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Review

The emerging role of the parabrachial complex in the generation of wakefulness drive and its implication for respiratory control☆

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ABSTRACT

The parabrachial complex is classically seen as a major neural knot that transmits viscero- and somatosensory information toward the limbic and thalamic forebrain. In the present review we summarize recent findings that imply an emerging role of the parabrachial complex as an integral part of the ascending reticular arousal system, which promotes wakefulness and cortical activation. The ascending parabrachial projections that target wake-promoting hypothalamic areas and the basal forebrain are largely glutamatergic. Such fast synaptic transmission could be even more significant in promoting wakefulness and its characteristic pattern of cortical activation than the cholinergic or mono-aminergic ascending pathways that have been emphasized extensively in the past. A similar role of the parabrachial complex could also apply for its more established function in control of breathing. Here the parabrachial respiratory neurons may modulate and adapt breathing via the control of respiratory phase transition and upper airway patency, particularly during respiratory and non-respiratory behavior associated with wakefulness.

1. Overview: anatomy and physiological functions of the parabrachial complex

The parabrachial complex is located in the dorsal lateral pons and can be subdivided into more than 10 distinct sub-nuclei that surround the superior cerebellar peduncle (Fulwiler and Saper, 1984). Over the last 40 years, neurons of the parabrachial complex were shown to play an important role in the processing and relaying of somato- and viscero-sensory information. The subnuclei of the parabrachial complex have well established functions in the mediation of pain (see Willis and Westlund, 1997; Gauriau and Bernard, 2002), and are involved in thermoregulation (Nakamura and Morrison, 2008; Morrison and Nakamura, 2011), taste processing (Norgren and Leonard, 1971; Yamamoto et al., 1994), and in the control of the cardio-respiratory systems (Mraovitch et al., 1982; Chamberlin, 2004; Dutschmann and Dick, 2012). In the context of the general role of the parabrachial complex in homeostasis, it is not surprising that the parabrachial subnuclei have important implications in the control of food, water and salt intake (Johnson and Thunhorst, 1997; Shin et al., 2011; Wu et al., 2012).

Therefore, on a larger scale, the parabrachial complex can be seen as a major brain area that relays primary sensory information of the body to autonomic and limbic forebrain areas, such as the hypothalamus and amygdala (Saper and Loewy, 1980; Fulwiler and Saper, 1984). The viscero- and somatosensory sensations transmitted via the parabrachial subnuclei are, in turn, converted into basic emotions such as hunger, thirst, feeling cold, or in case of the respiratory system, into emotions related to respiratory distress and the urge to breathe. These basic emotions are the source of a 'homeostatic behavioral drive' which is finally converted into specific motor behavior (for excellent reviews see Craig, 2002a,b, 2003).

Considering the role of the parabrachial complex in the generation of emotional and behavioral drive, it is intriguing to think about the implications of the parabrachial subnuclei in the generation of wakefulness. Indeed, a recent study from Patrick Fuller and colleagues showed that after a bilateral lesion of the entire parabrachial complex, including the pre-coeruleus region, animals fell into a deep coma (Fuller et al., 2011). This raises the question of whether parts of the parabrachial complex belong to the ascending reticular arousal system, and thus have direct influence on modulation of the wake-sleep cycle. The mammalian wake-sleep cycle is defined as the alternation of three different behavioral states: wakefulness, non-REM sleep (NREMS) and REM sleep (REMS). An extensive literature has been produced over the years in an attempt to analyze which brain areas are responsible for keeping us awake or making us fall asleep, and the circuitry responsible for REMS induction.

Here we review recent evidence proposing a critical role for several subnuclei of the parabrachial complex in the regulation of the wake-sleep cycle.

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2. An emerging role of the parabrachial complex in the neural control of wakefulness

One of the unchallenged doctrines of modern neurosciences is that wakefulness and global activation of cortical and limbic forebrain structures depend on synaptic drive arising from the ascending arousal system. Since the pioneer work of Moruzzi and Magoun (1949), which have shown that destruction of the reticular formation of the midbrain and pons caused persistent coma in cats, various midbrain, pontine but also hypothalamic brain nuclei have been implicated in the initiation and maintenance of wakefulness. Serotonergic neurons of the dorsal raphé nucleus in the midbrain and noradrenergic neurons of the locus coeruleus in the pons are seen as essential parts of the ascending arousal system. In the hypothalamus, histaminergic neurons in the tubero-mammillary nucleus and orexinergic neurons in the lateral hypothalamus are also considered to be key players for the maintenance of wakefulness (for comprehensive review see Saper et al., 2001, 2005; Fuller et al., 2006).

Extensive anatomical tract tracing studies have shown that the midbrain, pontine and hypothalamic arousal nuclei share extensive reciprocal connectivity, and thus may form a distinct neural network (see Fuller et al., 2006). Activating or disinhibiting just one of these nuclei of the ascending arousal system can, indeed, induce prolonged periods of active wakefulness in animal models (Berridge and Foote, 1991; Huang et al., 2001, 2003; Tao and Auerbach, 2003; Carter et al., 2010; Monti, 2010). However, lesions of single wakefulness-promoting brain areas demonstrated that none of the arousal nuclei are key players in initiating or maintaining wakefulness (Jacobs et al., 1974; Jones et al., 1977; Blanco-Centurion et al., 2007). As a matter of fact, the alertness of cats and rats was only mildly altered following these confined lesions, which certainly did not reproduce the comatose state observed after extensive midbrain and pontine lesions (Moruzzi and Magoun, 1949).

The classic hypothesis that wakefulness is controlled by a large and distributed network of neurons has recently been challenged. Fuller et al. (2011) showed that confined lesions of the entire parabrachial complex, including the pre-coeruleus region, induced a continuous slow wave EEG pattern similar to the coma state described in the early works of Moruzzi and Magoun (1949). Thus, while the connectivity of the parabrachial complex with all parts of ascending arousal system was well established in earlier studies (Saper and Loewy, 1980; Fulwiler and Saper, 1984; Krukoff et al., 1993), the experiments performed by Fuller et al. (2011) are the first to functionally show that the parabrachial complex and the adjacent pre-coeruleus region is essential for promoting wakefulness.

The absence of cortical arousal and the comatose state seen after parabrachial/pre-coeruleus lesions can be explained by a lack of an essential glutamatergic drive that arises from various parabrachial subnuclei. Fuller et al. (2011) revealed that ascending glutamatergic projections, particularly from the medial parabrachial nucleus, target cholinergic and non-cholinergic basal forebrain structures. Because the basal forebrain is critical for maintenance of cortical arousal (Alam et al., 1999; Sarter and Bruno, 2000; Fuller et al., 2011; Zant et al., 2012), the absence of fast excitatory glutamatergic input to the basal forebrain can be a straightforward explanation for the slow wave cortical EEG activity that follows a parabrachial complex lesion. Ascending glutamatergic projections from the lateral parabrachial nuclei also target the orexinergic neurons of the lateral hypothalamus (Niu et al., 2010) and the activity of these orexinergic neurons are considered to be fundamental in maintaining wakefulness (Hagan et al., 1999; Kiyashchenko et al., 2002; Berridge and España, 2005). The importance of the hypothalamic orexin neurons in maintaining wakefulness was demonstrated

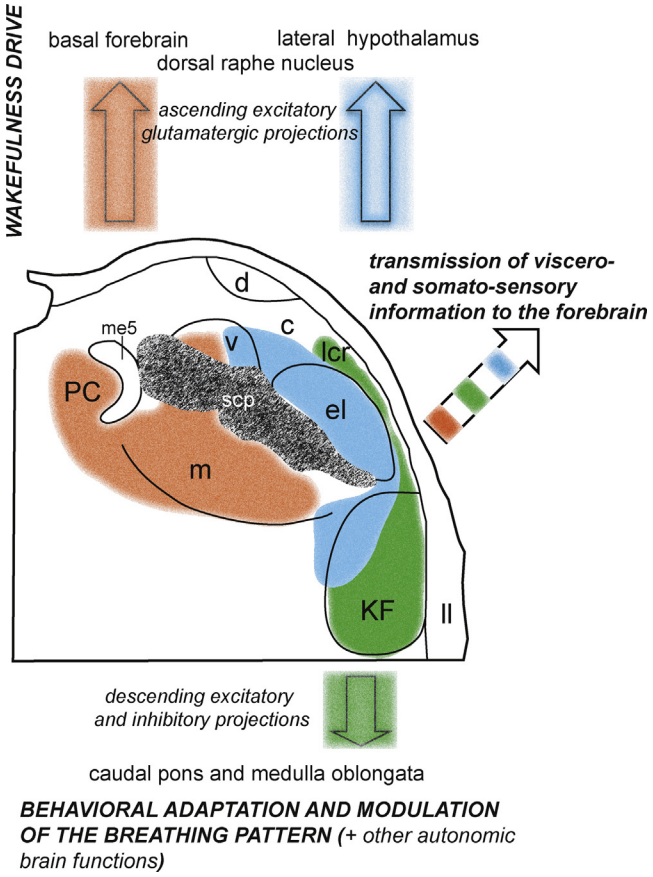

Fig. 1. Schematic illustration of the functions of the parabrachial complex during wakefulness. The orange shaded area overlapping with the medial (m) parabrachial subnucleus and the pre-coeruleus region (PC) mark the origin of ascending glutamatergic projections that target the basal forebrain and dorsal raphé nucleus of the midbrain. The blue shaded area illustrates the origin of ascending glutamatergic neurons that target the wake promoting areas of the lateral hypothalamus and the dorsal raphé nucleus. The green shaded area overlapping with the Kölliker-Fuse nucleus and lateral crescent nucleus indicate the respiratory regions of the parabrachial complex. Please note that the green area represents the area with the most pronounced descending projections of the parabrachial complex that innervate the medullary respiratory centers, including respiratory motor neurons in the brainstem and spinal cord. *Abbreviations*: ll = lateral lemniscus, scp = superior cerebellar peduncle, me5 = mesencephalic trigeminal nucleus. *Subnuclei of the parabrachial complex:* c = central, d = dorsal, el = external lateral, lcr = lateral crescent, KF = Kölliker-Fuse, m = medial, and v = ventral.

by *in vivo* single unit recordings showing that orexinergic neurons are most active during wakefulness, decrease their discharge rate during quiet waking, and virtually cease to fire during both REMS and NREMS (Lee et al., 2005). Nevertheless, orexinergic neurons can show occasional bursts of action potentials during REMS (Mileykovskiy et al., 2005), particularly during the transition from REMS to wakefulness (Takahashi et al., 2008). However, it appears that excitatory glutamatergic inputs from the lateral parabrachial nuclei may drive these lateral hypothalamic orexinergic neurons predominantly during wakefulness (Fig. 1).

Another important source of ascending excitatory input to the orexinergic neurons of the lateral hypothalamus comes from neuropeptide S (NPS) neurons in the parabrachial complex. NPS has been associated with a variety of physiological functions, and in particular, arousal and regulation of the wake-sleep cycle (Xu et al., 2004; Duangdao et al., 2009). According to current standing, NPS is expressed only in neurons of the locus coeruleus area, the principal sensory trigeminal nucleus, and the lateral parabrachial nucleus in rat (Xu et al., 2007), while in mice, only the Kölliker-Fuse nucleus and the pre-coeruleus region express NPS (Clark et al., 2011). Thus,