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Orexin-A and endocannabinoid signaling regulate glucose-responsive arcuate nucleus neurons and feeding behavior in obese rats

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ABSTRACT

Obesity is a global public health problem. Orexin and endocannabinoid signaling in the hypothalamus have been shown to regulate feeding and are promising molecular targets for obesity treatment. In this study, we attempted to analyze effects of orexin-A and endocannabinoid signaling modulation in the arcuate nucleus (Arc) on feeding and glucose-responsive (GR) neurons physiology in a diet-induced obesity (DIO) and diet-induced obesity resistant (DR) rat model. Administration of orexin-A or cannabinoid receptor type-1 (CB_1R) antagonist AM251 altered the firing of GR neurons in the Arc. The effects of orexin-A were eliminated by pre-administrating orexin-1 receptor (OX-1R) antagonist SB334867, respectively. Behavioral studies showed that orexin-A increased food intake, while AM251 reduced feeding. Histological studies showed that mRNA and protein expression of OX-1R (orexin-1 receptor) and CB_1R were increased in the Arc of DIO and DR rats. Our results strongly suggest that orexin-A and endocannabinoid signaling in Arc plays an important role in regulating GR neuronal excitability and food intake in obesity.

1. Introduction

Obesity is widely regarded as an important public health problem (Yach et al., 2006; Runge, 2007). Excessive feed could induce the obesity. Food intake is controlled by multiple neurochemical and endocrine signaling systems including several neuropeptides, such as orexin, ghrelin, cannabinoid and so on. Orexin-A, one of the few orexigenic peptides, regulates many obesity-related processes including feeding, energy homeostasis and reward (de Lecea et al., 1998; Sakurai et al., 1998). Recent studies have also shown that intracerebroventricular (i.c.v.) or perifornical lateral hypothalamus (PeFLH) administration of orexin-A increases food intake in the rats (Bülbü et al., 2010; Li et al., 2015). Orexin-A is mainly produced by lateral and dorsomedial hypothalamic, and perifornical neurons in the central nervous system (CNS) (de Lecea et al., 1998; Sakurai et al., 1998). These neurons have widespread projections throughout the brain including arcuate nucleus (Arc), ventromedial hypothalamic nucleus (VMH), parabrachial nucleus (PBN), central gray and nucleus of the solitary tract etc. (Peyron et al., 1998). Correspondingly, orexin-1 receptors (OX-1R) are expressed widely as well. Arc plays a pivotal role in the control of feeding. Arc lesions lead to severe metabolic disorders (Olney, 1996), and genetic defects in Arc function have been linked to obesity (Barsh et al., 2000). Arc contains neuropeptide Y (NPY) and POMC-expressing neurons (Cowley et al., 2001), which exert opposing effects on the regulation of food intake and energy balance (Wang et al., 2004), and the excitation of these neurons can be regulated by alteration of local glucose levels (Wang et al., 2004; Muroya et al., 1999). Earlier studies used i.c.v. or PeFLH administration of orexin-A. However, whether the Arc is responsible for these effects is not known. And it is unclear as well whether the excitability of the glucose-responsive (GR) neurons is controlled by orexin-A or endocannabinoid signal pathway in the Arc. Furthermore, these questions remain unanswered in the diet-induced obesity (DIO) rats or diet-induced obesity resistant (DR) rats.

The endocannabinoid system is another important regulator of appetite that may be a target for obesity treatment (Andre and Gonthier, 2010). Endocannabinoids stimulate food intake through homeostatic and non-homeostatic mechanisms via the cannabinoid 1 receptor (CB_1R) (Silvestri and Di Marzo, 2013). Intraperitoneal administration of CB_1R antagonists AM251 increased the orexin-A immunosignal density in the VMH (Cristino et al., 2013). The levels of cannabinoid 2-arachidonoylglycerol (2-AG) were increased in the Arc of orexin-A–injected DIO mice (Morello et al., 2016). The expressions of CB_1R and OX-1R are co-localized at the plasma membrane and that they are close enough to one another to allow direct physical interaction under an immunogold electronic microscopy (Hilairet et al., 2003). Brain patch-clamp study showed that endogenous cannabinoids could be released from orexin cells after postsynaptic depolarization, and they could also

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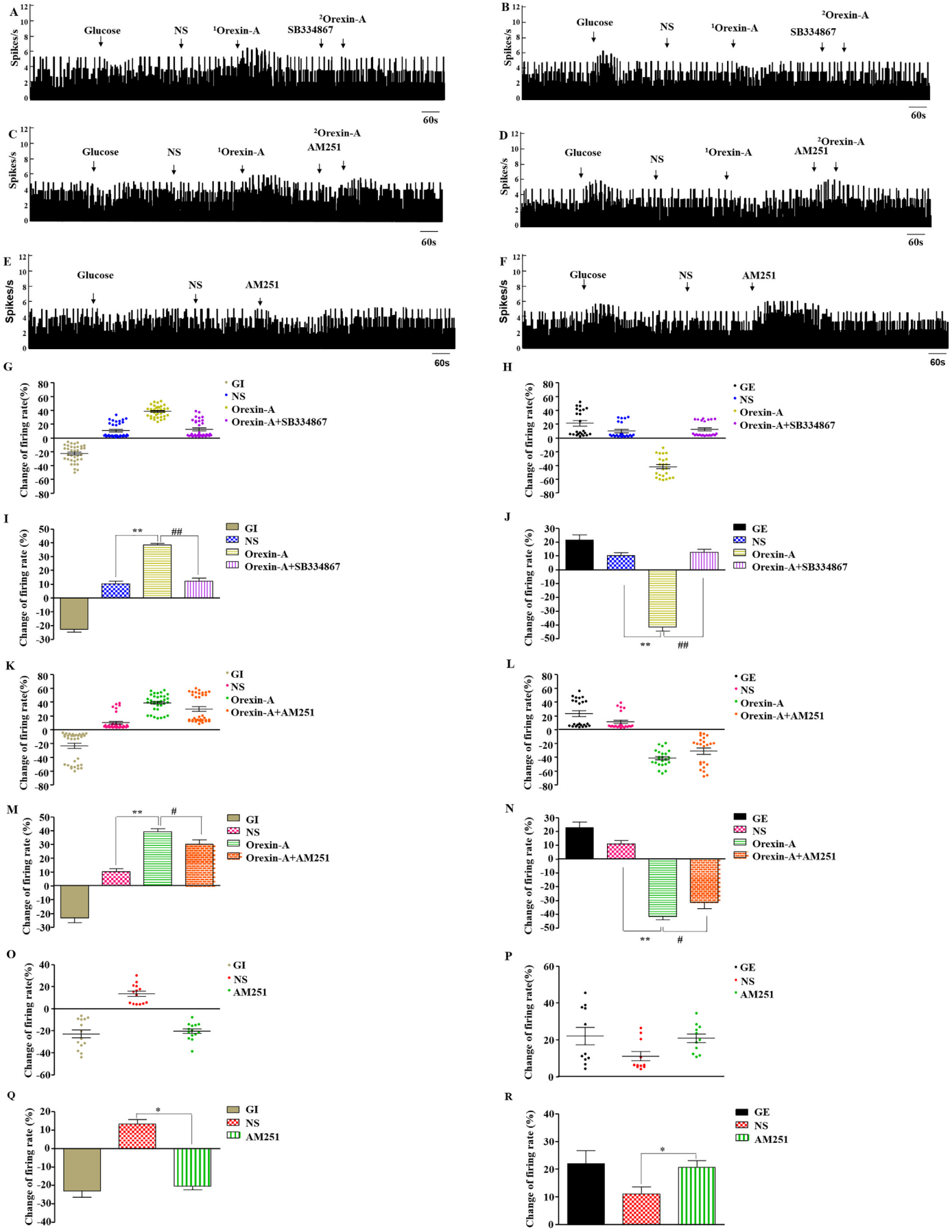

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