**Short Communication**

# Can melatonin improve the alteration of protein synthesis occurring in schizophrenia and bipolar disorder?

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## ABSTRACT

The prevalence of mental illnesses has significantly increased globally in recent decades due to multifactorial causes. Of these, schizophrenia and bipolar disorder, due to their high incidence and high associated disability, stand out. However, the effective treatments on these disorders are lagged behind their increased incidence. Melatonin, as an essential molecule in the regulation of sleep-wake rhythm and the naturally occurring antioxidant, has only received attention for the treatment of such psychiatric disorders in relation to its circadian rhythm regulation, but its overwhelming role as a regulator of oxidative stress that facilitates the amelioration of neuronal damage has not been addressed for this respect. In this communication, the novel aspects of melatonin on mental illnesses have been discussed. We provide the necessary literature to justify the beneficial roles and the mechanisms of melatonin to treat schizophrenia and bipolar disorder. These mechanisms include that melatonin enhances reticulum stress, potentiates the unfolded protein response, and increases endoplasmic reticulum synthesis to facilitate autophagy and even suppresses apoptosis. This process involves not only the expected organelles but is a more complex cohesion that even includes the mitochondria, a well-known target of melatonin, which reinforces the robustness of our hypothesis, i.e., melatonin prevents the development of protein aggregates and abnormal structures typically observed in brain damage. Its documented capacity and the need to improve treatment efficiency in a growing population afflicted by mental illnesses are the basis of this hypothesis and support a role of melatonin, as antioxidant, in psychiatric disorders.

**Key words:** Melatonin, schizophrenia, bipolar disorder, oxidative stress, UPR, unfolded protein response, mitochondrial endoplasmic reticulum stress

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## 1. INTRODUCTION

The last Mental Health Action Plan developed by the World Health Organization (2013-2020) focused on the urgency of responding to the world's mental health needs, allowing visibility to be given to ailments that affect more than 700 million people in the world and directing its focus to prevention (1). Among all the mental disorders included in this report ,

schizophrenia and bipolar disorder have a prevalent position among the others, due to their relatively high incidence and debilitated potential (2). Similarities between the two disorders often come with their overlapped symptoms that are detected at the debut of the pathology leading to great diagnostic uncertainty. However, there are other common features between the two, such as their heterogeneous aetiology including genetic and environmental factors and their marked circadian rhythm disturbances, which are the characteristics of these two disorders but also involved in the vast majority of psychiatric disorders (3).

Among melatonin's pleiotropic functions, its well-known role serves as the most important natural antioxidant known to date, and its beneficial effects described at the level of cellular functioning have been well documented to date in many research areas (4). Surprisingly, however, in psychiatric disorders in general and schizophrenia and bipolar disorder in particular, studies related to this indolamine have been largely inconclusive and its role as an antioxidant and transcriptional and transductional regulators has been poorly studied. Although it should always be noticed that the few studies carried out in this field have shown that the amount of melatonin needed to have the positive effects on neurodegeneration (5) or cell survival (6) are always higher than that for circadian rhythm regulation, which has classically been the basis for studies of melatonin for psychiatric illnesses (7–9).

It is necessary to re-evaluate the capacities of melatonin on neuropsychiatric disorders, identifying its real capacity to affect physiopathological processes coinciding with these pathologies and observations reported in the previous studies.

## 2. THE ROLES OF MELATONIN IN ENDOPLASMIC RETICULUM (ER) STRESS AND UNFOLDED PROTEIN RESPONSE (UPR)

Protein synthesis mainly occurs in the ER. It is important for the cell having correctly synthesized and folded proteins, but this process can easily be destabilized in multiple pathologies because of the delicate balance between protein synthesis and degradation. ER dysfunction has been highlighted in multiple neurological pathologies such as Alzheimer's, Parkinson's and Huntington's diseases (10), also, more recently, in schizophrenia (11). This phenomenon, whereby the ER produces an excess of unfolded or misfolded proteins, is referred as ER stress (12). When this happens, the cell responds by triggering a multifactorial processes composed of three pathways that act sequentially, activating several compensatory mechanisms ranging from an increase in endoplasmic reticulum synthesis to the triggering of apoptosis, depending on the severity of the process and the cell's capacity to respond (13). Thus, under mild stress, the cell starts triggering the ATF-6 (Activating Transcription Factor 6) and IRE-1-α (inositol-requiring enzyme 1-α) response cascades, named after the first activated molecule of each pathway, leading to what is known as an adaptive response that includes the activation of ERAD (ER-associated protein degradation), the synthesis of more proteins and lipids aimed at increasing the ER surface area and favoring mitochondrial biogenesis (14). If this response is insufficient and fails to eradicate ER stress, a new pathway is triggered, i.e., the PERK (double-strand RNA-activated protein kinase (PRK) like endoplasmic reticulum kinase) pathway, which activates much more drastic mechanisms aimed at acting on the protein aggregates accumulated in the cell. This pathway blocks protein synthesis (14) and activates autophagy as a survival mechanism. If these steps continue to be unsuccessful, this pathway is also capable of triggering apoptosis, which is why this pathway is also called the apoptotic UPR response (15) or non-adaptive UPR response.

Development of ER-stress, as well as UPR, has been described in various neurological disorders ranging from Alzheimer's disease (16) and neurodegenerative diseases (17) to neurophysichiatric disorders such as schizophrenia or bipolar disorder (13).

Damage or alteration of the UPR cascade, described in multiple pathologies (18–20), and/or alteration of the proteasome (21, 22), would lead to a continuous production of misfolded proteins which would be directly responsible for their accumulation and, thus, for the formation of protein aggregates and aggresomes (23), observed in multiple neurological diseases (1, 24), although not exclusively, but it favors exacerbation of neurodegeneration (25).

Melatonin has undoubtedly shown, in various pathologies, its ability to reduce ER stress, as well as to activate the different UPR pathways depending on the conditions the cell exposed (26, 27), favoring to reduce oxidative stress and improve cell status , even under the condition of neurodegenerative disorders (4, 10, 28). This actions to reduce misfolded proteins, as well as to activate UPRs, may be independent to its widely documented effect on reducing protein aggregates (29). Based on the existing literature, it seems plausible that melatonin could promote correct protein synthesis in the psychiatric disorders, therefore, triggering an efficient UPR-based response. In turn, its response pathways involve important processes in which melatonin may also act beneficially, which are detailed below:

A. ***Mitochondrial energy capacity***.

The ATF-6 pathway, as an integral part of the UPR, induces a rapid bioenergetic response to alterations in protein synthesis, favoring mitochondrial biogenesis and improving mitochondrial function (14). Mitochondrial alterations have been reported on many occasions to relate to neurodegenerative damage (30, 31) and psychiatric disorders such as schizophrenia and bipolar disorder (32, 33). Melatonin, for its part, has amply demonstrated its capacity for mitochondrial improvement and reduction of oxidative stress derived from mitochondrial dysfunction (34, 35), even in neurodegenerative diseases (36, 37), so that, once again, a beneficial effect of this indolamine at mitochondrial level would seem to be expected in the psychiatric disturbances, mainly schizophrenia and bipolar disorder we are concerned with.

**B.** ***Autophagy*.**

The PERK pathway activates, as an essential survival mechanism, autophagy as the final step before triggering of apoptosis. Therefore, the importance of this mechanism can result in cellular conservation, of particular importance for the neurons. This autophagy, the general name given to macroautophagy, develops a series of membranous formations, usually originating from the ER. These ER derived membrane structures envelop the elements to be degraded in structures called autophagosomes that will be directed to the lysosome for their complete degradation (38). Their role in the degradation of protein aggregates is well characterized (39, 40). This degradative system can, in turn, specialize in the degradation of specific cellular organelles. For example, the mitophagy is specific to clean the dysfunctional mitochondria with high efficiency (41, 42). Both mitophagy, in particular, and autophagy, in general, have been extensively studied in multiple neurodegenerative (43, 44) and even psychiatric pathologies, especially for the schizophrenia and bipolar disorder (45, 46). Again, increased evidence supports the role of melatonin in the regulation of this survival mechanism, favoring cellular improvement in various pathologies (47, 48), including neurodegeneration (49, 50). Therefore, extrapolating the beneficial effect of melatonin in the regulation of autophagy in psychiatric disorders does not seem at all far-fetched.

Finally, increasingly documented, an association among the ER, mitochondria and autophagy via mitochondria-associated membranes has been well documented (51). To in-depth understand this association will allow us to define the ER-mitochondria organizing network (ERMIONE) (52), within which ATPase family AAA domain-containing protein 3 (ATAD3) is crucial in the interaction of both organelles and it inhibits target of rapamycin

(TOR) signalling, thus indirectly favoring the activation of autophagy. Although no study has yet been carried out on the possible modulation of melatonin on this network and ATAD3 specifically, the indirect evidence suggests that the role of melatonin could be even more pleiotropic than described so far. Mutations of ATAD3A gene in humans appear to be involved in the development of neurological syndromes (53). We hypothesize that melatonin could be, at this as yet unknown level, to alleviate these neurological disorders.

## 3. CONCLUSIONS

Psychiatric disorders are currently the subject of intense research to try to unravel the altered cellular mechanisms involved in these pathologies. The findings so far seem to leave beyond doubt the involvement of ER-stress and UPR in the development of most of these pathologies. Schizophrenia and bipolar disorder pathologies, due to their high prevalence and severity, are concerning of this report. For this reason, melatonin, based on the results from the extensive bibliography search which show its beneficial effect in retarding the damage to the aforementioned mechanisms, seems an excellent molecule for, at the very least, neutralizing these neurological alterations. If we also take into account that one of the most evident sequelae of ER damage and the subsequent increase in misfolded proteins resulted protein aggregation, the severity of the damage and the importance of its destruction make melatonin a highly promising treatment molecule. Therefore, clinical trials are needed, at least for both Schizophrenia and bipolar disorder pathologies, to use melatonin as a potential therapeutic agent. To weight the existing literature to date, the severity and extent of these pathologies and the safety of melatonin (54, 55) are the keys to encourage such necessary and beneficial trials for a very large percentage of the world's population, many of whom are afflicted by these devastating disorders.

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## AUTHORSHIP

All authors contributed equally to the writing of this paper.

## CONFLICT OF INTEREST

Authors declare no conflict of interest.

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