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BRAIN RESEARCH

Research Report

Amylin–leptin coadministration stimulates central histaminergic signaling in rats☆

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ABSTRACT

Combined amylin+leptin (AMN+LEP) can reduce diet induced obesity and is very effective in combating LEP resistance. The purpose of this study was to evaluate the effect of AMN+LEP on central histaminergic signaling in lean and obese rats. Male rats were administered LEP (300 μg/kg/d), AMN (100 μg/kg/d), AMN+LEP or vehicle (SAL, 0.9% normal saline), via a subcutaneous mini-osmotic pump or single injection (LEP, 300 μg/kg and AMN, 100 μg/kg) for acute studies. AMN+LEP administration increased expression of histamine H1 receptor (HIR) and histidine decarboxylase (HDC) mRNA in the hypothalamus. Increased levels of H1R were seen in arcuate (Arc) and ventromedial hypothalamus (VMH) as well as the area postrema (APOS) and nucleus of solitary tract (NTS) following AMN+LEP administration. APOS and NTS also showed expression of immediate early gene c-FOS in the hindbrain in AMN+LEP-treated rats. We confirmed previous evidence indicating that AMN+LEP increased STAT-3 protein phosphorylation in Arc and VMH. Finally, by *in vivo* microdialysis, we observed an increase in methyl HIS levels in the VMH of AMN, LEP and AMN+LEP-treated rats. Taken together, these observations are consistent with an important role that neuronal HIS may play in mediating the potent effects of AMN+LEP on food intake and body weight.

1. Introduction

The pancreatic hormone amylin (AMN), in combination with adipose hormone leptin (LEP), reduces food intake in diet induced obese rats in a very potent manner (Chan et al., 2009; Roth et al., 2006, 2008; Seth et al., 2011; Trevaskis et al., 2008). Since, both LEP (Skibicka and Grill, 2009; Williams et al., 2009) and AMN (Lutz, 2006) have binding sites in the hind brain, we could expect a possible interaction between the two at this level. AMN binding in area postrema (APOS) activates the forebrain via the nucleus of the solitary tract (NTS) and the lateral parabrachial nucleus (lPBN) (Riediger et al., 2004). The lPBN, appears to act as an important relay station between the hindbrain and the lateral hypothalamic area (LHA), where AMN regulates fasting induced c-Fos expression (Potes and Lutz, 2010). Furthermore, AMN-induced activation of the ascending projections from the lPBN may function as a key relay site for the transmission of AMN signaling from the hindbrain to the ventromedial hypothalamus (VMH) (Boyle and Lutz, 2011; Potes et al., 2010a). The overlap of hypothalamic and hindbrain targets between AMN and LEP suggests a central action that may be up-regulated in synergistic fashion. Another

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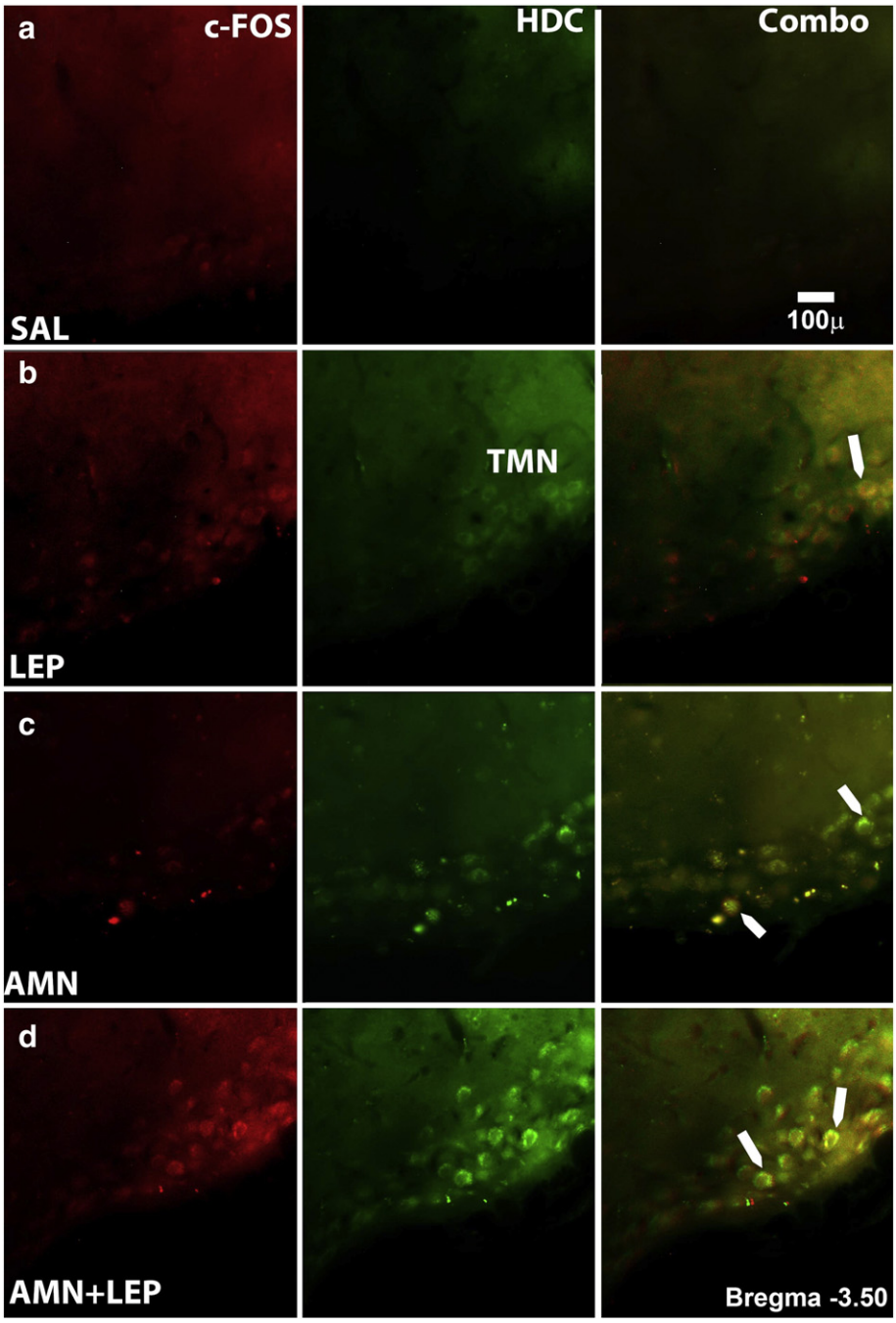

Fig. 1 – AMN+LEP administration upregulates HDC enzyme activity (green) and c-FOS activity (red) in tuberomammillary nucleus (TMN). Animals were treated for 23 h with SAL, LEP (300 μg/kg/d), AMN (100 μg/kg/d), or AMN+LEP using subcutaneous osmotic pumps. Panel (a) is from SAL-treated rat (b) LEP-treated rat (c) AMN-treated rat and (d) AMN+LEP-treated rat. Arrows show co-localization of c-FOS and HDC in the TMN. Scale bar is 100 μM, brain slices correspond to Bregma –3.5.

interpretation of the potent effects of combined AMN+LEP is that AMN is a treatment for LEP resistance, and AMN injection amplifies low-dose LEP-stimulated pSTAT-3 signaling within the arcuate nucleus (Arc) in lean rats (Turek et al., 2010).

Several lines of evidence suggest that hypothalamic histamine (HIS) may be involved in anti-obesity actions of this combination. HIS is a key target of LEP (Morimoto et al., 2000, 2001) and AMN (D Este et al., 2001; Lutz et al., 1996) action in the brain. Central administration of LEP increases HIS turnover in the hypothalamus (Yoshimatsu et al., 1999). Furthermore, AMN's anorexigenic effect in rats is reduced by the administration of the HIS H1 receptor antagonists, pyrilamine or chlorpheniramine, into the VMH, and acute effects of both AMN and LEP on eating are blunted in H1 receptor deficient mice (Mollet et al., 2003). Histaminergic neurons, with their cell bodies located in the tuberomammillary nucleus (TMN), project to the VMH and paraventricular nuclei (PVN) (Ookuma et al., 1989; Sakata et al., 1988). Similarly, histidine decarboxylase (HDC),