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REVIEW ARTICLE

Melatonin: an overlooked factor in schizophrenia and in the inhibition of anti-psychotic side effects

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Abstract This paper reviews melatonin as an overlooked factor in the developmental etiology and maintenance of schizophrenia; the neuroimmune and oxidative pathophysiology of schizophrenia; specific symptoms in schizophrenia, including sleep disturbance; circadian rhythms; and side effects of antipsychotics, including tardive dyskinesia and metabolic syndrome. Electronic databases, i.e. PUBMED, Scopus and Google Scholar were used as sources for this review using keywords: schizophrenia, psychosis, tardive dyskinesia, antipsychotics, metabolic syndrome, drug side effects and melatonin. Articles were selected on the basis of relevance to the etiology, course and treatment of schizophrenia. Melatonin levels and melatonin circadian rhythm are significantly decreased in schizophrenic patients. The adjunctive use of melatonin in schizophrenia may augment the efficacy of antipsychotics through its anti-inflammatory and antioxidative effects. Further, melatonin would be expected to improve sleep disorders in schizophrenia and side effects of anti-psychotics, such as tardive dyskinesia, metaboilic syndrome and hypertension. It is proposed that melatonin also impacts on the tryptophan catabolic pathway via its effect on stress response and cortisol secretion, thereby impacting on cortex associated cognition, amygdala associated affect and striatal motivational processing. The secretion of melatonin is decreased in schizophrenia, contributing to its etiology, pathophysiology and management. Melatonin is likely to have impacts on the metabolic side effects of anti-psychotics that contribute to subsequent decreases in life-expectancy.

Keywords Melatonin · Schizophrenia · Anti-psychotics · Metabolic · Inflammation · Vitamin D

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Introduction

Schizophrenia is associated with a dramatic decrease in life expectancy, not entirely explained by increased suicide rates (Flaum 2010). The effects of anti-psychotics, via the induction of metabolic syndrome, are widely thought to contribute to this. The moral dilemma of containing psychotic symptoms, whilst likely contributing to decreased longevity and longer-term health problems, is arguably the major practical issue faced in the treatment of schizophrenia today. Out with its well-known efficacy in sleep induction and circadian rhythm modulation (Marczynski et al. 1964), melatonin's role in the etiology, course and treatment of schizophrenia has received relatively little attention. Melatonin has a number of potential effects relevant to the context of schizophrenia, including in its etiology, pathophysiology and on the prevention of the metabolic and other side effects induced by anti-psychotics (Bushe and Leonard 2007; Tardieu et al. 2003).

This review aims to highlight the relevance of alterations in melatonin in the etiology and maintenance of schizophrenia. It is proposed that its adjuvant use will prevent many side effects of typical and atypical antipsychotics that contribute to decreased longevity and quality of life.

Methods

Electronic databases, i.e. PUBMED, Scopus and Google Scholar were used as sources for this review using keywords:

schizophrenia, psychosis, tardive dyskinesia, antipsychotics, metabolic syndrome, drug side effects and melatonin. Articles were selected on the basis of relevance to the etiology, course and treatment of schizophrenia.

Melatonin and schizophrenia

Accumulating evidence suggests that melatonin plays a role in the pathophysiology of schizophrenia. Decreased nocturnal secretion of melatonin has been detected in drug-free as well as paranoid schizophrenic patients (Monteleone et al. 1992, 1997). Many patients with schizophrenia lack the typical diurnal variation in melatonin (Bersani et al. 2003). Jiang and Wang (1998) also found disrupted melatonin patterns in medicated schizophrenic patients. Generally decreased melatonin has been found in schizophrenic patients, although not always (Vigano et al. 2001). A phase advance in melatonin circadian rhythms was also detected (Rao et al. 1994). There is evidence for pineal calcification in schizophrenia that is associated with CT measurements of cortical atrophy (Sandyk and Kay 1991). Chronic treatment with antipsychotics improves psychotic symptoms, but does not normalize decreased baseline melatonin (Monteleone et al. 1992). Monozygotic twins discordant for schizophrenia show significant alterations in levels of melatonin (Afonso et al. 2010). This indicates that the impaired activity of the pineal gland may be a trait marker of schizophrenia. The promoter of the melatonin receptor 1A gene is significantly associated with schizophrenia (Park et al. 2011).

Melatonin and the immune pathophysiology of schizophrenia

Two recent meta-analyses showed that schizophrenia is accompanied by monocytic activation including increased levels of proinflammatory cytokines (PICs) with altered T cell activation and a Th1-like pattern (Miller et al. 2011; Potvin et al. 2008). However, increased Th2-like cytokines have also been found (Drexhage et al. 2011), suggestive of a mixed immune response. There is also evidence for increased neuroinflammation in schizophrenic patients (Meyer et al. 2011).

Developmental neuroinflammation caused by maternal prenatal infections is pathophysiologically relevant and may contribute to progressive brain changes and thus progression of schizophrenia (Meyer et al. 2011). Additional evidence shows that oxidative pathways are involved in the pathophysiology of schizophrenia via lipid peroxidation, DNA damage and oxidatively modified proteins (Bošković et al. 2011). Melatonin is not only a hypnotic and circadian rhythm resynchronizing compound, it is also a strong antioxidant and anti-inflammatory agent (Maldonado et al. 2009a, b). Melatonin attenuates PICs and other inflammatory mediators, additionally acting as a free radical scavenger protecting against oxidative damage (Esposito and Cuzzocrea 2010). As such melatonin has neuroprotective capacities and has therapeutic potential in chronic (neuro)inflammatory and neurodegenerative disorders (Esposito and Cuzzocrea 2010). Melatonin, in combination with anti-psychotic drugs, may augment the efficacy of these drugs via the targeting of (neuro)inflammation and oxidative stress (Maldonado et al. 2009a, b).

As well as being a powerful anti-oxidant, melatonin increases the phosphorylation and inhibition of glycogen synthase kinase-3b (GSK-3b), thus increasing endogenous antioxidants via enhanced nuclear factor erythroid-derived-2 (NF-E2)-related factor (Nrf-2) (Olcese et al. 2009). Melatonin is also a significant inhibitor of cortisol's Gcr (glucocorticoid receptor) nuclear translocation (Quiros et al. 2008). This latter effect is likely mediated via increased Bcl-2 associated anthanogene-1 (BAG-1). If so, then this would link melatonin effects to those of lithium and valproate, both of which increase BAG-1 in the brain (Zhou et al. 2005). This suggests that melatonin would lead to a decrease in the dosage of such classical mood stabilizers, contributing to a decrease in their side effects.

Schizophrenia and bipolar disorder (BD) have been conceptualized as both circadian and metabolic disorders (Wulff et al. 2012). Both these aspects will be regulated by melatonin. Melatonin increases the longevity protein Sirtuin-1 in neurons (Tajes et al. 2009), increasing peroxisome proliferator activated receptor gamma coactivator 1 alpha (PGC-1a), driving mitochondrial bioenergetics and increasing mitochondrial mass (Wareski et al. 2009). Melatonin increases mitochondrial oxidative phosphorylation and would offset mitochondrial deficits previously shown in schizophrenia, which drive wider aspects of metabolic syndrome (Martín et al. 2002).

Melatonin, vitamin D and schizophrenia early developmental etiology

Vitamin D3 (vit D3) is significantly lower in schizophrenic patients than in normal controls (Schneider et al. 2000). A decrease in vit D3 prenatally and in the first post-natal year has long been associated with increased schizophrenia rates in the offspring (McGrath et al. 2003). Decreased vit D3 is significant in a number of contexts associated with the etiology of schizophrenia, including maternal stress/infection (Brown and Derkitis 2010), pre-eclampsia (Byrne et al. 2007), and season of birth variations (Marzullo and Fraser 2009). Between 38 % and 46 % of schizophrenia cases have been estimated to be caused by prenatal infection (Brown and Derkitis 2010), and a decrease in vit D3 is a significant contributor to this (Holmes et al. 2009), due to its powerful role in the modulation of both the innate (Miller and Gallo 2010), and adaptive (Bikle 2009) immune systems.

How relevant are melatonin's interactions with vit D3 in these developmental etiologies to psychosis? No data currently exists looking at the interactions of melatonin and vit D3 in the modulation of immunity, and it remains to be tested as to whether this would be a significant interaction in maternal infection induced schizophrenia. Nevertheless, melatonin is known to interact with vitamin D3 in a number of human disorders, including synergistic interactions in breast cancer (Proietti et al. 2011). There may be some scope for relevant interactions of melatonin and vit D3 in the context of an early developmental etiology to schizophrenia. There are overlaps in their pathways e.g. both are inducers of the intracellular C/EBPb (CCAAT/enhancer-binding perotin beta) pathway (Alonso-Vale et al. 2009). Both also significantly modulate the immune response and would inhibit the increased levels of osteoporosis, evident in schizophrenia (Graham et al. 2011). Melatonin increases osteoblast differentiation from mesenchymal stem cells, decreasing the differentiation of adipocytes (Zhang et al. 2010). The putative increase in the levels of BAG-1 by melatonin may be relevant to its interactive effects with vit D, as BAG-1 is a chaperone for vit D3 to the nuclear Vit D receptor, potentiating the effects of vit D3 (Chun et al. 2008).

Preeclampsia is another risk factor for an increase in schizophrenia in the offspring, and this too is associated with decreased maternal vit D3 (Grant 2010), as well as decreased placental melatonin (Aversa et al. 2012). It seems likely that vit D3 mediates its effects via the inhibition of decidual natural killer (NK) cells, with consequent impacts on trophoblast migration and survival (Evans et al. 2006). Trophoblasts can produce melatonin (Lanoix et al. 2008), N-acetylserotonin and probably serotonin. It remains to be determined as to whether vit D3 modulates such serotonin-melatonin paths in trophoblasts, either directly and/or via its inhibition of NK cells. This would seem another potential site for vit D3 and melatonin interactions that would be relevant to an early developmental etiology to schizophrenia.

Seasonal variations often occur in both vit D3 and melatonin, and this may have some relevance to the seasonal variations that are known to occur in the levels of the serotonin transporter (SERT). The increase in winter SERT (Praschak-Rieder et al. 2008), and presumably a decrease in available serotonin, may make some contribution to the season of birth effect associated with schizophrenia (Watson and McDonald 2007). It is unknown as to whether such seasonal variations in the levels of SERT also occur in the placenta. Serotonin effects in the placenta are currently being investigated in the context of preeclampsia, so any seasonal variations in SERT may have relevance to other early developmental susceptibility factors. Again it is not known if the proven interactions of melatonin and vit D3 would be relevant in this context. The seasonal fluctuations in melatonin and vit D3 do contribute to altered immune responses, as well as having direct effects on CNS development, driving season of birth influences on the development of schizophrenia.

General etiology pathways

A general corollary of both maternal stress/infection and preeclampsia is a decrease in the levels of placental 11b-Hydrosteroid-dehydrogenase type 2 (11b HSD2), increasing cortisol to both the placenta and the foetus (Aufdenblatten et al. 2009; Causevic and Mohaupt 2007). Such cortisol effects on foetal development include a decrease in neurogenesis, and an increase in the renin-angiotensin system (RAS) both centrally and peripherally. The changes in the RAS lead to increases in childhood and adult blood pressure, and increases in adult hypertension susceptibility (Reynolds et al. 2009). Melatonin decreases hypertension and increases neurogenesis and will directly inhibit cortisol's prenatal effects (Rennie et al. 2009).

Chronic unpredictable mild stress (CUMS) leads to an increase in the levels of quinolinic acid (QA) in the amygdala and striatum, and a trend increase in kynurenic acid (KYNA) in the frontal cortex (Laugeray et al. 2010). In the context of neurodegenerative disease, stress induced cortisol, at least transiently, increases interleukin-18 (IL-18) (Anderson and Ojalla 2010). IL-18 levels positively correlate with increased cortisol (Kristo et al. 2002) and are increased in schizophrenia (Reale et al. 2011). IL-18, independent of gamma-Interferon (IFNy), can increase indoleamine-2,3-dioxygenase (IDO) (Anderson 2011), including in microglia. This would lead to an increase in QA induced N-methyl D-aspartate receptor (NMDAr) activation, with excitotoxicity occurring at higher concentrations (Anderson and Ojalla 2011). Would prenatal stress/infection or preeclampsia induced increases in placental cortisol transfer also increase IL-18 and the tryptophan catabolite (TRYCAT) pathway, especially in the prefrontal cortex, amygdala and striatum, paralleling the effects of CUMS? This would drive tryptophan down the TRYCAT pathway and away from melatonin and serotonin production (Anderson 2011). This remains to be examined, but such putative effects of cortisol are likely to be inhibited by both melatonin and vit D3, perhaps acting synergistically. Activation of the TRYCAT pathway additionally could explain the low melatonin levels that are frequently found in schizophrenia.

Accumulating data shows an increase in KYNA in the frontal cortex in schizophrenia (Miller et al. 2006), and this is thought to contribute to the evident cognitive deficits and hypofrontality (Zmarowski et al. 2009). Tryptophan 2,3-dioxygenase type 2 (TDO2) is a susceptibility gene for schizophrenia (Miller et al. 2009) suggesting that an increase in astrocyte KYNA production is a significant susceptibility and maintenance factor in psychosis. Cortisol significantly induces TDO and therefore KYNA, contributing to cortex inhibition and

cognitive deficits. Melatonin and vit D3, via increased BAG-1, would be expected to inhibit cortisol's induction of TDO. Astrocyte TDO and KYNA production can also be potentiated by the cAMP/PKA pathway (Luchowska et al. 2009). Melatonin is a significant inhibitor of the cAMP path, and therefore would be expected to make some contribution to the inhibition of KYNA induced cognitive deficits and hypofrontality in schizophrenia. Melatonin has been shown to have a positive impact on cognitive processing in a stress paradigm (Rimmele et al. 2009), and is therefore likely to modulate stress effects on cognition in the etiology and course of schizophrenia.

The role of the TRYCAT pathways in schizophrenia is further highlighted by the data showing increased tryptophan breakdown and associated inflammatory markers (Kim et al. 2009). Also the importance of the TRYCAT, 3-hydroxykynurenine (3-OHK), is emphasized by its altered level in schizophrenia and in its significant associations with both clinical symptoms and response to treatment (Condray et al. 2011; Myint et al. 2011). As to how melatonin would interact with level of expression of, and antipsychotic induced changes in, specific TRYCATs remains to be examined.

Melatonin, sleep and schizophrenia

Sleep disturbance occurs in over 80 % of people with schizophrenia, with many showing severe circadian and melatonin misalignment, which can occur despite stability in mental state and mood (Wulff et al. 2012). Such sleep disturbance is associated with poor quality of life and may be particularly evident when positive symptoms are present (Afonso et al. 2011a). One study shows not only improved sleep, but also improved mood and daytime functioning in a random control trial of adjunctive melatonin in schizophrenic patients (Suresh Kumar et al. 2007). Given the commonly found decrease in melatonin production at night in schizophrenia (Bersani et al. 2003), this would suggest that melatonin could have wider benefits on patient quality of life. However, It has been suggested that the sleep-promoting effects of melatonin may be altered in schizophrenia (Afonso et al. 2011b).

Potential utility of melatonin adjunctive to anti-psychotics

Anti-psychotic induced metabolic syndrome in schizophrenia is associated with increased hypertension, undoubtedly contributing to decreased life expectancy in schizophrenia (Chwastiak and Tek 2009). Melatonin is a peripheral vasodilator decreasing blood pressure. Its maintenance of sirtuin-1 levels in neurons under challenge (Chang et al. 2009), gives it links to pathways that have been classically associated with increases in longevity (Cantó and Auwerx 2009). Melatonin decreases obesity and increases mitochondria oxidative phosphorylation (Martín et al. 2002), in turn decreasing metabolic syndrome. As with neuroleptics, both lithium and valproate have metabolic side effects, including weight gain and glucose dysregulation (Bushe and Leonard 2007; Tardieu et al. 2003). Melatonin affords protection against these side effects (Shieh 2009; Sartori et al. 2009).

Olanzapine in rodents decreases melatonin by 55 % (Raskind et al. 2007). However, in a short duration trial, olanzapine was found to have no significant impact on melatonin levels in a sample of schizophrenic patients (Mann et al. 2006). This requires replication over a longer time frame. There is only one ongoing clinical trial looking at the effects of melatonin in offsetting the side effects of olanzapine in psychosis (Kilzieh, clinicaltrials.gov). Given the above, it would seem not unlikely that melatonin would inhibit these longevity decreasing antipsychotic side effects. Among the anti-psychotics clozapine is especially associated with an increased risk of pneumonia, particularly at the time of initial prescription (Kuo et al. in press). The susceptibility to pneumonia will be modulated by variations in vit D and the vit D regulation of the endogenous anti-microbial cathelicidin (Leow et al. 2011). Decreased cathelicidin induction by vit D increases the risk of, and mortality from, pneumonia. Melatonin has efficacy in attenuating bacteria induced lung inflammation in animal models (Lee et al. 2009). In a pilot study, melatonin has shown clinical utility in the management of pneumonia and COPD (Shilo et al. 2000), particularly in the regulation of sleep, which is often disturbed in these lung disorders. Given the cell-mediated immune and inflammation model of schizophrenia and the effects of clozapine within this model (Maes et al. 1994), the optimization of melatonin and vit D at the time of the initial prescribing of antipsychotics may help to decrease the likelihood of pneumonia emerging as a side effect.

Tardive dyskinesia (TD) is a serious adverse effect often associated with the first generation antipsychotic medications used in the management of schizophrenia. A number of risk factors for TD have been found, including the single nucleotide polymorphisms in the dopamine D3 receptor (Utsunomiya et al. 2012) and TNFa (Wang et al. 2012). In relatively small samples of schizophrenia patients, melatonin, at a low dose (2 mg/day), does not seem to have any significant impact on TD (Shamir et al. 2000). However at 10 mg/day melatonin significantly decreases TD (Shamir et al. 2001). Recent interest in the treatment of TD has centred on the utility of anti-oxidants, including melatonin (Lerner and Miodownik 2011).

Conclusions

In summary, melatonin plays a role in the pathophysiology, developmental etiology, course and treatment of schizophrenia.

Its optimization, along with vit D3, could significantly attenuate the development of psychosis, and the extent of psychotic symptoms. At the very least, it would be expected to decrease anti-psychotic side effects, and decrease the hypertension, sleep disorders, glucose dysregulation, obesity and tardive dyskinesia as well as increasing the longevity of a population of people whose life expectancy is 25 years less than the general population (Flaum 2010).

Declaration of financial interests None.

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