Orexins and the Autonomic Nervous System

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1. INTRODUCTION

Hyperphasia (overeating) is often associated with energy overstorage and obesity, which may lead to a myriad of serious health problems, including heart disease, hypertension, and type 2 diabetes. The hypothalamus, in which a number of neuropeptides have been demonstrated to stimulate or suppress food intake, is considered an important organ for the regulation of appetite and energy homeostasis (1). Recently, a novel hypothalamic peptide family (subsequently termed orexins) was discovered in a cytoplasmic calcium-level assay on several cells expressing individual orphan G-protein–coupled receptors (2). The mRNA for the precursor of these peptides is abundantly and specifically expressed in the lateral hypothalamus (LH) and adjacent areas, a region classically implicated in the regulation of feeding and energy homeostasis. The LH also participates in the reciprocal relation of sympathetic activity and feeding. The neuropeptides, monoamines, and many drugs involved with modulating food intake and fat stores have reciprocal effects on cardiovascular response, sympathetic nerve activity, and thermogenesis (3–5). Within the hypothalamus, orexin/hypocretin nerve fibers (6) and orexin/hypocretin receptors (OX1R and OX2R), especially OX2R (2,7), are found extensively in the hypothalamic paraventricular nucleus (PVN), which is thought to be involved in control of the autonomic nervous system, cardiovascular function, and neuroendocrine system (8,9). On the other hand, OX1R is most abundant in the ventromedial hypothalamic nucleus (VMH). Thus, orexins may have a functional role in regulation of the cardiovascular and autonomic nervous systems. The aim of this chapter is to summarize our recent studies, in which we used direct recording of sympathetic nerve activity in conscious rats and an in vitro whole cell patch-clamp technique to examine the direct effect of orexins on PVN neurons using a hypothalamic slice. These studies were performed to elucidate the central actions of orexins on cardiovascular functions and the autonomic nervous system.

2. OREXINS AND CARDIOVASCULAR AND SYMPATHETIC FUNCTIONS IN VIVO

Several studies have reported that central administration of orexins induces c-fos expression in the locus coeruleus, arcuate nucleus, central gray, raphe nuclei, nucleus tractus solitarius (NTS), supraoptic nucleus (SON), and PVN in rats (6,10), indicating that central administration of orexins activates specific nuclear groups in the hypothalamus and brainstem known to regulate autonomic and neuroendocrine functions. Accordingly, we hypothesized that orexins may affect cardiovascular and sympathetic functions mediated via a central nervous system (CNS) site of action.
To examine this possibility, the cardiovascular and renal sympathetic nerve responses produced by intracerebroventricular (icv) administration of orexin-A and -B were studied in conscious, unrestrained Wistar rats (11), since there is overwhelming evidence that autonomic and endocrine responses are profoundly influenced by anesthetics, even to the extent that, using the same intervention, opposite results may be produced in conscious and anesthetized animals (12,13). Administration of orexin-A icv provoked a dose-related increase in the mean arterial pressure (MAP), heart rate (HR), and renal sympathetic nerve activity (RSNA) in