Origins of arousal: roles for medullary reticular neurons

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The existence of a primitive CNS function involved in the activation of all vertebrate behaviors, generalized arousal (GA), has been proposed. Here, we provide an overview of the neuroanatomical, neurophysiological and molecular properties of reticular neurons within the nucleus gigantocellularis (NGC) of the mammalian medulla, and propose that the properties of these neurons equip them to contribute powerfully to GA. We also explore the hypothesis that these neurons may have evolved from the Mauthner cell in the medulla of teleost fish, although NGC neurons have a wider range of action far beyond the specific escape network served by Mauthner cells. Understanding the neuronal circuits that control and regulate GA is central to understanding how motivated behaviors such as hunger, thirst and sexual behaviors arise.

Introduction

Contrary to the *zeitgeist* of concentrating on specific problems such as the neurochemistry of dendritic spines or the importance of particular single nucleotide polymorphisms, we entertain a global concept intended to express the most powerful and essential force in the nervous system: GA of the CNS. We begin by presenting three independent lines of evidence that GA exists. We then propose central integrative roles for large medullary reticular neurons, those in the NGC and the adjacent medullary reticular cell group, the paragigantocellularis. The most impressive among such neurons in vertebrate brains are the Mauthner cells in the fish medulla, which we propose as possible evolutionary predecessors of neurons in the NGC of the mammalian brain. By emphasizing a central role for NGC neurons as nodes in the circuits regulating CNS arousal, we do not argue for some 'unique' feature of neurons in the NGC. Rather, we seek to understand what important features they add to the facilitation of CNS arousal as they work in concert with other reticular neurons to accomplish a crucial brain function that is the foundation for diverse motivated behaviors.

GA of the CNS

Why does any vertebrate animal do anything at all? We argue here that there are primitive mechanisms in all vertebrate brains that are important for initiating the activation of all behaviors. We assert that there exists a primitive function in the vertebrate brain, GA, thought of as the most powerful and essential force in the nervous system for the activation of behavioral responses [1]. An operational definition that leads to physical, quantitative measurements states [1] that a more aroused animal or human is (1) more responsive to sensory stimuli in all sensory modalities; (2) emitting more voluntary motor activity; and (3) more reactive emotionally. The operating requirements of GA systems have been presented previously [2] (Box 1). Thus far, three independent lines of evidence – statistical, genetic and mechanistic – have been adduced to demonstrate that a force called GA actually operates in the brains of laboratory animals.

First, previous studies have found statistical evidence that GA exists. Specifically, factor analysis of a large amount of data from several arousal-related experiments indicated that approximately 25–40% of arousal-related variance can be attributed to a GA component [3,4]. Control calculations showed that this result was robust in three ways: (1) the GA factor was never identical to the first factor of any particular multifactor analysis; (2) it accounted for significantly more real data than in any random-number control; and (3) nothing similar to the GA factor appeared in a stringent control in which marginal averages were held constant but the individual data entries were scrambled randomly [3,4].

The second line of evidence supporting the existence of GA is genetic. Because one cannot breed for a function that does not exist, success in breeding for GA would indicate its existence. Indeed, mouse lines with high and low GA are being successfully established [3]. Such lines were generated using the operational definition of GA discussed above, and began with a founder generation that had high genetic heterogeneity. Subsequently, males and females high in GA were selected and mated. Likewise, males and females low in GA were paired, and at this point in time, significant separation between the high and low arousal lines has been achieved [3].

Third, one also cannot have mechanisms for a neural process that does not exist. Thus, the third independent line of evidence for the existence of GA is mechanistic. That is, a substantial amount of information already exists about the neuroanatomical, neurophysiological and molecular mechanisms that produce GA. Here and below, in reviewing neuroanatomical, neurophysiological and molecular mechanisms that provide further evidence for the existence of GA, we show how NGC neurons could contribute to the three operationally defined components of GA (i.e., sensory responsiveness, motor activity and emotional

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Box 1. Operating requirements of CNS arousal systems

To provide the elements of the operational definition of GA – alertness to all sensory stimuli, production of voluntary motor activity and provision for emotional reactivity [2] – certain operational features are required.

- GA systems have to be labile, not sluggish. Furthermore, they must be sensitive to the momentary state of the organism.
- Their 'geometry' is crucial. On the one hand, convergence is required. All sensory stimuli activate the same set of arousal subsystems, which, in turn, support each other.
- On the other hand, they diverge. They activate cerebral cortex, autonomic nervous systems, and endocrine organs to initiate behavior.
- Finally, they must be robust; they cannot fail. Survival of the organism depends on adequate CNS arousal.

reactivity). Neuroanatomical investigations have revealed five ascending systems (noradrenergic, dopaminergic, histaminergic, cholinergic and serotonergic [1]) and several descending systems, including oxytocinergic, vasopressinergic and axons descending from hypocretin/orexin neurons. Among arousal systems, the large spread of inputs and outputs of medullary reticular neurons are particularly impressive (Figure 1). Importantly, many of the large cells in the medullary reticular formation have axonal bifurcations that would allow them to contribute to both ascending and descending arousal systems (Figure 2) [5–9]. Among NGC neurons, the latter cells may be the most influential for regulating both cortical and autonomic arousal.

Regarding the three components of the operating definition of GA, neurons in the NGC are involved in the first, sensory responsiveness, as follows. Medullary neurons in this region have neurophysiological properties that would allow them to act as 'first responders' to arousing stimuli. As discussed below, they have multimodal responses to sensory stimuli (Figure 3), their responses habituate, they are associated with activation on cortical electroencephalography (EEG) and neck muscle electromyography (EMG), and their increased firing rates precede the activation of behavioral responses from a state of quiescence [10]. The second GA component relates to the regulation of voluntary motor activity. Reticulospinal neurons originating in the medulla are widely recognized in the classical neurophysiological literature to regulate motor activity [11,12] through spinal interneurons and through direct connections to motoneurons, having reticulospinal axons that terminate in all spinal cord segments bilaterally. The third component of GA relates to emotional responsiveness. For work with laboratory animals, sexual arousal and fear represent heightened states of emotional systems that can be replied on. Medullary reticular neurons have clear roles in sexual arousal, in both males and females. With respect to male sexual behavior, there are strong inputs from the penis to medullary reticular formation [13], which in turn regulates erection and ejaculation [14]. In agreement with such data, androgen receptors for regulating this exquisitely androgen-sensitive emotional state are found in NGC neurons [15]. Regarding females, NGC

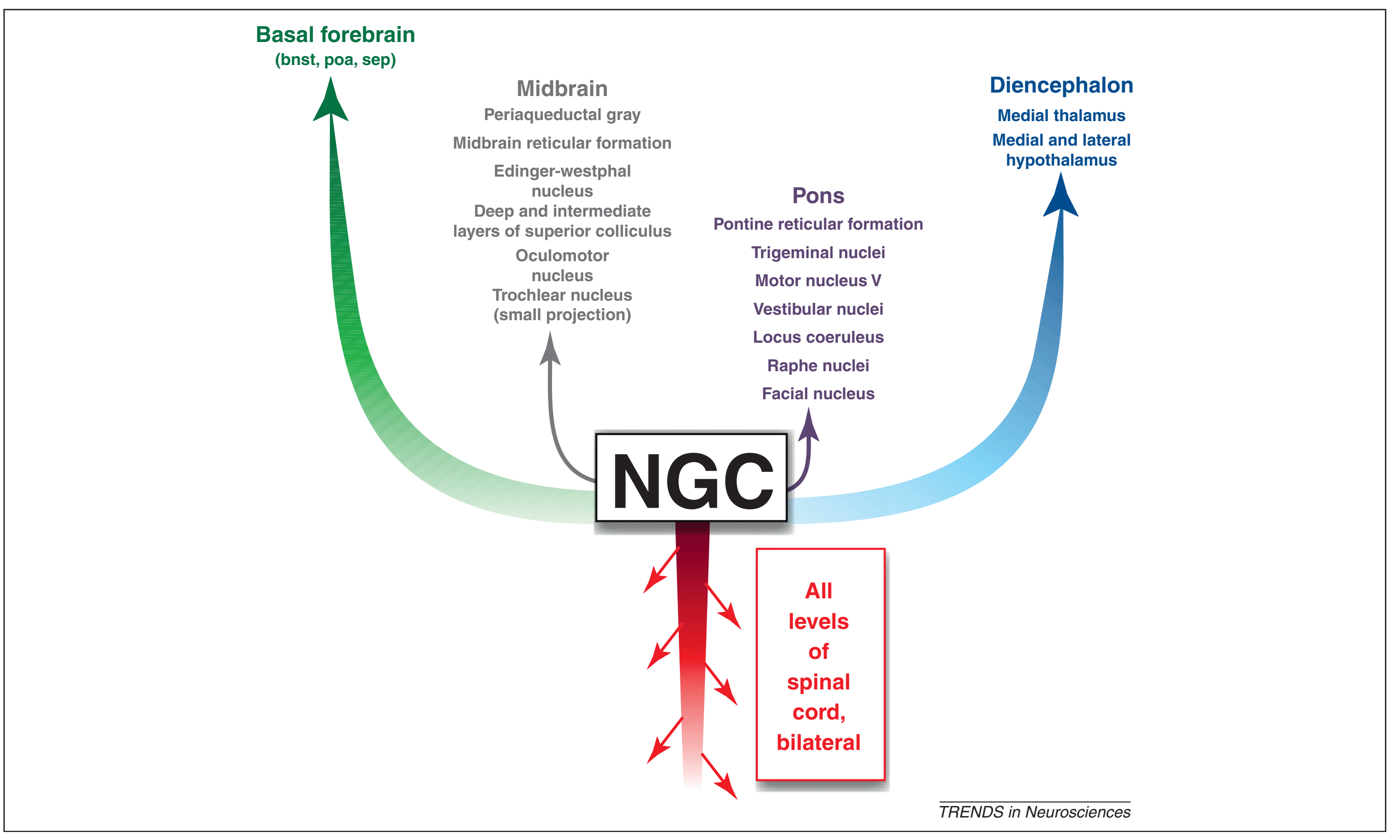

Figure 1. Anatomical projections originating in the NGC of the vertebrate brainstem. Large medullary reticular neurons in the NGC not only have powerful descending projections to all levels of the spinal cord but also have significant, multiple ascending projections. These ascending projections reach the parts of the midbrain reticular formation essential for consciousness, and the portions of the medial thalamus where deep brain stimulation supports conscious behavior [2], as well as basal forebrain sites important for modulating neocortical activity. Together with their broad dendritic spreads in the medulla, NGC neurons' widespread distribution of axons serves their functions proposed here as 'master cells' for the regulation of CNS arousal. bnst, bed nucleus of the stria terminalis; poa, preoptic area; sep, septum.