ACTA SCIENTIFIC NUTRITIONAL HEALTH (ISSN:2582-1423)

Volume 4 Issue 1 January 2020

Short Communication

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

Kulvinder Kochar Kaur[1]*, Gautam Allahbadia[2] and Mandeep Singh[3]

[1]*Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, Jalandhar, Punjab, India*

[2]*Scientific Director, Rotunda-A Centre for Human Reproduction, Mumbai, India*

[3]*Consultant Neurologist, Swami Satyanand Hospital, Jalandhar, Punjab, India*

***Corresponding Author:** Kulvinder Kochar Kaur, Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, Jalandhar, Punjab, India.

Received: October 14, 2019; **Published:** December 05, 2019

DOI: 10.31080/ASNH.2020.04.0565

The metabolic syndrome (MetS) by definition is the presence of 3/5 symptoms at the same time, like abnormal fasting glycaemia, abdominal obesity, increasedblood pressure (BP), hypertrigyceridaemia 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 α1-adrenoceptor results in vasodilation, with fall of BP [8]. Further the α1-adrenoceptor antagonists cause a positive action on lipid and carbohydrate profiles [9]. Blockade of α2-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 α2-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 α1 and α2-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 α1B and α2A 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 α2A-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 inhibibitors 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 Histamine 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]. Pitolistant 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).

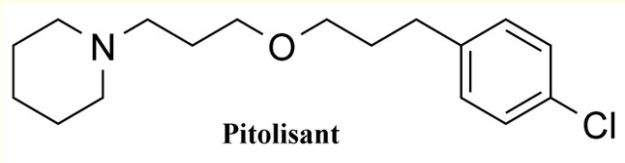

Figure 1: Chemical structure of pitolisant.

Thus Kotanska., *et al*. Evaluated the effect of Pitolistant 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 adlibitum. 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. Pitolistant 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 Pitolistant (for next 14 days) displayed significantly lower weight gain than mice in the control group taking HFD. In the group receiving Pitolistant 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].

Bibliography

1. Grundy SM., *et al*. "Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung and Blood Institute Scientific Statement". *Circulation* 112 (2005): 2735-2752.

2. Zimmert P., *et al*. "Global and societal implications of the diabetes epidemic". *Nature* 414 (2001): 782-787.

3. Grassi G. "Sympathetic overdrive and cardiovascular risk in the metabolic syndrome". *Hypertension Research* 29 (2006): 11.

4. Grassi G., *et al*. "Noradrenergic and reflex abnormalities in pts with metabolic syndrome". *Diabetologia* 48 (2005): 1359-1365.

5. Grassi G., *et al*. "Adrenergic reflex abnormalities in obesity related hypertension". Hypertension 36 (2000): 538-542.

6. Thorpe AA and Schlaich MP. "Relevance of sympathetic nervous system activation in obesity and metabolic syndrome". *Journal of Diabetes Research* (2015).

7. Kabra NK. "Alpha blockers and metabolic syndrome". *The Journal of the Association of Physicians of India* 52 (2014): 13-16.

8. Zareba P., *et al*. "α-adrenoceptor antagonists and hypertensive properties of novel arylpiperazine derivatives of pyrrolidin -2-one". *Bioorganic and Medicinal Chemistry* 348 (2015): 2104-2111.

9. Pessina AC., *et al*. "Clinical efficacy and tolerability of alpha-blocker doxazosin as add on therapy in patients with hypertension and impaired glucose metabolism". *Nutrition, Metabolism and Cardiovascular Diseases* 16 (2006): 137-147.

10. Lafontan M., *et al*. "Alpha-2 adrenoceptors and lipid metabolizing in lipolysis". *The American Journal of Clinical Nutrition* 55 (2013): 219-225.

11. Yang SN., *et al*. "Subthreshold α2-adrenergic activation counteracts glucagon like peptide1 potentiation of glucose stilulated insulin secretion". *Experimental Diabetes Research* (2011).

12. Sarpa J., *et al*. "Evaluation of anticonvulsant activity of novel pyrrolidin -2-one derivatives". *Pharmacological Reports* 66 (2014): 708-711.

13. Sarpa J., *et al*. "Antiarrythmic and antioxidant activity of novel pyrrolidin -2-one derivatives with adrenolytic properties". *Naunyn-Schmiedeberg's Archives of Pharmacology* 383 (2011): 13-25.

14. Zareba P., *et al*. "Antiarrythmic and α-adrenoceptor antagonists properties of novel pyrrolidin -2-one derivatives". *Archives of Pharmacal Research* (Weinheim) 348 (2015): 861-7.

15. Dudek M., *et al*. "Pyrrolidin -2-one derivatives may reduce body weight in rats with diet induced obesity". *European Journal of Pharmacology* 776 (2016): 146-155.

16. Kotanska M., *et al*. "Metabolic benefits of 1-(3-(4-(o--(o-tolyl) piperazin-1-yl)-propyl) pyrrolidin -2-one: a nonselective α-adrenoceptor antagonists". *Journal of Endocrinological Investigation* t 41 (2018): 609-619.

17. Walter J and Stark H. "Histamine receptor subtypes: a century of national drug design". *Frontiers in Bioscience* S4 (2012): 461-488.

18. Provensi G., *et al*. "The Histaminergic system as a target for the prevention of obesity and metabolic syndrome". *Neuropharmacology* 106 (2016): 3-12.

19. Feuerstein TJ. "Presynaptic receptors for dopamine, Histamine and serotonin pharmacology of neurotransmitter release". Handbook of Experimental pharmacology. 184, Springer-Verlag, Berlin, Heidelberg (2008): 289-338.

20. Passani MB., *et al*. "The Histamine H3 receptor and eating behaviour". *Journal of Pharmacology and Experimental Therapeutics* 336 (2011): 24-29.

21. Wang KY., *et al*. "Histamine regulation of lipid and glucose metabolism via Histamine receptors". *The American Journal of Pathology* 177 (2010): 713-722.

22. Mamelof K., *et al*. "Increase of neuronal Histamine in obese rats is associated with decreases in body weight and plasma triglycerides". *Obesity* 14 (2006): 2154-2162.

23. Nakamura T., *et al*. "The expression and function of Histamine H3 receptors in pancreatic beta cells". *British Journal of Pharmacology* 171 (2014): 171-185.

24. Barbier AJ., *et al*. "Acute wake promoting actions of JNJ-5207852, a novel, diamine –based H3 antagonist". *British Journal of Pharmacology* 143 (2004): 649-661.

25. Barak N., *et al*. "Effect of histaminergic manipulation on weight on weight in obese adults: a randomized controlled trial". *International Journal of Obesity* 32 (2008): 1559-1565.

26. Lian J., *et al*. "Preventing olanzapine –induced weight gain using betahistine: a study in a rat model with chronic olanzapine treatment". *PLoS One* 9.8 (2014): e104160.

27. European Medicines Agency.

28. Kotanska M., *et al*. "The Histamine H3 receptor inverse agonist pitolisant reduces body weight in obese mice". *Naunyn-Schmiedeberg's Archives of Pharmacology* 391 (2018): 875-881.

Volume 4 Issue 1 January 2020