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Review

Executive and modulatory neural circuits of defensive reactions: Implications for panic disorder

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ABSTRACT

The present review covers two independent approaches, a neuroanatomical and a pharmacological (focused on serotonergic transmission), which converge in highlighting the critical role of the hypothalamus and midbrain periaqueductal gray matter in the generation of panic attacks and in the mechanism of action of current antipanic medication. Accordingly, innate and learned fear responses to different threats (i.e., predator, aggressive members of the same species, interoceptive threats and painful stimuli) are processed by independent circuits involving corticolimbic regions (the amygdala, the hippocampus and the prefrontal and insular cortices) and downstream hypothalamic and brainstem circuits. As for the drug treatment, animal models of panic indicate that the drugs currently used for treating panic disorder should work by enhancing 5-HT inhibition of neural systems that command proximal defense in both the dorsal periaqueductal gray and in the medial hypothalamus. For the anticipatory anxiety, the reviewed evidence points to corticolimbic structures, such as the amygdala, the septo-hippocampus and the prefrontal cortex, as its main neural substrate, modulated by stimulation of 5-HT_{2C} and 5-HT_{1A} receptors.

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1. Introduction

In an attempt to explain why both drugs and psychotherapy are effective in the treatment of panic disorder, Gorman et al. (1989), addressing to its three cardinal manifestations, suggested that the neural substrate of panic attacks lies in the brain stem, that of anticipatory anxiety in limbic structures, and that of phobic avoidance in the prefrontal cortex. Drugs are supposed to act on the first two components, whereas psychotherapy would act through the latter. This working hypothesis guided a wealth of clinical and preclinical research that was comprehensively reviewed by Dresler et al. (2013). Among their conclusions, one that is central to the present discussion is that the prevalent view assuming the so-called fear network, determined on the basis of the conditioned fear paradigm, underpins panic attacks should be reconsidered. In particular, the central role attributed to the amygdala in the triggering of panic attacks became difficult to sustain, at least for internal threats, after the results recently reported by Feinstein et al. (2013) showing that inhalation of 35% CO_2 evoked strong fear and panic attacks in three patients with bilateral amygdala damage.

Therefore, a finer analysis of the neural circuitry underlying panic as compared to anxiety and fear is necessary. For this purpose, the present review covers two independent approaches, one neuroanatomical and the other pharmacological, which converge in highlighting the critical role of the hypothalamus and of the midbrain periaqueductal gray matter in the generation of panic attacks and in the mechanism of action of current anti-panic medication. Both approaches assume the evolutionary perspective that relates different defensive strategies that are common to all mammalian species to normal emotions and to specific anxiety disorders (see e.g., Graeff, 1994, 2010).

The first part of the article describes the neural systems that organize behavioral and neurovegetative responses to innate external and internal threats of different kinds (Section 2), as well as of learned defensive reactions (Section 3). The second part deals with the differential modulation by serotonin (5-HT) of the neural structures involved in anxiety and panic, respectively (Section 5).

2. Neural organization of innate defensive responses

The use of ethologically based threats, like predator exposure and attack by conspecifics, has provided an interesting prospective on how innate fear responses should be organized. Moreover, interoceptive cues, such as those derived from suffocation conditions that threaten homeostasis of blood CO_2 concentrations, may also work as important stimuli to elicit innate aversive panic responses. In this part of the review, we shall first discuss how these different threats are processed by parallel circuits, likely to be preserved across species. We shall start discussing how the amygdala and hypothalamus respond to integrate these different threats and how this information targets the periaqueductal gray (PAG), a critical brain site for the organization of innate fear responses. Next, we shall discuss how the cerebral cortex and hippocampus would be involved in these responses.

2.1. Neural system underlying innate fear to predator threats

Predator exposure represents a life threatening event and induces vigorous innate defensive responses without the need of previous relevant experience. In particular, cat exposure to rats produces in the latter intense freezing, avoidance (and hiding, if a place of concealment is available), and elements of risk assessment, such as orientation to the predator (see Blanchard et al., 1989). Notably, responses to predator exposure are very resistant to habituation. Previous functional studies have shown, in rodents, that predator exposure mobilizes distinct amygdalar and hypothalamic sites. Thus, exposure to a predator or its odor has been shown to up-regulate Fos expression in a hypothalamic circuit formed by the anterior hypothalamic nucleus, the dorsomedial part of the ventromedial nucleus, and the ventrolateral part of the dorsal premammillary nucleus (PMD) – the predator-responsive medial hypothalamic circuit (Fig. 1A; Canteras, 2002; Martinez et al., 2008). As shown in Fig. 1A, the predator-responsive medial hypothalamic circuit receives inputs from two amygdalar paths that integrate predator-related cues. The first one is related to predator odor, processed by prey species in the accessory olfactory bulb, and transmitted to the medial amygdalar nucleus (Dielenberg et al., 2001; Canteras, 2002). Rats exposed to cat odor show substantial activation of this nucleus, particularly in its posteroventral part (Dielenberg et al., 2001). In line with this view, rats with cytotoxic lesions in the medial nucleus, but not in the central nucleus, exhibited a significant reduction in unconditioned fear responses to a live cat or its odor (Li et al., 2004; Martinez et al., 2011). The second amygdalar path related to predator detection comprises the lateral and posterior basomedial amygdalar nuclei, known to receive inputs from the medial amygdala as well as from visual and auditory association areas, and is likely to integrate a wealth of predator-derived cues, from olfactory to non-olfactory ones (Canteras, 2002). Cytotoxic lesions of these amygdalar sites have also been shown to reduce unconditioned defensive responses during exposure to a live predator (Martinez et al., 2011). Both amygdalar paths target the predator-responsive medial hypothalamic circuit mostly by projecting to the dorsomedial part of the ventromedial nucleus.

The predator-responsive medial hypothalamic circuit seems to be preserved across species, and at least part of it is also present in humans and has been shown to organize fear responses. Functional magnetic resonance imaging (fMRI) studies in human participants have shown that video clips of threatening actions were able to induce a clear activation in the posterior half of the medial hypothalamus (Pichon et al., 2012). This finding is particularly revealing, showing that, in humans, the hypothalamus is particularly responsive to psychological threats. Moreover, findings obtained from an awake patient undergoing bilateral implantation of deep brain stimulation electrodes into the hypothalamus have shown that the dorsomedial part of the ventromedial hypothalamic nucleus (VMHdm) presented the lowest threshold to induce panic attacks (Wilent et al., 2010). Similar to what has been found for rodents during predatory exposure, in humans, the VMHdm may be thought to be part of a circuit that organizes complex active programs to support impending death situations, such as exposure to a war zone or gun threatening. Therefore, like predatory threats in rodents, psychological threats in humans seem to engage an analogous medial hypothalamic circuit, which is likely to have a large impact on fear responses, and perhaps on fear memory processing.

The predator-responsive medial hypothalamic circuit preferentially targets the dorsolateral part of the PAG (Fig. 1A; PAGdl). Stimulation of the PAGdl elicits species-specific autonomic and behavioral defensive responses in cats and rats, as well as feelings of fear, impending death and apprehensive avoidance in humans (Hunsperger, 1956; Nashold et al., 1969; Bittencourt et al., 2004). The kind of fear responses to a predator-related cue depends on its degree of ambiguity for signaling the predator presence. Thus, fear responses to the actual predator include mostly freezing and, depending on the proximity of the predator, also flight responses when the predator is close by (Ribeiro-Barbosa et al., 2005). On the other hand, fear responses to a more ambiguous threat, like predator odor, are characterized by risk assessment responses, including a careful scanning of the environment in the crouch position (crouch sniffing) and attempts to approach the threatening stimulus by stretching the body (stretch postures) (Canteras et al.,