5-HT_3 Receptor Antagonists: New Promising Therapeutic Agents in Diabetes and Its Complications

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The role of serotonin and its diverse serotonin (5-HT) receptors has been investigated in glucose metabolism and pathogenesis of diabetes. In rats, activation of central serotonergic system induces hyperglycemia which can be reverted by prior administration of a serotonin type 3 (5-HT_3) receptor antagonist, ondansetron, indicating the involvement of 5-HT_3 receptor subtype in this hyperglycemic effect. Of note, tropisetron, another 5-HT_3 receptor antagonist, was found to enhance the insulin release by INS-1 cells. The effect was interestingly more pronounced in the presence of serotonin at the highest concentration used (500 μM). Serotonin *per se* reduced the glucose-stimulated liberation of insulin in a concentration-dependent fashion, while tropisetron abolished this inhibition. Such observation points out the involvement of 5-HT_3 receptors in tropisetron-induced insulin secretion (1,2). The underlying mechanism concerning secretagogue action of 5-HT_3 antagonists is, however, wrapped up in obscurity as the main target for classical insulin secreting agents is inhibition of ATP sensitive potassium channels leading to Ca^{+2} entry and beta cell depolarization (3). 5-HT_3 ion channel blockade, in contrast, is associated with a reduction in inward cation currents, in particular Ca^{+2}. We and others showed that 5-HT_3 receptor antagonist, tropisentron can inhibit calcineurin activity in neuron and lymphocytes. Interestingly although conventional calcineurin inhibitors (cyclosporine and tacrolimus) lead to hyperglycemia via calcineurin/NFAT pathway, tropisetron exerts notable anti-inflammatory properties without affecting the blood glucose levels. Alongside these promising effects 5-HT_3 receptor antagonists have potential to combating diabetes related complications such as neuropathy, memory impairment and depression (4). Ample evidence implicates the role of 5-HT_3 receptor subtype in pain and inflammation. The analgesic effect of 5-HT_3 antagonists emerges from their aptitude to inhibit the release of sensory neuropeptides which trigger the development of neurogenic inflammation (5). 5-HT_3 receptor antagonists tropisetron and ondansetron enhanced ACh release in human cortical tissue via blocking the inhibitory effect of 5-HT. Moreover, new investigations indicate that 5-HT_3 receptor antagonists protect against beta-amyloid-induced apoptosis in cortical primary cell cultures (3). Recent researches showed that classic antidepressants are functional antagonists at 5-HT_3 receptor, and this antagonism may constitute a novel pharmacological principle of antidepressants (6).

According to vast pharmacological effects of 5-HT_3 receptor antagonists many of which have potential to be considered in attenuation diabetes complications, they can be scrutinized in diabetes research.

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