



## Does olanzapine impair pancreatic beta-cell function directly?

Takahiko Nagamine, M.D., Ph.D.

*Division of Psychiatric Internal Medicine, Ishii Memorial Hospital,  
3-102-1 Tada, Iwakuni City, Yamaguchi, 741-8585, Japan*

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The metabolic disturbance caused by second-generation antipsychotics (SGAs) is not a class effect because SGAs differ in many of their properties. The risk is higher for antipsychotics having a tricyclic ring structure, including olanzapine, clozapine, and quetiapine [1]. It is speculated that this chemical structure of antipsychotics may be the underlying factor of the metabolic disturbance. Although it had been assumed that their affinity for serotonin 2C receptors and histamine H1 receptors resulted in increased appetite and obesity, their chemical structure may damage insulin secretion directly. Does olanzapine impair pancreatic beta-cell function in the absence of body weight gain?

Olanzapine and clozapine were found to induce insulin resistance and decrease insulin sensitivity in the intravenous glucose tolerance test for non-obese patients [2]. SGA-naïve schizophrenic patients showed decreased insulin secretory response to a hyperglycemic challenge after 2 weeks of olanzapine treatment, suggesting that olanzapine initially acted directly on beta cells and decreased insulin secretion [3]. Chronic schizophrenic patients treated with olanzapine showed an increase in the level of remnant-like lipoprotein that was not related to obesity and insulin resistance, suggesting that olanzapine decreases insulin secretion [4]. Sporadic cases of rapid-onset diabetes induced by the use of olanzapine have been reported in the literature [5][6][7]. In these cases, the patients were negative for anti-glutamic acid decarboxylase (anti-GAD) antibodies, which indicate type 1 diabetes, and the discontinuation of olanzapine therapy and a careful insulin replacement treatment regimen reversed their diabetes. This suggested that

their insulin secretion was temporarily impaired by olanzapine.

The question is then: Is olanzapine the cause of adverse event signals of diabetes or absolute insulin deficiency in pharmacoepidemiological studies? There is a famous database known as the Adverse Events Reporting System (AERS), in which data since 1997 are available online. Japan's National Institute of Health Sciences used Bayesian statistics to analyze the AERS database, and the author participated in this analysis. There were significantly more reports of diabetes associated with olanzapine, quetiapine, and risperidone than with aripiprazole or haloperidol [8]. Which agents are more likely to cause the conditions of absolute insulin deficiency, such as diabetic coma and diabetic ketoacidosis? Baker and colleagues [9] conducted a detailed study of diabetes-related adverse events using the AERS database. Their study showed that the incidence of detectable signals of diabetic coma and ketoacidosis was extremely high for olanzapine, followed by clozapine and quetiapine [9]. There is a relatively new signal detection method called prescription sequence symmetry analysis (PSSA). PSSA analyzes the asymmetry in the prescribed agents using sequence ratios. For example, if insulin is prescribed for severe hyperglycemia or absolute insulin deficiency caused by an antipsychotic agent, the temporal sequence would show that the prescription of insulin is preceded by the prescription of the antipsychotic agent. Such sequence asymmetry is used to detect an adverse event signal. Most of the databases showed that the use of olanzapine tended to increase the use of insulin. The USA-Public data

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Corresponding Author: Takahiko Nagamine, M.D., Ph.D., Division of Psychiatric Internal Medicine, Ishii Memorial Hospital, 3-102-1 Tada, Iwakuni City, Yamaguchi, 741-8585, Japan  
e-mail: anagamine@yahoo.co.jp

(adjusted sequence ratio [ASR]: 1.14, 95%CI: 1.10-1.17) and the Swedish data (ASR: 1.53, 95%CI: 1.13-2.06) revealed a significant difference [10]. Thus, according to pharmacoepidemiological studies, olanzapine is highly likely to induce absolute insulin deficiency.

The basic mechanism explaining these clinical phenomena is as follows. Olanzapine has an undue influence on unfolded protein response in the endoplasmic reticulum (ER), which is required for insulin secretory homeostasis. Protein folding is the last hurdle for expression of genome information. The ER stress sensor molecule, protein kinase R-like ER kinase (PERK), and its downstream effector, the alpha subunit of eukaryotic translation initiation factor 2 (eIF2 $\alpha$ ), have a profound impact on islet cell function and survival. Under physiological conditions, activation of this PERK-eIF2 $\alpha$  pathway leads to reduced rates of initiation of protein translation during ER stress, which results in reduced ER stress. As a pathological example, PERK-deficient mice exhibit progressive diabetes due to sustained ER stress [11]. Olanzapine evoked mild ER stress, as evidenced by mild activation of the ER stress sensor molecule PERK on a hamster pancreatic beta cell line. However, phosphorylation of eIF2 $\alpha$  was not observed in cells treated with olanzapine. Thus, protein synthesis continued despite PERK activation, and ER stress was sustained, which resulted in marked apoptosis of beta cells by olanzapine [12]. Antipsychotic structural differences may be key to the effect on eIF2 $\alpha$  [13]. It is speculated that the chemical structure of olanzapine interferes with recruitment of eIF2 $\alpha$  by interacting with PERK's large kinase insert loop, which is particularly important when PERK is only mildly activated [12].

In conclusion, olanzapine seems to directly impair pancreatic beta cell function. Asians are said to have about one-half of the insulin secretion ability of Caucasians. Impaired insulin secretion is a more common problem than insulin resistance in Japanese people [14]. Therefore, it is important to look closely at the direct action of olanzapine on insulin secretion in Japanese patients. In cases treated with olanzapine, clinicians should monitor serum levels of both insulin and glucose.

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