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Elevated plasma orexin A levels in a subgroup of patients with schizophrenia associated with fewer negative and disorganized symptoms

Yi-Ling Chien[a,b,c], Chih-Min Liu[a,b,d], Jia-Chi Shan[a,b,e], Hsin-Jung Lee[f], Ming H. Hsieh[a,b,g], Hai-Gwo Hwu[a,b,d,g], Lih-Chu Chiou[d,f,g,h,*]

[a] *Department of Psychiatry, College of Medicine, National Taiwan University, Taipei, Taiwan*
[b] *Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan*
[c] *Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan*
[d] *Graduate Institute of Brain and Mind Sciences, College of Medicine, National Taiwan University, Taipei, Taiwan*
[e] *Department of Psychiatry, Cathay General Hospital, Taipei, Taiwan*
[f] *Department of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan*
[g] *Neurobiology and Cognitive Science Center, College of Medicine, National Taiwan University, Taipei, Taiwan*
[h] *Graduate Institute of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan*

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Summary
Background: Orexin A and B, a pair of hypothalamic neuropeptides also named hypocretin 1 and 2, play a role in the regulation of arousal, appetite, reward, attention, and cognition. Animal studies showed that antipsychotics can activate orexin neurons in a manner correlated with their weight gain liability. However, little is known about the role of orexin in patients with schizophrenia. This study aimed to investigate the correlation of plasma orexin level with clinical symptom profile, neurocognitive functioning and weight gain liability of the antipsychotics taken in patients with schizophrenia.
Methods: We measured plasma levels of orexin A in 127 patients with schizophrenia and 34 healthy controls by radioimmunoassay. In patients, we assessed clinical symptoms on the

Abbreviations: CSF, cerebrospinal fluid; CPZ, chlorpromazine; PANSS, the Positive and Negative Syndrome Scale; PFC, prefrontal cortex; RIA, radioimmunoassay; WCST, Wisconsin Card Sorting Test.

* Corresponding author at: Department of Pharmacology, College of Medicine, National Taiwan University, No. 1, Jen-Ai Rd., Section 1, Taipei 100, Taiwan. Tel.: +886 2 2312 3456x88323; fax: +886 2 2341 4788.
E-mail address: lcchiou@ntu.edu.tw (L.-C. Chiou).

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Positive and Negative Syndrome Scale and executive function by the Wisconsin Card Sorting test (WCST), and examined their associations with plasma orexin A level.
Results: Patients with schizophrenia had a significantly higher mean orexin A level than healthy controls (60.7 ± 37.9 *vs.* 38.8 ± 15.5 pg/ml). Patients were divided into two subgroups based on their orexin A levels that were distributed in two clusters divided by 80 pg/ml. Patients in the high-orexin subgroup had significantly fewer negative and disorganized symptoms, and tended to have fewer perseverative errors, more failure to maintain set yet comparable category achieved on the WCST than the normal-orexin subgroup. There was no significant difference in orexin A levels among patients taking antipsychotics with different weight gain liabilities.
Conclusion: Higher level of orexin A seems to be related to favorable clinical symptom profiles of schizophrenia, but the causal relationship needs further clarification.

1. Introduction

Orexin A and B, two hypothalamic neuropeptides also known as hypocretin 1 and 2, are endogenous ligands of a pair of Gq-protein coupled receptors, orexin 1 receptor (OX1R) and orexin 2 receptor (OX2R) (de Lecea et al., 1998; Sakurai et al., 1998). Orexin-containing neurons are located only in the lateral hypothalamus and perifornical area. However, their projection fibers are widely distributed in the central nervous system, including the basal forebrain, thalamus, and prefrontal cortex (PFC), crucial areas involved in attention and cognitive functions (Peyron et al., 1998).

In animal studies, orexins have been found to play an important role in attention (Fadel and Burk, 2010). In sustained and divided attention tasks, rats with the orexinergic fiber de-afferentation in the PFC showed impaired performance (Newman et al., 2007). Besides, intra-PFC infusion of orexin B improved the accuracy of high attention demand tasks in rats (Lambe et al., 2005). In a human study, Weinhold et al. (2014) also found a better performance in the divided attention test in narcolepsy patients treated with intra-nasal orexin A than in saline-treated ones.

It has been reported that patients with schizophrenia have a higher rate of cigarette smoking than patients with other psychiatric diagnoses or without definite psychiatric diagnoses (Kumari and Postma, 2005). Nasal spray nicotine can reduce psychiatric symptoms and enhance cognition, including attention and working memory, in patients with schizophrenia (Smith et al., 2006). Interestingly, orexin B was found to display the same neuronal excitatory effect as nicotine in rat brain slices containing the PFC (Lambe et al., 2005). Nicotine-induced improvement of attention and working memory in rats (Hahn et al., 2003) was attributed to its activation of orexin neurons (Pasumarthi and Fadel, 2008). It is unclear whether this also applies to humans, but it suggests that smoking status should be controlled in the analysis of neurocognitive performance.

In a comprehensive animal study, Fadel et al. (2002) found that antipsychotics activated hypothalamic orexin neurons and the activation magnitudes are well-correlated with their weight gain liabilities clinically. Hypothalamic orexin neuron activation in rodents can release orexins that activate dopamine neurons in the ventral tegmental area, increasing dopamine levels in the PFC and/or striatum (Rasmussen et al., 2007a,b). The therapeutic response to antipsychotics is proposed to be positively correlated with their weight gain liability (Meltzer et al., 2003; Ascher-Svanum et al., 2005). Therefore, it is suggested that the therapeutic efficacy of the antipsychotic is associated with its ability in increasing PFC dopamine level due to orexin neuron activation (Deutch and Bubser, 2007).

The orexin system is also involved in anxiety and depression (Yeoh et al., 2014) as well as fatigue (Papuc et al., 2010), which are frequently manifested in patients with schizophrenia. Orexin receptor antagonists reduced stress-induced, but not basal, anxiety-like behaviors in rodents (Johnson et al., 2010; Plaza-Zabala et al., 2010; Heydendael et al., 2011; Staples and Cornish, 2014). A human study also demonstrated an association between OX2R polymorphism and panic disorder (Annerbrink et al., 2011). Intracerebral injection of orexin A in mice reduced depressive-like behaviors (Ito et al., 2008). Lower orexin level or reduced orexin neuron number has been reported in several animal models of depression (Allard et al., 2004; Lutter et al., 2008; Nocjar et al., 2012). Human studies also showed that depressed patients had lower orexin levels in the cerebrospinal fluid (CSF) (Brundin et al., 2007a,b) and that their depression scores were negatively correlated with orexin A levels in the CSF (Brundin et al., 2007a,b, 2009) and orexin mRNA transcripts (Rotter et al., 2011). Genetic studies also showed associations between OX1R polymorphism and major mood disorders, and between elevated orexin CSF level and positive emotions and social interaction (Rainero et al., 2011; Blouin et al., 2013). The involvement of orexin in fatigue has been proposed by the finding of a negative correlation between orexin A levels and fatigue symptoms in patients with multiple sclerosis (Papuc et al., 2010). Recently, orexin A was found to restore chemotherapy-induced fatigue in rodents, suggesting that suppression of hypothalamic orexin neuron activity has a causal role in cytotoxic chemotherapy-induced fatigue (Papuc et al., 2010).

To the best of our knowledge, there is no study investigating the association of orexin level with clinical symptoms, cognitive function, or the weight gain liability of the antipsychotic in patients with schizophrenia. Therefore, in this study, we measured and compared plasma levels of orexin A in patients with schizophrenia and normal controls, aiming to explore the correlations of plasma orexin level with clinical symptom profiles, cognitive functions and the weight-gain liability of taken antipsychotics in patients with schizophrenia.