Increased Serotonin 2C Receptor Editing in a Mouse Model of Obesity

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Introduction

Obesity is rapidly increasing in prevalence in developed countries. It is well established that increased 5-HT neurotransmission in the brain regulates feeding habits by inducing hypophagia. Within the serotonergic system there are 14 different receptors many of which have been shown to influence food intake. In particular 5-HT1A, 5-HT1B, 5-HT2A and 5-HT4 have received attention as promising anti-obesity therapeutic targets. In addition, 5-HT2C pre-mRNA transcripts are known to undergo RNA editing by enzymatic adenosine to inosine conversions at 5 nucleotide positions (termed A, B, E, C, and D). The “edited” 5-HT2C receptor isoforms display different constitutive activity, affinity and potency, suggesting important implications for serotonergic signal transduction in vivo. Feeding behaviour and fat mass have been demonstrated to be altered by 5-HT2C receptor RNA editing in the brain, suggesting a potential role for 5-HT2C edited isoforms in obesity (Kawahara et al., 2008).

Aim

This study aims to examine the expression of 5-HT1A, 5-HT1B, 5-HT2C and 5-HT4 mRNA levels in several brain areas of the leptin deficient mouse model of obesity (ob/ob) and to analyse differential editing of the 5-HT2C receptor in this mouse model of obesity.

Method

Mice, 8 ob/ob and 8 lean control (wt/−), were sacrificed between 8 and 9 weeks using cervical dislocation. Receptor expression was analysed using quantitative real-time PCR. In addition, the 5-HT2C receptor editing frequency was analysed using direct sequencing and a recently described real-time PCR method (Lanfranco et al., 2009).

Results

- **During ad libitum conditions, leptin deficient mice consumed 50% more food compared to their controls, and displayed significantly ↑ body weights.**

- **Serotonergic Receptor mRNA Expression**

- **5-HT2C Receptor Editing via direct sequencing**

Unpaired, two-tailed T-test; statistical significance is notated as "*" p<0.0001, "**" p<0.004, "***" p<0.0047 compared to control.

Unpaired, two-tailed T-test; statistical significance is notated as "*" p=0.0047 compared to control.

Unpaired, two-tailed T-test; statistical significance is notated as "*" p=0.0046 compared to control.

Unpaired, two-tailed T-test; statistical significance is notated as "*" p=0.0004 compared to control.

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References

Kawahara, Y., et. al., 2008. Dysregulated editing of serotonin 2C receptor mRNAs results in energy dissipation and loss of fat mass. J Neurosci 28, 12364-12364


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