urgent studies.

Key words: Melatonin, schizophrenia, oxidative stress, neuronal plasticity, parvalbumin interneurons, late adolescence, mental disorders

1. DEBUT OF SCHIZOPHRENIA: ROLE OF PARVALBUMIN INTERNEURONS

Schizophrenia is one of the most serious neuropsychiatric disorders, both in terms of its pathophysiological development and its social course. Thus, in terms of clinical evolution, its onset is determined by a first psychotic episode, although some authors point to certain cognitive alterations that precede the onset of the disease and seem to worsen in the prodromal phase (1). Once the disease has occurred , it is characterized mainly by affective symptoms (1), including depression or mania, obvious impairments in attention, memory, planning (2, 3) and social relationships. Neuroimaging and neuropsychological studies show changes mainly in the temporolimbic and frontal lobe regions (4). But this disorder also causes drastic changes in the

lives of the patients. Statistics show that most of them are condemned to social isolation, stigmatization, unemployment rates of between 70% and 90% in Europe, and significantly reduced chances of finding a partner (5). All this, combined with poorer health habits and co-morbidities, leads to a reduction in life expectancy of 13-15 years (6) and a suicide rate of around 5% of those diagnosed (7). In view of these devastating characteristics, it is imperative to develop new therapeutic strategies to improve the quality of life of these patients, which will necessarily require an increase in research efforts to understand the etiology and pathophysiology of the disease, which is currently very limited. We propose to focus the research on the early stages of the onset of this pathology, corresponding to late adolescence or early adulthood, since this is a particularly critical period for the onset of this disorder, while at the same time it is particularly complex due to the large number of hormonal changes that it involves, which, however, are not fully understood (8).

Far from being the static system that it has been considered for decades, the central nervous system has certain regions that have a remarkable capacity for remodeling and this capacity is preserved not only during the early stage of life but it is also carried out into adulthood (9), in particular the prefrontal cortex and the hippocampus (10). Two main populations of neurons arise in both regions: excitatory or glutamatergic neurons, which therefore use glutamate to communicate, and inhibitory or GABAergic interneurons, whose dependence on the expression of different calcium chelating proteins allows their classification (11). A malfunction or alteration in any of these regions that affects their integrity leads to different types of disorders (12, 13), among which schizophrenia stands out as a neuropsychiatric disorder that coincides with damage in one of the two mentioned areas (14, 15).

Although the alterations in both excitatory and inhibitory pathways triggering the onset of schizophrenia have been suggested (8), there is greater agreement in emphasizing the importance of alterations in interneurons triggering this disorder (16, 17). Therefore, calcium-binding protein parvalbumin (PV) interneurons from both cortical (18) and hippocampal (19) areas have received particular attention in relation to this disorder. In fact, it has recently been shown that a significant reduction PV interneuron, as well as those whose neurotransmitter is somatostatin, during embryonic development causes neurophysiological and behavioral changes consistent with human schizophrenia in adult rats (20).

Due to their high activity, PV interneurons require a high energy input, corresponding to the large number of mitochondria of these cells (21), making them particularly susceptible to oxidative stress (22). The ability of oxidative stress to cause significant cellular damage, particularly in the central nervous system, has been well established. However, if we consider this new information of the long lasting plasticity of these neurons until to the adulthood, the possible role of oxidative stress as an inducer of neuronal functional changes (23), as well as an imbalance in the excitatory/inhibitory status (8), takes on a new meaning. Recently, the increased evidence has shown that the free radicals, which alter the maturation of PV interneurons, modulates the development of mental illness (24). If considering the modulatory role of the circadian rhythm on the maturation of PV interneurons (25), especially during critical developmental periods such as adolescence, the potential beneficial role of melatonin, at least, in the onset of this disorder, seems undeniable, although to our knowledge no article has yet mentioned it.

2. MELATONIN AS A PROTECTIVE MOLECULE

Melatonin has been shown to play a protective and beneficial role in a wide range of pathologies and disorders (26–29), due to its dual capacity as both a circadian rhythm regulator, marking the sleep-wake cycle (30, 31), and as a multifunctional antioxidant and free radical scavenger with anti-inflammatory capacity (32, 33). However, data on the benefits of melatonin

in schizophrenia are still scattered and inconclusive (34), although not without importance and significance in this disorder. During embryonic development, the role of melatonin, mainly through its MT1 and MT2 receptors present in the fetal brain and leptomeninges (35), appears to be essential for neurodevelopment (36) and neuroprotection (37), as an anti-inflammatory agent with beneficial effects on the normal development of neurobehavioral functions (38), often affected in schizophrenia (39). Indeed, in human olfactory neuronal precursors (ONPs), the markedly reduced differentiation capacity observed in schizophrenia patients has been demonstrated, particularly with regard to melatonergic receptors (40).

In late adolescence and the transition to adulthood, the drastic decrease in melatonin production during this period is well known (41). Both cortical and hippocampal PV interneurons, which have not fully matured in late adolescence, are particularly sensitive to oxidative stress due to their high demanding on mitochondrial energy (21). This oxidative stress can be particularly dangerous at this stage of life, as it can induce an excitatory-inhibitory imbalance in these areas (8) and increase the risk of psychotic disorders (24, 42). In fact, a reduction of these interneurons has been observed in both the prefrontal cortex and the hippocampus in patients with schizophrenia (20, 43), which indirectly justifies their importance in the development of the disorder. At the same time, MT1 and MT2 receptors have been identified in these neurons, and their activation appears to increase the expression of the calcium-binding protein parvalbumin, thereby reducing neuronal inflammation (44). Suppression of MT1 and MT2 leads to increased glutamate toxicity in PV interneurons , which can be partially reversed by melatonin (44). Thus, the possible protective role of melatonin in this strategic phase of the transition to adulthood on the possible damage in these PV interneurons seems evident. Although the protective role of melatonin on mitochondria is well known (45, 46), and it has even been found that patients with schizophrenia show a reduction in the size of their pineal gland (47), and the ability of melatonin to restore the reduced differentiation capacity of ONPs in schizophrenia patients has been demonstrated (40), few studies have addressed the potential role of melatonin in protecting these neurons during the crucial period of life which is closely associated to the onset of the first psychotic episode. The potential association of occurrence of Schizophora and the natural melatonin drop-out was illustrated in Figure 1.

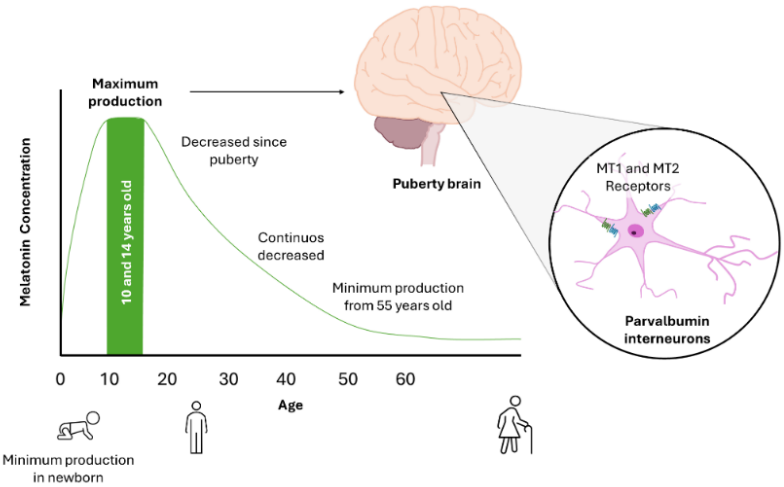

Fig. 1. The potential effects of the natural melatonin drop-out at the late adolescence and the transition to adulthood on the occurrence of Schizophora.

Melatonin levels fluctuate throughout a person's life, with an abrupt increase in melatonin production from childhood to adolescence (10-14 years), when melatonin production is maximal, and then with a rapid decline, reaching minimum production levels after the age of 55. The onset of the decline in melatonin production (adolescence - early adulthood) coincides

with the maturation of parvalbumin interneurons, melatonin-sensitive neurons (with MT1 and MT2 receptors) whose involvement appears to be closely linked to the pathogenesis of schizophrenia. Graph of melatonin levels modified from information provided by the International Melatonin Institute (IiMEL).

The extent, severity and disability caused by this pathology make it necessary to develop therapies. But it also makes it crucial to discover those processes that could reduce or prevent the onset of psychosis. And there are enough indirect data to support the possibility that melatonin could preserve and thus protect the PV interneurons and prevent the onset of schizophrenia.

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AUTHORSHIPS

ACM designed the idea for the article. CCV, JAB, YP and ACM performed the literature search and wrote the first draft of the manuscript. ACM reviewed and revised the manuscript. ACM reviewed and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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