

MODULATION OF LEPTIN BY HISTAMINE H1 RECEPTORS AS A NOVEL THERAPEUTIC APPROACH FOR TREATMENT OF CLOZAPINE INDUCED SEIZURE

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According to the WHO adverse drug reactions database, clozapine is one of the neuroactive drugs most frequently associated with convulsion (Kumlien and Lundberg 2010). So, the use of clozapine in the elderly is extremely limited by the possibility of side effects such as seizures, weight gain and metabolic effects (Gareri et al. 2008). The incidence of side effects of clozapine in children is higher, and it is a second-line medication for children with refractory schizophrenia (Gogtay and Rapoport 2008). Now, some of the recommended strategies to decrease clozapine related seizures are dose reduction, changing medication to typical antipsychotics (Behere et al. 2009), and prophylactic antiepileptic treatment (Herceg et al. 2010).

While, to the best of author's knowledge, there are many reports about the association of clozapine and seizure, the underlying mechanism for this association is not clear. Herein, considering the following evidence, a possible novel explanation for this association is provided. Finally, studies and clinical implications are mentioned.

Atypical antipsychotics increase leptin level (Sentissi et al. 2008). There are many studies which indicate that treatment with clozapine is also associated with an increased level of leptin (Hagg et al. 2001). Olanzapine is another atypical antipsychotic drug which may increase leptin level as does clozapine in patients with schizophrenia (Melkersson et al. 2000; Melkersson and Hulting 2001; Kluge et al. 2009). The elevated leptin level is accompanied with a lack of food intake reduction suggesting drug-induced leptin insensitivity in the hypothalamus (Reynolds & Kirk 2010).

Clozapine or olanzapine probably acts as an antagonist at the postsynaptic histamine H1 receptors which is a suggested receptor for downstream signaling of leptin. This activity may increase leptin level (Masaki and Yoshimatsu 2006). So, histamine H1 receptor agonists may decrease leptin (Masaki and Yoshimatsu 2006). In addition, the administering of the histamine H1 receptors agonist and histamine-3 receptor antagonist histidine (that increases the neurotransmission of histamine) with olanzapine decreases weight gain (Poyurovsky et al. 2005).

On the other hand, there are contradictory reports about the role of leptin in seizure. While some studies

suggested that leptin may have a therapeutic role in the treatment of seizure (Diano and Horvath 2008) and intranasal leptin administration is suggested for the management of seizure in emergency situations (Xu et al. 2008). A review article reported increased blood levels of leptin in patients with epilepsy (Hamed 2007).

Given that atypical antipsychotics such as clozapine increase leptin level (Sentissi et al. 2008; Kluge et al. 2009), the increased level of leptin in some patients with epilepsy (Hamed 2007), the possible antagonistic effect of clozapine on histamine H1 receptors (Masaki and Yoshimatsu 2006), and the role of histamine H1 receptor agonists for decreasing leptin level (Masaki and Yoshimatsu 2006), it is hypothesized that leptin may be an important link between weight gain, epilepsy and atypical antipsychotics such as clozapine. It is worthwhile to conduct translational clinical studies to investigate this. This hypothesis may open novel therapeutic approaches for children taking atypical antipsychotics and suffering seizures.

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