



Review article

The periaqueductal gray and primal emotional processing critical to influence complex defensive responses, fear learning and reward seeking



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ARTICLE INFO

Article history:

Received 7 July 2016

Received in revised form

26 September 2016

Accepted 13 October 2016

Keywords:

Emotional states

Panic

Anxiety

Fear learning

Seeking

Defensive behavior

ABSTRACT

The periaqueductal gray (PAG) has been commonly recognized as a downstream site in neural networks for the expression of a variety of behaviors and is thought to provide stereotyped responses. However, a growing body of evidence suggests that the PAG may exert more complex modulation of a number of behavioral responses and work as a unique hub supplying primal emotional tone to influence prosencephalic sites mediating complex aversive and appetitive responses. Of particular relevance, we review how the PAG is involved in influencing complex forms of defensive responses, such as circa-strike and risk assessment responses in animals. In addition, we discuss putative dorsal PAG ascending paths that are likely to convey information related to threatening events to cortico-hippocampal-amygdalar circuits involved in the processing of fear learning. Finally, we discuss the evidence supporting the role of the PAG in reward seeking and note that the lateral PAG is part of the circuitry related to goal-oriented responses mediating the motivation to hunt and perhaps drug seeking behavior.

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1. Introduction

The periaqueductal gray (PAG) has been commonly recognized as a downstream site in neural networks for the expression of a vari-

ety of behaviors, i.e., sexual, maternal and defensive behaviors and the accompanying modulation of nociceptive transmission, autonomic changes and vocalization (Bandler and Shipley, 1994; Besson et al., 1991; Carobrez et al., 1983; Cezario et al., 2008; Fanselow, 1991; Gruber-Dujardin, 2010; Jurgens, 1994; Lonstein and Stern, 1997, 1998; Lovick, 1993; Sakuma and Paff, 1979). By and large, PAG-related responses have been regarded as being mostly stereotyped and dependent on descending projections to the brainstem and spinal cord.

Data show that fear of painful stimuli, predators and aggressive members of the same species are processed in independent neural circuits that involve the amygdala and downstream hypothalamic and brainstem circuits. In the brainstem, the PAG is the main target of these downstream circuits meditating different types of fear (see Gross and Canteras, 2012). The PAG is organized in longi-

Abbreviations: ACA, anterior cingulate area; AHN, anterior hypothalamic nucleus; CEA, central amygdalar nucleus; ILA, infralimbic area; lateral PAG, periaqueductal graylateral part; LDT, laterodorsal tegmental nucleus; LHA, lateral hypothalamic area; MEPO, median preoptic nucleus; PL, prelimbic area; PPN, pedunculo-pontine nucleus; PRNr, reticular pontine nucleusrostral part; SCL, superior colliculuslateral part; VTA, ventral tegmental area.

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tudinally organized functional columns, namely the dorsomedial, dorsolateral, lateral and ventrolateral columns (Bandler and Keay, 1996; Bandler and Shipley, 1994; Carrive, 1993). Notably, different prosencephalic fear circuits target different parts of the PAG in a way that circuits mediating fear of painful stimuli, predators and aggressive conspecifics preferentially influence the dorsolateral, dorsomedial/lateral and ventrolateral, respectively, which are thought to be involved in the expression of a wide array of innate fear responses (see Gross and Canteras, 2012).

However, a growing body of evidence suggests that the PAG plays a critical role in a number of complex behavioral processes influencing ascending targets in prosencephalic sites likely to mediate fear behavior.

Neurosurgeons investigating deep brain stimulation at mid-brain sites as a method for relieving intractable pain have reported that the procedure often evoked intolerable side effects that resembled symptoms of panic (Amano et al., 1982; Nashold et al., 1969; Richardson and Akil, 1977). As reported by Nashold et al. (1969), stimulation by electrodes implanted in the PAG evoked fearful and unpleasant sensations in a way that patients did not tolerate. Notably, the stimulation applied to areas involved in pain transmission outside of the PAG did not evoke unpleasant feelings, and the patients could tolerate the stimulation well (Nashold et al., 1969). Similar findings were reported by Amano et al. (1982), where electrical stimulation of the dorsal PAG produced marked changes in patients' psychological conditions, and depending on the frequency of the electrical stimulation, patients reported terror feelings "...as something horrible is coming...". These feelings of fear and horror certainly depend on the influence that the PAG exerts on cortical sites processing cognitive aspects of fear sensation. At this point, it remains to be addressed how the PAG has such a dramatic influence on the cognitive feeling of fear sensations.

In fact, the PAG occupies a particularly privileged position to provide, as called by Panksepp, the "instinctual" primary process and should be critical in orchestrating the emotional system of the brain (Panksepp, 2016). In this regard, it is particularly relevant to understand how the PAG influences primal emotional affects, which, as defined by Panksepp (2016), are likely to be integrated by subcortical emotional networks, labeled seeking, rage, fear, lust, care, panic, and play systems. Among these networks, we shall pay particular attention to the fear, panic and seeking systems.

In the present review, we provide behavioral evidence showing the involvement of the PAG in modulating a number of complex responses, such as complex motor actions related to fear and anxiety, fear memory processing and reward seeking. In parallel, we shall explore possible paths by which the PAG communicates with ascending prosencephalic targets to influence these responses.

2. PAG and fear and panic responses

Deakin and Graeff (1991) suggest that panic is a malfunction of the dorsal PAG, and experiments using animal models, such as the elevated T-maze and the mouse defense test battery, showed that serotonergic agonists acting at the 5HT1A-receptor reduced escape responses in both tasks, suggesting a panicolytic-like effect (Pobbe et al., 2011; Zanoveli et al., 2003). In addition, up-regulation of Fos expression in the dorsal PAG, suggesting an increase in PAG activation particularly in the dorsomedial and, to a lesser degree, in the dorsolateral parts, has been found in panic responses induced by inhalation of hypercarbic gas (Johnson et al., 2011). In animals, as reported in humans, dorsal PAG stimulation is highly aversive, and animals may present acute avoidance, withdrawing rapidly from the stimulation chamber (Deng et al., 2016) and can learn to perform operant behavior to switch off the stimulus (Jenck et al., 1995). Moreover, dorsal PAG stimulation evokes behavioral and

autonomic changes characteristic of panic (Bandler and Shipley, 1994; Fanselow, 1991; Lovick, 1993; Yardley and Hilton, 1986), and drugs known to acutely reduce or precipitate panic attacks in patients were found to acutely and dose-dependently reduce or enhance, respectively, aversion induced by dorsal PAG stimulation (Jenck et al., 1995).

Predator-elicited defensive responses also induce behavior and autonomic responses characteristic of panic (see Blanchard et al., 1989). The type of fear response to a predator is determined by predatory imminence (Blanchard et al., 1989; Fanselow, 1991). After a predatory encounter, rodents express the species-typical defense response of freezing (post-encounter defense), and as predatory imminence and the potential of attack increases, rodents switch from freezing to a circa-strike defense, including escape attempts and jumps (Fanselow, 1991). In other words, "post-encounter" reflects the initial detection of the potential threat, whereas "circa-strike" is associated with the direct interaction with the predator (i.e., when the predator attacks). Accordingly, both post-encounter and circa-strike defensive behaviors have been ascribed to the dorsomedial, dorsolateral and lateral columns of the PAG, where electrical, pharmacological and optogenetic stimulation have been shown to produce freezing, escape and flight behavior in the absence of a predatory threat (Assareh et al., 2016; Bandler and Keay, 1996; Bittencourt et al., 2004; Carrive, 1993; Deng et al., 2016). Interestingly, dorsal and lateral PAG stimulation may evoke either freezing or escape and jumps, where low magnitude stimuli produced freezing, and slightly higher intensities evoked circa-strike responses (Assareh et al., 2016; Bittencourt et al., 2004; Vianna et al., 2001). Recent findings in mice using optogenetic tools have shown that higher frequency or higher intensity optogenetic stimulation in the dorsal PAG induced running followed by post-stimulation freezing, with progressively increasing levels of freezing with increases in laser stimulation strength (Deng et al., 2016).

On the other hand, the ventrolateral PAG has been shown to be involved in organizing immobility and freezing during the post-defense recuperative-like quiescent behavior (Assareh et al., 2016; Bandler and Keay, 1996; Bittencourt et al., 2004; Carrive, 1993). However, in contrast to this idea, recent observations by our lab have suggested that the ventrolateral PAG is also seemingly involved in organizing freezing during a predatory encounter (S. R. Mota-Ortiz and N.S. Canteras, personal observations).

While it has been well established that freezing behavior depends on descending PAG projections to pre-motor targets in the magnocellular nucleus of the medulla (Tovote et al., 2016), the neural circuits underlying the expression of circa-strike responses remain poorly understood. In fact, flight is a very complex response made up of trotting, galloping and jumping responses (see Bittencourt et al., 2004). Interestingly, dorsal PAG stimulation evokes complex behavioral responses that may depend on the testing conditions. Thus, in animals tested in a foraging environment, where they could search for food pellets placed away from a nesting area, dorsal PAG stimulation yielded a fleeing response back to the nesting area when the animals approached a food pellet (Kim et al., 2013). It is reasonable to believe that this elaborated display of PAG-evoked fleeing responses would be organized by prosencephalic circuits. Corroborating this idea, Kim et al. (2013) have shown that basolateral amygdalar lesions completely blocked fleeing responses evoked by dorsal PAG stimulation, suggesting that the basolateral amygdala is downstream of the dorsal PAG in mediating such behaviors. However, a great deal remains to be learned on how the PAG communicates with prosencephalic circuits to influence fear and panic responses, particularly the mediation of the complex array of circa-strike behaviors.

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