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Effects of High fat diet and repeated restraint stress on food intake and energy metabolism in 5-HT2C mutant mice

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Stress is a factor in many psychiatric and metabolic disorders such as depression, anorexia nervosa, obesity and type2 diabetes (1). The attenuation of food intake as induced by an increase in serotonergic (5-hydroxytryptamine; 5-HT) efficacy has been a target of antiobesity pharmacotherapies, while hypothalamus is a brain region which is known to be involved in the regulation of appetite and energy metabolism (2). Taking consideration of evidence of 5-HT2C receptor agonists in feeding, the present study was designed to investigate the role of 5-HT2C receptors in stress related hyperphagia and obesity in high fat fed rodents.

Mice were randomly assigned to various groups and habituated to the handling during 5 days before experimentation. For acute administration two groups of animals labelled as (1); stressed/ 5-HT2C receptor KO; received a single injection of m-CPP (meta-chlorophenylpiperazine; m-CPP) at a dose of 3.0mg.kg^{-1} and (2): unstressed/ wild type controls were injected with vehicle (Saline; 0.9% NaCl). For chronic administrations, stressed/ KO mice were injected with m-CPP at doses of 2.5mg.kg^{-1} for 15 days (at 10:00 A.M. daily) and controls received an equal amount of saline (1.0mg.ml^{-1}.kg^{-1}) injections. Route of administration for drug and vehicle was intraperitoneal (i.p.). Effects of two intensities repeated restraint stress and High fat diet (HFD) on food intake and body weight was examined in mice restrained repeatedly for 3 days (2h/day). Food intake and body weights were monitored weekly in a balanced design in all groups. Behavioural testing was carried out in home cages, plus maze and light/dark transition boxes. The protocol for experimentations were approved and performed in strict accordance with the Guide for the Care and Use of laboratory Animals (Institutional Animal Ethical Committee; IAEC University of Karachi Pakistan).Data were presented as means$\pm$SEM (n=24). Statistical significance was tested using one-or two-way analysis of variance (ANOVA) followed by Newman-keuls *post hoc* tests using Graph Pad Prism (6.0) software. The study demonstrated that prototypical 5-HT2C receptor agonist m-CPP at acute (3.0mg.kg^{-1}) and chronic (2.5mg.kg^{-1}) injections reduced feeding behaviour and produced significant ($p<0.01$) reduction in body weights of KO mice treated with HFD. Results revealed that the anorectic function of the m-CPP is mediated by 5-HT2C receptors. Behavioural observations in animal models of stress and obesity were associated with the modulation of serotonergic functions in brain hypothalamus. Energy expenditure as inferred from VO2 was significantly ($p<0.01$) lowered in 5-HT2C mutant mice fed on high fat diet. Overall, m-CPP administrations (acute and chronic) induced

significant ($p<0.01$) hyperlocomotive effect in 5-HT2C receptor KO mice. Mutant mice also exhibited significant response to high fat feeding, leading to hyperglycemia, hence indicative of fact that brain serotonin system can predispose to type2 diabetes.

In conclusion, our observations are consistent with the hypothesis that signalling via 5-HT2C receptors contribute to nutrient sensing and metabolic control and are implicated in the regulation of food intake and energy expenditure. Hence, 5-HT2C receptors represent the most promising serotonin-receptor therapeutic targets of depression and antiobesity pharmacotherapies.

1. Dalton GL *et al.* (2006). *Pyschopharmacology* **185:** 45-47.
2. Chou-Green JM *et al*. (2003). *Physiology & Behavior* **79:** 217-226.