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Research Report

# AdipoR1 and 2 are expressed on warm sensitive neurons of the hypothalamic preoptic area and contribute to central hyperthermic effects of adiponectin

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ABSTRACT

Adiponectin can act in the brain to increase energy expenditure and reduce body weight by mechanisms not entirely understood. We found that adiponectin type 1 and type 2 receptors (AdipoR1 and AdipoR2) are expressed in warm sensitive neurons of the hypothalamic preoptic area (POA) which play a critical role in the regulation of core body temperature (CBT) and energy balance. Thus, we tested the ability of adiponectin to influence CBT in wild-type mice and in mice deficient for AdipoR1 or AdipoR2. Local injection of adiponectin into the POA induced prolonged elevation of core body temperature and decreased respiratory exchange ratio (RER) indicating that increased energy expenditure is associated with increased oxidation of fat over carbohydrates. In AdipoR1 deficient mice, the ability of adiponectin to raise CBT was significantly blunted and its ability to decrease RER was completely lost. In AdipoR2 deficient mice, adiponectin had only diminished hyperthermic effects but reduced RER similarly to wild type mice. These results indicate that adiponectin can contribute to energy homeostasis by regulating CBT by direct actions on AdipoR1 and R2 in the POA.



## 1. Introduction

Adiponectin is an important regulator of energy homeostasis proposed to be involved in metabolic and vascular diseases (Dridi and Taouis, 2009; Kadowaki and Yamauchi, 2005; Kadowaki et al., 2006, 2007). Produced and secreted by adipose tissue, adiponectin regulates glucose and fatty acid metabolism in tissues such as muscle and liver (Berg et al., 2002), as

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well as insulin-sensitizing effects (Berg et al., 2001; Fruebis et al., 2001; Yamauchi et al., 2001). In rodents, peripheral administration of adiponectin enhanced both fatty acid oxidation and glucose uptake in muscle, and reduced hepatic glucose production (Berg et al., 2001; Fruebis et al., 2001; Qi et al., 2004; Shklyaev et al., 2003; Tomas et al., 2002; Yamauchi et al., 2001). Conversely, adiponectin deficiency leads to glucose intolerance, insulin resistance, dyslipidemia and increased susceptibility to vascular injury and atherosclerosis (Kubota et al., 2002; Maeda et al., 2002; Nawrocki et al., 2006).

The two structurally similar adiponectin receptors (AdipoR1 and AdipoR2) were found to be differentially expressed in different brain regions including the hypothalamus (Coope et al., 2008; Fry et al., 2006; Guillod-Maximin et al., 2009; Hoyda and Ferguson, 2010; Kos et al., 2007; Kubota et al., 2007; Psilopanagioti et al., 2009; Thundyil et al., 2011; Yamauchi et al., 2003) . Bjursell generated and characterized mice null for AdipoR1 and R2 and concluded that while both receptors are involved in the regulation of energy metabolism, they mediate opposite effects (Bjursell et al., 2007).

Intracerebroventricular (icv) administration studies recapitulate the peripheral effects of adiponectin and suggested that this adipokine may have a central role in modulating energy homeostasis by influencing temperature and/or nutrient homeostasis (Qi et al., 2004). Qi and colleagues demonstrated that icv injection of adiponectin elevated energy expenditure by increasing the expression of the uncoupling protein 1 (UCP1) in brown adipose tissue (BAT), elevating colonic CBT and reducing body weight (Qi et al., 2004). A different group found that icv injection reduced food intake in fasted animals by 40% suggesting adiponectin may reduce energy intake acting as pro-anorexigenic. These effects were mediated by AdipoR1 and involved the classical insulin and leptin signaling pathways (Coope et al., 2008). Conversely, Kubota and colleagues reported that icv administration of the hexameric form of adiponectin increased food intake during re-feeding and that intravenous injection of full length adiponectin lowered oxygen consumption and BAT UCP1 expression, reducing energy expenditure without affecting body weight (Kubota et al., 2007). Finally, in experiments on agouti yellow mice, icv injection of adiponectin did not alter food intake or body weight (Masaki et al., 2003). The reason for these differences may, at least partially, be the type of adiponectin utilized and the fact the icv route of administration

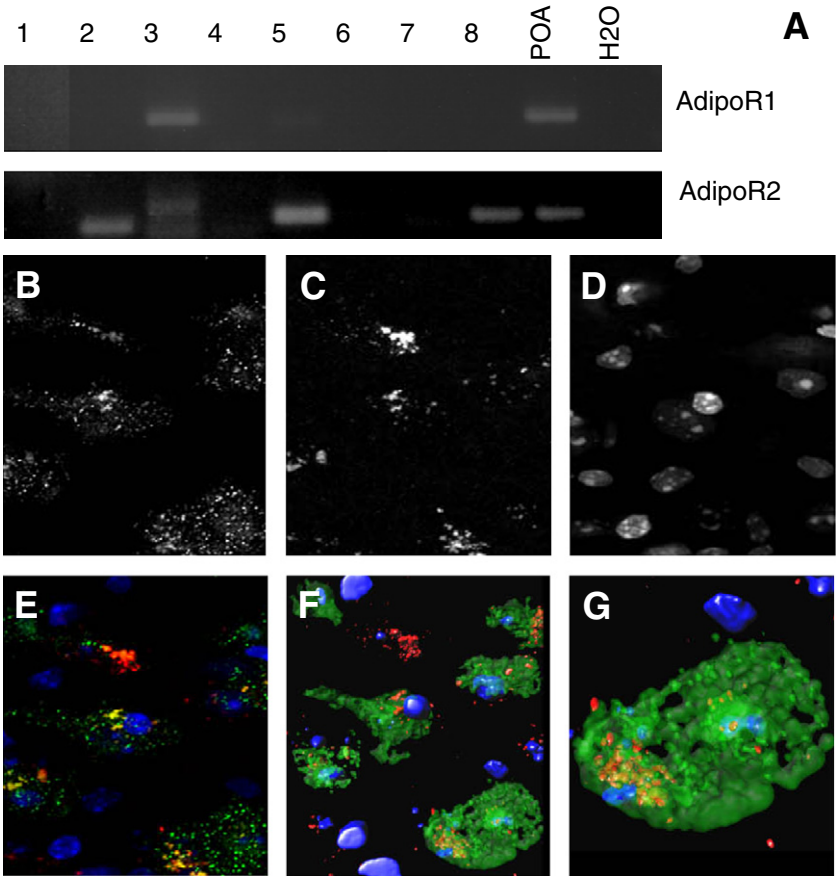


**Fig. 1 – Expression of adiponectin type 1 and type 2 receptor in WSN and POA. (A) Ethidium bromide stained agarose gel of amplification products of PCR carried out on cDNA from the POA or from POA single WSNs subject to aRNA amplification. 1 out of 8 WSN expressed AdipoR1 transcript; 2 expressed AdipoR2 (B–G) Representative immunohistochemistry of adiponectin receptor 1 (green) (B) in the POA after retrograde transport tracing with Texas red (red) (C) and nuclear staining with DAPI (blue) (D). Images were merged (E) and reconstructed in three-dimension at same (F) or at higher magnification (G).**