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Review article

Orexin, Stress and Central Cardiovascular Control. A Link with Hypertension?

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ABSTRACT

Orexin, the arousal peptide, originates from neurons located in an area of the dorsal hypothalamus well known for integrating defense responses and their cardiovascular component. Orexin neurons, which are driven in large part by the limbic forebrain, send projections to many regions in the brain, including regions involved in cardiovascular control, as far down as sympathetic preganglionic neurons in the spinal cord. Central injections of orexin evoke sympathetically mediated cardiovascular responses. Conversely, blockade of orexin receptors reduce the cardiovascular responses to acute stressors, preferentially of a psychological nature. More importantly, lasting upregulation of orexin signaling can lead to a hypertensive state. This can be observed in rats exposed to chronic stress as well as in strains known to display spontaneous hypertension such as the spontaneously hypertensive rat (SHR) or the hypertensive BPH/2J Schlager mouse. Thus, there is a link between orexin, stress and hypertension, and orexin upregulation could be a factor in the development of essential hypertension. Orexin receptor antagonists have anti-hypertensive effects that could be of clinical use.

Contents

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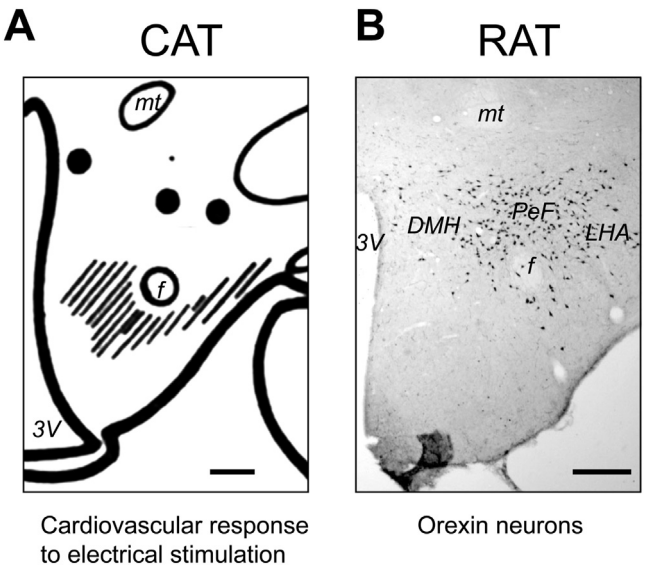

Fig. 1. The hypothalamic defence area in the cat and the distribution of orexin neurons in the rat. A. Drawing of a coronal view of the hypothalamus showing sites at which electrical stimulation in the anesthetized cat evoked large hindlimb vasodilation, a characteristic feature of the cardiovascular response evoked from the hypothalamic defence region. The large dots above the fornix show sites at which strong responses were obtained. The hatched area marks the region where vasodilation was regularly obtained, probably in part as a result of stimulation of fibers of passage originating from the regions where the large dots are. *Reproduced with permission from*Abrahams et al. (1960). B. Location of orexin neurons in the rat. Note that the bulk of the neurons are located above the fornix in the area that corresponds to the sites were strong responses were obtained in the cat (Carrive, unpublished). Abbreviations: 3V, third ventricle; DMH, dorsomedial hypothalamus; f, fornix; LH, lateral hypothalamus; mt, mamillothalamic track; PeF perifornical area. Scale bar: 500 μm.

1. Introduction: from the hypothalamic defense area to orexin

A major discovery was made by Hess and Bruger in the early 1940's when they stimulated the hypothalamus of conscious cats. Electrical stimulation of the tuberal hypothalamus could evoke a powerful and well coordinated fight and flight response that looked practically identical to the natural defense response normally seen in reaction to threatening stimuli (Carrive, 2011; Hess and Brugger, 1943). Twenty years later, Hilton and co-workers demonstrated that the same region, and indeed the same sites of stimulation that produced defence responses in the conscious animal, could evoke a characteristic cardiovascular response characterized by rises in mean arterial pressure, heart rate and a redistribution of blood flow to the muscles at the expense of the viscera (Abrahams et al., 1960; Hilton, 1982). This region was located around the fornix, including what is now known as the perifornical area (PeF) extending medially in the dorsomedial nucleus of the hypothalamus (DMH), and laterally in the lateral hypothalamus (LH) (Fig. 1A). The region became known as the hypothalamic defense area (Carrive, 2011; Smith et al., 1990). Further work in the following 20 years showed its importance as an integrating center of the behavioral and autonomic components of stress responses. However, interest in the area waned in the 1980's after it was shown that amino acid microinjections had little effects, which raised the possibility that the effects of electrical stimulation were due to activation of fibers of passage rather than neurons (Carrive, 2011). DiMicco and collaborators ended the debate by demonstrating that these effects were indeed due to activation of neurons since disinhibition of this region with GABA antagonists could reproduce practically the same cardiovascular and behavioral effects as electrical stimulation (Carrive, 2011; DiMicco and Abshire, 1987; DiMicco et al., 2002) (Fig. 2A and B).

The next milestone in the history of the hypothalamic defense area was the discovery of orexin in 1998 and the demonstration that the neurons that make this neuropeptide are located in a similar perifornical area (Fig. 1B) (de Lecea et al., 1998; Sakurai et al., 1998). This gave the hypothalamic defense area a specific neurochemical marker which, from an anatomical and functional point of view, was a major breakthrough. First, it provided a convenient histochemical marker of neurons in the area and more importantly of their projections throughout the central nervous system. Second, it turned out that orexin was a neuroactive peptide making a significant contribution to the output of the hypothalamic defense area. This is best shown in two studies published 10 years apart. The first study, which was done by Kayaba et al. (2003) in orexin knock out mice showed that the increase in blood pressure, heart rate and respiratory frequency evoked by disinhibition of the hypothalamic defence region with a GABA antagonist could be reduced by 50–75%. The second study, done in rats by Iigaya et al. (2012) showed that the increase in blood pressure, heart rate, renal sympathetic nerve activity and breathing frequency evoked by disinhibition of the PeF were reduced by nearly 50% or more after systemic injection of almorexant, an antagonist of orexin receptors (Fig. 2). These two experiments demonstrate the physiological importance of orexin in terms of cardiovascular regulation in the context of stress.

The focus of this review will be the cardiovascular functions of orexin and how orexin can contribute to the cardiovascular responses to psychological stress as well as to the development of a chronic state of hypertension. The organization of the orexin system will be described first.

2. The orexin system

Orexin was discovered in 1998 by two separate groups working in parallel (de Lecea et al., 1998; Sakurai et al., 1998). De Lecea et al. called it hypocretin. Sakurai et al. called it orexin. Orexin is now the most commonly used name. There are two isoforms of orexin, Orexin A (OxA) which is 33 amino acid long and Orexin B (OxB) which is 28 amino acid long, both derived from the pre-pro orexin gene (Hcrt). OxA and OxB act on two G-protein coupled receptors called Ox1R and Ox2R. OxA has equal affinity to Ox1R and Ox2R while OxB preferentially acts on Ox2R. Orexin can be detected in the rat embryo as early as embryonic day 18, but starting from the third week, a marked increase is observed both in orexin expression and in the number of orexin neurons (de Lecea et al., 1998; Sawai et al., 2010). Interestingly, the third week corresponds to the weaning period, which is when the young rat starts interacting with its environment.

Much work has been done in the last 2 decades to understand the role of orexin in the central nervous system. Put simply, orexin is involved in the regulation of arousal. Its first role is in the maintenance of wakefulness during the day. Its second role is in the expression of motivated behaviors (ie, hyperarousal) which can be for obtaining a reward or escaping a danger (Giardino and de Lecea, 2014; Li et al., 2014; Sakurai, 2014; Sakurai and Mieda, 2011). Thus orexin is involved in defence responses and responses to potential stressors, which is consistent with the effects originally described by stimulation of the area where it comes from. However, it is also involved in reward. It has been proposed that orexin neurons located medially are preferentially involved in stress responses whereas those located laterally are preferentially involved in reward responses (Clifford et al., 2015; Harris and Aston-Jones, 2006), although this still needs to be investigated in more detail (Giardino and de Lecea, 2014). Nevertheless, the com-