



Utilization of a Pyrrolidin-2-One Based Nonselective α -Adrenoceptor Antagonist for Metabolic Syndrome (MetS) Therapy Along with Histamine H3 Inverse Agonist Pitolistant in High Fat Diet Induced Obesity in Mice and Future Role in Humanbeing

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The metabolic syndrome (MetS) by definition is the presence of 3/5 symptoms at the same time, like abnormal fasting glycaemia, abdominal obesity, increased blood pressure (BP), hypertriglyceridaemia and low amounts of high density lipoprotein (HDL) [1]. With MetS chances of acquiring serious problems like type2 diabetes mellitus (T2DM), coronary heart disease (CHD), Ischemic stroke and atherosclerosis is present. Statistics conducted recently display that MetS takes place in 20-25% of adult population which has taken epidemic levels [2]. With it becoming a big therapeutic problem in developed countries, emphasis is being laid on producing efficacious, safe cures.

Earlier researchers had displayed that an enhanced activation of sympathetic nervous system (SNS) correlates with various parts of MetS. Like the adrenergic nervous system has a crucial role in inducing along with increments of BP, changes in the cardiac output, peripheral vascular resistance along with regulating triglyceride and glucose metabolism [3]. Sympathetic nerve activation has been documented to be much > in patients with MetS, in contrast to healthy subjects [4]. Further on concomitant presence of obesity and hypertension > sympathetic nerve activation is observed in MetS subjects as compared to patients presenting with a single disease [5]. Thus inhibiting adrenergic nervous system becomes a proper method of curing MetS components [6].

The α -adrenoceptor system appears to be an attractive molecular target, as many of the unwanted reactions get manifested

through activation of MetS, like vasoconstriction, along with release of free fatty acid (FFA) and glucose. There has been a posit that especially non-selective adrenoceptor antagonists might help the MetS patients [7]. Inactivating α 1-adrenoceptor results in vasodilation, with fall of BP [8]. Further the α 1-adrenoceptor antagonists cause a positive action on lipid and carbohydrate profiles [9]. Blockade of α 2-adrenoceptor by antagonists caused a reduction in body weight because of enhanced catecholamine liberation, along with SNS stimulation and lipolysis and thermogenesis getting induced [10]. Further α 2-adrenoceptor antagonists also may manipulate pancreatic function and abnormal insulin secretion in a promising manner [11]. Over last some years marked work on pyrrolidin -2-one derivatives and its pharmacological activity has been carried on. The structure activity relationship (SAR) within this group of compounds showed that they have a great affinity for the α -adrenoceptors and cause an antagonistic activity [12,13]. Till now pyrrolidin -2-one derivatives have shown anti-arrhythmic and anti-hypertensive actions [8,14], and decrease body weight in animal obesity models [15]. Thus Katanska, *et al.* aimed to find the metabolic advantages of delivering a nonselective α -adrenoceptor antagonists from the group of pyrrolidin -2-one derivatives. The α 1 and α 2-adrenoceptor affinities of the compounds tested-1-(3-(4-(o-tolyl)piperazin-1-yl)-propyl) pyrrolidin -2-one had been evaluated earlier by the radioligand binding assay. Now they further expanded the pharmacological profile properties of the selected

molecules by extra intrinsic activity assays. After that the influence of the tested compound on body weight, hyperglycemia, hypertriglyceridemia, BP in the animal model of obesity induced using a high fat diet (HFD) and further they measured spontaneous activity and body temperature. The intrinsic activity assays showed that the compounds evaluated is a potent nonselective α -adrenoceptors antagonist of α 1B and α 2A adrenoceptors. Following chronic delivery of the tested compound, decreased levels of enhanced triglycerides and glucose were seen in the rat plasma. But the tested compound did not cause a decrease in body weight and had no effect on BP on testing in normotensive rats. Further no changes in spontaneous activity and body temperature of the animal was observed. Thus concluding that nonselective α -adrenoceptors antagonist appeared to have a potential advantage in normalizing the enhanced triglycerides and glucose amount. Absence of effect on BP pointed that the compounds with this type of pharmacological profile might be of help in patients having altered lipid and carbohydrate profile, who don't have hypertension. These results are especially important, as right now no safe α 2A-adrenoceptor antagonist agents present in clinical arena having the capacity to manipulate hyperglycemia without changing the BP [16].

Histamine H3 receptors as compared to presynaptic inhibitors autoreceptors in the central nervous system (CNS), i.e. inverse agonists and antagonist of these receptors enhance the synthesis along with release of histamine [17]. Histamine by itself may control food intake and metabolic disturbances by affecting the histamine H1, H2 and H3 receptors [18]. Further histamine controls the release along with interaction of other neurotransmitters like dopamine, acetyl choline, serotonin (5HT), norepinephrine, γ -amino butyric acid, glutamine and substance P by influencing Histamine H3 heteroreceptors [19]. Via this pathway, it regulates indirectly food intake. Also Histamine influences the peripheral metabolism by increasing white adipose tissue (WAT) lipolysis [20].

In lipid and glucose metabolism Histamine H1 and H2 receptors signalling pathway have significant part, that appears to get modulated via both central along with peripheral pathways. Histamine H1 receptor signalling pathway participates in central nervous system (CNS) and pancreatic tissue for the regulation of glucose metabolism while H2 receptors control lipid and glucose metabolism in the liver along with skeletal muscles through the adiponectin system [21]. Additionally compounds blocking Hista-

mine H3 receptor action can decrease triglycerides in plasma [22]. Peripherally Histamine H3 receptors get expressed in neuroendocrine organs and control their functions, like in pancreatic β cells in both mouse as well as humans, with crucial part in insulin secretion [23]. Earlier studies suggested that Histamine H3 receptor ligands might be displaying probable antiobesity action [18]. Histamine H3 receptor antagonists like NNC38-1049, NNC 38-1202, JNJ-5207852, GT-2394, A-423579;A-631972, A-331440) inhibit food intake and effect marked weight loss in different rodent obesity models [22, 24]. Beta histine, that is a partial inverse Histamine H3 receptor agonist, initiated masked weight loss having least side effects in women <50yrs of age [25] and in animals having obesity following olanzapine therapy [26]. Pitolisant is an antagonists/inverse agonist at the Histamine H3 receptor (EC_{50} (Histamine H3 receptor)=1.5nM) [27], and may help in weight reduction and metabolic impairments and be of help in therapy for obesity (structure in figure 1).

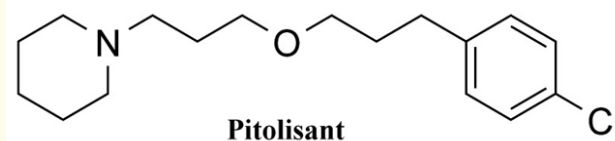


Figure 1: Chemical structure of pitolisant.

Thus Kotanska., *et al.* Evaluated the effect of Pitolisant on body weight, water along with sucrose intake in addition to metabolic impairments in the HFD and high sugar diet induced obesity (DIO) model in mice. For inducing obesity, male CD1 mice were given a HF blend for 14wks, water and 30% sucrose solution that was present ad libitum. Glucose tolerance test (GTT) was done at the start of week 15. Insulin tolerance was evaluated a day after. By the end of study, plasma triglycerides and cholesterol was evaluated. Pitolisant at a dose of 10mg/kg bw (ip)was utilized as a reference agent. Mice receiving HFD and sucrose solution displayed >weight gain all through the 12wk time schedule of obesity induction. Animals getting HFD and therapy with Pitolisant (for next 14 days) displayed significantly lower weight gain than mice in the control group taking HFD. In the group receiving Pitolisant significantly lower glucose amounts were seen as compared to glucose amounts of control obese mice following glucose load. Plasma triglycerides

levels in Pitolistant treated mice were significantly less in Pitolistant treated mice in comparison to the control obese group, Thus concluding that Pitolistant possesses a promising effect on body weight and improving GTT and lipid profile in obese mice [28].

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