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Sleep disturbance and kynurenine metabolism in depression

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ABSTRACT

Objective: Although the interrelationships between sleep disturbance, inflammation, and depression have been found, molecular mechanisms that link these conditions are largely unknown. Kynurenine metabolism is hypothesized to be a key mechanism that links inflammation and depression. Inflammation activates the kynurenine pathway, leading to increases in 3-hydroxykynurenine (3HK) and quinolinic acid (QA), potentially neurotoxic metabolites, and decreases in kynurenic acid (KynA), a potentially neuroprotective compound. This relative neurotoxic shift in the balance of kynurenine metabolites has been associated with depression, but never been examined regarding sleep disturbance. We tested the association between sleep disturbance and this relative neurotoxic shift in 68 currently depressed, 26 previously depressed, and 66 never depressed subjects.
Methods: Sleep disturbance was assessed using the Pittsburgh Sleep Quality Index. Serum concentrations of kynurenine metabolites were measured using high performance liquid chromatography. Putative neuroprotective indices reflecting the relative activity of neuroprotective and neurotoxic kynurenine metabolites were calculated as KynA/QA and KynA/3HK (primary outcomes).
Results: Sleep disturbance was associated with reduced KynA/QA in the currently depressed group only (unadjusted beta -0.43, $p < 0.001$). This association remained significant even after controlling for age, sex, analysis batch, body-mass index, and depressive symptoms in currently depressed subjects (adjusted beta -0.30, $p = 0.02$). There was no significant association between sleep disturbance and KynA/3HK in any of the groups. Sleep disturbance was associated with increased C-reactive protein in currently depressed subjects only (unadjusted beta 0.38, $p = 0.007$; adjusted beta 0.33, $p = 0.02$).
Conclusion: These data support the hypothesis that altered kynurenine metabolism may molecularly link sleep disturbance and depression.

1. Introduction

Sleep disturbance, characterized as insomnia complaints and extremes of sleep duration, has a major public health impact because approximately 25% of the US population report insomnia symptoms [1] and almost 10% fulfill diagnostic criteria for chronic insomnia [2–4]. Furthermore, sleep disturbance increases the risk of several major medical and mental illnesses including infectious disease, cardiovascular disease, cancer, and depression, ultimately contributing to all-cause mortality [5–10]. Depression by itself is also a major public health burden because it is highly prevalent—the lifetime prevalence of major depression is almost 20% in the US general population [11]—and it represents a leading cause of disability worldwide [12].

Although sleep disturbance is an important risk factor for depression [7,13,14] and thus a prime target for depression prevention [15,16], the mechanisms underlying this association remain poorly understood. Inflammation is one potential mechanism underlying the relationship between sleep and depression; sleep disturbance increases inflammation [17–23], which in turn causally contributes to or is intimately associated with certain forms of depression occurring in the context of immune-activating treatments (e.g., interferon-α) or chronic diseases (e.g., cardiovascular, infectious, and autoimmune) [24–26]. Poor sleep

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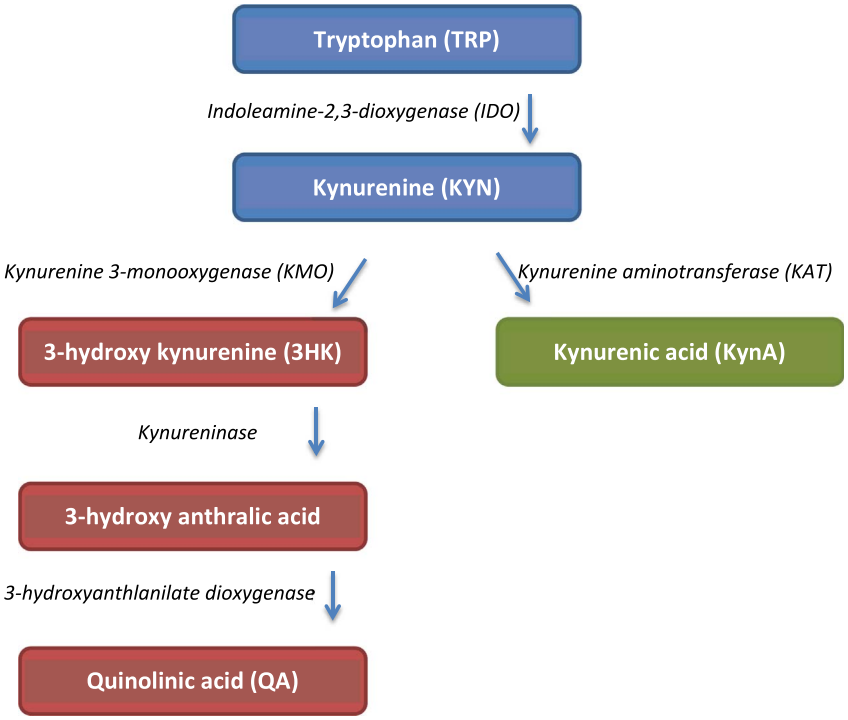

Fig. 1. Main branches of the kynurenine pathway. Each box represents a metabolite resulting from the oxidation of tryptophan. Putative neurotoxic metabolites are colored red whereas KynA, which is putatively neuroprotective, is colored green. The black italicized text shows the enzymes that catalyze each step in the metabolic pathway. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

quality strongly predicts risk for developing major depressive disorder during interferon-α treatment [27]. We have shown that preexisting mild sleep disturbance increases vulnerability to inflammation-induced depression in a human experimental model using endotoxin [28]. However, the downstream molecular mechanisms underlying the link between sleep disturbance, inflammation, and depression are not yet clear.

Inflammatory mediators activate indoleamine 2,3 dioxygenase (IDO), an enzyme that metabolizes tryptophan (TRP) to kynurenine (KYN); hence the ratio of kynurenine/tryptophan (KYN/TRP) represents a measure of IDO activity. In turn, KYN is metabolized into 3-hydroxykynurenine (3HK) by the enzyme kynurenine monooxygenase (KMO), which is also upregulated under inflammatory conditions [29,30], leading to an increase in quinolinic acid (QA) on the putatively neurotoxic branch of the kynurenine pathway (Fig. 1). Concurrently, these inflammation-induced metabolic steps lead to a relative decrease in kynurenic acid (KynA) on the putatively neuroprotective branch of the kynurenine pathway. While 3HK is a free radical generator and QA is an *N*-methyl-D-aspartate (NMDA) receptor agonist that has been associated with a plethora of neurotoxic effects, KynA is an antagonist of NMDA receptors [31,32] and is protective against the excitotoxic action of QA [33,34]. Neuroprotective indices of kynurenine metabolites calculated as KynA/QA and KynA/3HK reflect the relative activity of the two distinct branches of the kynurenine pathway [35]. Activation of glutamate receptors—specifically NMDA receptors—by excessive QA could conceivably cause neuronal damage through the process of excitotoxicity, ultimately leading to the development of depression [36].

Kynurenine metabolism is increasingly recognized as a potential mechanistic pathway in the link between inflammation and depression. For example, when activation of the kynurenine pathway is genetically or pharmacologically blocked, systemic immune stimulation (i.e., lipopolysaccharide administration) fails to induce depression-like behavior in rodents, which would otherwise occur following increases in levels of pro-inflammatory cytokines [37,38]. Similarly, in studies of patients with inflammatory diseases or patients treated with interferon-α, there is a robust association between depressive symptoms and the production of neurotoxic kynurenine metabolites, implicating the kynurenine pathway as a potential mechanism [39–41]. Additionally, several cross-sectional studies have reported that patients with depressive spectrum disorders, including major depression [42,43], bipolar depression [44], and suicidality [45,46], display a decrease in KynA and/or an increase in 3HK or QA in blood [42–44] and CSF [45,46]. Further, electroconvulsive therapy was demonstrated to significantly reduce QA [43] and increase KynA as well as KynA/3HK [47] in patients with depression. However, it should be noted that there have also been more nuanced or negative findings regarding the role of the kynurenine pathway in depression pathophysiology. For example, in one study, somatization but not depression was characterized by disorders in the kynurenine pathway [48]; and in another study, kynurenine pathway markers were not significantly different between patients with major depressive disorder and healthy controls [49].

In sum, sleep disturbance is associated with higher levels of inflammation [17], and kynurenine metabolism is increasingly recognized as a potential pathway linking inflammation to depression [50]. However, the relationship between sleep disturbance and kynurenine metabolism has never been examined in depressed subjects. This study aimed to examine the associations between sleep disturbance and kynurenine metabolism in currently depressed, previously depressed, and never depressed subjects. We hypothesized that sleep disturbance would be associated with reduced neuroprotective indices of circulating kynurenine metabolites (i.e., reductions in the ratio of neuroprotective KynA relative to neurotoxic 3HK and QA). We tested this hypothesis in currently depressed, previously depressed, and never depressed subjects using a cross-sectional study design. Furthermore, consistent with prior findings, we hypothesized that sleep disturbance would be associated with increased systemic inflammation as assessed by circulating high-sensitivity C-reactive protein (hs-CRP). Lastly, the associations between sleep disturbance and biomarkers of inflammation and kynurenine metabolism would be stronger among currently depressed subjects