1. INTRODUCTION

The past several years have provided important insights into the physiological significance of the central orexin system. An important component of these is an increased understanding of the unique neuroanatomy of the orexin/hypocretin system. The orexin peptides, orexin-A and orexin-B, are produced in a restricted region of the central nervous system, the neurons of the lateral hypothalamic area. From this small neuronal source, on the order of a few thousand neurons, orexin-expressing neurons project over virtually the entire brain and spinal cord. At the terminals of these projections, orexin interacts with two distinct receptors, the orexin-1 receptor and the orexin-2 receptor. Given the diffuse projection pattern of orexin-containing axons, it is not surprising that orexin receptor expression has been described in a large number of brain areas. This chapter briefly outlines the brain regions innervated by hypothalamic orexin neurons and provides an overview of the distribution of each receptor subtype.

The location of orexin neurons combined with the orexin fiber innervation and receptor distribution pattern have been used to formulate anatomic hypotheses as to the likely physiological roles of the orexin system. These roles include the control of wake and sleep states, feeding and drinking behavior, neuroendocrine and autonomic regulation, locomotor activity, and many others. Notably, several of these models have been supported by physiological, pharmacological, and genetic evidence. The physiological importance of orexins in these different systems is addressed in detail by others in this text; in this chapter we consider the anatomical evidence for the role of orexins in these multiple systems.

2. LOCATION AND NEUROCHEMICAL PROPERTIES OF OREXIN NEURONS

The discovery of the orexin (hypocretin) peptides was met with enthusiasm, in part because of the unique expression pattern of the peptides (1,2). It was immediately evident that neurons expressing orexin peptides are found in a very small region of the central nervous system. These neurons are located predominantly in the perifornical region and the lateral hypothalamus, at the tuberal level of the hypothalamus where the median eminence is evident. This region of the lateral hypothalamus has classically been implicated in a wide variety of behavioral and homeostatic regulatory systems, and thus the simple location of orexin-expressing neurons generated hypotheses as to their physiological relevance (3,4).
Within the rat brain, in the rostral to caudal plane, the orexin neuronal field extends from just caudal to the paraventricular hypothalamic nucleus to just rostral to the tuberomammillary nucleus. In the medial to lateral plane, whereas orexin neurons encroach medially through the dorsomedial nucleus as far as the third ventricle and laterally as far as the optic tracts, most orexin neurons reside within the perifornical area. Similarly, the vast majority of orexin neurons are found dorsal to the fornix, and only scattered cells exist in the ventral portion of the hypothalamus. Although some orexin neurons clearly exist outside of the perifornical lateral hypothalamus including portions of the dorsal medial hypothalamus, for the remainder of the chapter we will refer to the location of orexin-containing neurons as the lateral hypothalamic area (LHA).

The orexin peptide family consists of two known peptides, orexin-A (33 amino acids) and orexin-B (27 amino acids), which are proteolytically cleaved from one gene product, the prepro-orexin peptide. Whereas the pharmacological and physiological effects of each singular orexin peptide may differ and have yet to be fully characterized, it appears that neurons expressing prepro-orexin probably contain both orexin-A and orexin-B peptides. Orexin peptides localize within secretory vesicles, implying that both orexin-A and orexin-B are coreleased at orexinergic synapses. There is general agreement in immunohistochemical staining for prepro-orexin, orexin-A, orexin-B, further implying that both orexin peptides are produced in orexin-containing neurons.

Several other neurochemical features distinguish the population of orexin-expressing neurons. Orexin neurons contain the peptide dynorphin and express the secretory marker secretogranin II. Galanin and neuropeptide (NPY)-Y4 receptors have also been reported to be coexpressed by orexin neurons. Many orexin neurons express vesicular glutamate transporters, suggesting that many if not all orexin neurons are glutamatergic.

In contrast, orexin neurons do not express GAD-67 mRNA, suggesting that orexin neurons are not GABAergic. Given their location in the LHA, it is likely that orexin neurons receive multiple inputs. For example, norepinephrine and serotonin have direct inhibitory actions on orexin neurons, implying the presence of adrenergic and serotinergic receptors on orexin neurons. In contrast, histamine and acetylcholine have little direct effect.

Given the purported role of the central orexin system in regulating metabolic homeostasis, it is also important to note that orexin neurons reside in the lateral hypothalamus intermingled among, but completely distinct from, another group of peptidergic neurons, those expressing melanin-concentrating hormone (MCH). Thus, the orexin- and MCH-expressing cells comprise two neurochemically unique neuronal populations in the lateral hypothalamus, both of which have been suggested to play a role in regulating body weight homeostasis. Notably, the orexin population is distinct from yet a third neuronal population within the lateral hypothalamus, those neurons that express neuronal nitric oxide synthase (nNOS).

Studies on identified orexin neurons have shown that several circulating metabolic cues can influence their electrical activity. For example, orexin neurons are excited by application of ghrelin and glucagon-like peptide-1 (GLP-1). In contrast, orexin neurons are inhibited in response to application of leptin. Orexin neurons can also be activated by decreases and inhibited by increases in the extracellular glucose concentration. Whereas it is possible that these factors may influence orexin neurons directly in vivo, it is apparent that orexin neurons may also be regulated indirectly through afferents to the LHA from regions that are directly affected by circulating cues, such as the arcuate nucleus and the dorsal vagal complex.