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Research Report

# Preference for a high fat diet, but not hyperphagia following activation of mu opioid receptors is blocked in AgRP knockout mice

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ABSTRACT

Activation of mu opioid receptors (MOR) makes animals hyperphagic and selectively increases their preference for a high fat diet independent of their dietary preference. The orexigenic peptide Agouti Related Peptide (AgRP) also produces hyperphagia and increased the preference for a high fat diet. In this paper, we tested the hypothesis that the effect of MOR on feeding behavior will be attenuated in the absence of the orexigenic peptide AgRP. Immunohistochemical studies demonstrated that MOR are co-localized on AgRP neurons located in the arcuate nucleus. This finding is consistent with a role of MOR in mediating the release of AgRP. Our data also demonstrated that the wild-type (FVB) animals preferred a diet high in fat whereas the AgRP knockout (AgRP KO) mice did not. mRNA expression of MOR in the hypothalamus was not significantly different between AgRP KO mice and their wild-type control. In a dose–response experiment, the low dose (0.025 μg) of a MOR agonist, DAMGO, increased cumulative food intake in wild-type and AgRP KO mice. The low and middle (0.25 μg) dose of DAMGO significantly increased the amount of high fat diet eaten by the wild-type animals, but did not significantly change the amount of high fat diet eaten by the AgRP KO mice. The highest dose of DAMGO (2.5 μg) reduced food intake in the control and AgRP KO mice, probably due to somnolence. These data demonstrate that the increased preference for a high fat diet after stimulation of MOR is attenuated in the absence of AgRP, but the increase in food intake (i.e. hyperphagia) is not.

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## 1. Introduction

The level of fat in the diet, together with portion size, is thought to play a major role in the current epidemic of obesity (Hill and Peters 1998), and emphasizes the need to understand the factors that modulate food intake as well as the preference for a high fat diet. Of the many peptides, neurotransmitters and receptor populations that affect food intake, only a few have been demonstrated to make animals hyperphagic and simultaneously increase their preference for a diet high in fat. Included in this list are mu opioid receptors (MOR) and Agouti Related Peptide (AgRP).

Mu opioid receptors (MOR) belong to a family of seven-transmembrane domain receptors that are coupled to G-

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proteins (Chen et al., 1993). This receptor population is located in many areas of the central nervous system that are involved in feeding such as the hypothalamus, nucleus accumbens, amygdala, ventral tegmental area and the nucleus tractus solitarius (Zhang et al., 1998, Zheng et al., 2005). In the early 1980s, investigators made the observation that after the injection of a non-selective opioid agonist (i.e. morphine) animals increased their fat intake while suppressing carbohydrate intake and exhibiting little modification in protein intake (Marks-Kaufman 1982, Marks-Kaufman and Kanarek 1980). Later studies by Zhang et al (1998) suggested that endogenous opioids within the ventral striatum participate in the mechanisms governing preferences for highly palatable foods, especially those rich in fat. From these studies and others (Evans and Vaccarino 1990; Gosnell and Krahn 1993), it has been concluded that activation of MOR makes animals hyperphagic and selectively increase their preference for a diet high in fat.

The mechanism(s) by which activation of this receptor population increases food intake and the preference for a high fat diet is unknown. This paper tested the hypothesis that the effect of MOR on feeding behavior would be attenuated in the absence of the orexigenic peptide Agouti Related Peptide (AgRP).

AgRP is an orexigenic peptide that is co-localized with neuropeptide Y (NPY) in neurons located in the arcuate nucleus (Chen et al., 1999, Hahn et al., 1998). When released from its neurons in the arcuate nucleus, AgRP increases food intake by functioning as an antagonist to the melanocortin 3 and 4 receptors (Fong et al., 1997, Ollmann et al., 1997). The effect of AgRP on food intake lasts up to 72 h (Hagan et al., 2000). Administering AgRP into the central nervous system selectively increases the preference for a diet high in fat (Hagan et al., 2001).

Ubiquitous overexpression of AgRP in transgenic mice leads to hyperphagia, severe obesity and reduced corticosterone levels (Graham et al., 1997). However, AgRP knockout mice which we utilized in this manuscript have been reported to exhibit normal feeding behavior without changes in body weight and cumulative food intake (Qian et al., 2002). AgRP knockout mice live 10% longer than their wild-type littermates while consuming a high fat diet but without exhibiting differences in food intake or body weight (Redmann and Argyropoulos, 2006).

In the present studies, we demonstrate that MOR are co-localized on AgRP neurons located in the arcuate nucleus. We also demonstrate that activating MOR in AgRP knockout mice does not increase their preference for a high fat diet. However, activation of MOR does make AgRP knockout mice hyperphagic. Taken together, these data suggest that the effect of MOR on dietary preference for a high fat diet is dependent on the presence of the orexigenic peptide AgRP, but that stimulation of food intake is not.

## 2. Results

### 2.1. *Experiment 1: immunohistochemical (IHC) identification of mu opioid receptors and AgRP neurons*

Fig. 1 provides a representation of the co-localization of MOR and AgRP that was observed in the arcuate nucleus. Panel A is a representation of the area of the brain (medial arcuate nucleus; Bregma –3.30mm) that was used to identify the mu opioid receptors. High power (40×) magnification in panel B provides an image of a neuron (green) that is positively labeled with MOR. Panel C shows positively labeled AgRP neurons (red). The final panel, panel D, is an overlay of panels B and C which demonstrates that MOR are located on AgRP neurons located in the arcuate nucleus.

### 2.2. *Experiment 2: mRNA expression of MOR and AgRP in FVB and AgRP KO mice*

mRNA expression of AgRP was statistically different between the two groups, $t(10)=3.384$, $p<0.05$ (Fig. 2A). As expected, we were able to detect the mRNA expression of AgRP in the hypothalamus of the control animals, but it was not detectable in AgRP KO mice. In contrast, the expression of MOR was similar between the control and the AgRP KO mice, $t(11)=1.723$, $p>0.05$ (Fig. 2B).

### 2.3. *Experiment 3: dietary preference of AgRP KO and FVB mice*

Fig. 3 shows the intake of high fat and low fat diet as a percentage of total intake consumed when the FVB and AgRP knockout mice were given a choice between a low fat diet and a high fat diet. FVB mice ate significantly more of the high fat diet, $t(6)=2.760$, $p<0.05$ (Fig. 3A). In contrast, the AgRP KO mice did not have a preference for either diet, $t(6)=1.287$, $p>0.05$ (Fig. 3B).

### 2.4. *Experiment 4: effect of DAMGO (selective mu opioid receptor agonist) on high fat intake of AgRP KO and FVB mice*

Figs. 4 and 5 show a dose–response to a mu opioid receptor agonist DAMGO [(D-Ala$^2$-N-Me-Phe$^4$-Glycol$^5$)-enkephalin] on cumulative food intake and dietary preference for either a low fat or a high fat diet, respectively in the control and AgRP KO mice. Cummulative food intake was increased in the wild-type mice and in the AgRP KO mice (Figs. 4A and 5A, respectively). The low dose (0.025 μg) caused a significant increase in cumulative food intake in the wild-type mice, $F(3,4)=20.61$, $p<0.05$ and the AgRP KO mice, $F(3,6)=11.69$, $p<0.05$. The middle (0.25 μg) and high (2.5 μg) doses of DAMGO resulted in a decrease in cumulative food intake, probably due to somnolence.

Main effects of treatment, $F(3,24)=3.53$, $p<0.05$, and diet, $F(1,24)=13.65$, $p<0.05$, were found when the preference for either a low fat or high fat diet was analyzed in Fig. 4. These data demonstrated that the low dose and the middle dose of DAMGO were able to significantly increase the wild-type animal's preference for a high fat diet. However, the same doses were not able to alter the dietary preference of the AgRP KO mice. There was not an effect of diet, $F(3,56)=0.13$, $p>0.05$, or treatment, $F(3,56)=1.49$, $p>0.05$.

## 3. Discussion

While the role of mu opioid receptors (MOR) in modulating the palatability and taste preference of animals has been established and is an active area of ongoing research, the precise

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