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OXFORD

LETTER TO THE EDITOR

Dysfunctional Relationship Between the Prefrontal Cortex and Amygdala for Explaining Posttraumatic CRPS Syndrome

Dear Editor,

After limb trauma, the first short lasting response corresponds to a facilitatory supraspinal influence exerted at the spinal cord with sympathoexcitation. A descending sympathoexcitatory response with analgesia, peripheral vasoconstriction, and facilitated motor reflexes could be an active adaptive response for helping to maintain the capacity to use an injured body part for flight or fight in case of emergency. After that, a descending sympathoinhibitory response with hyperalgesia, vasodilatation, and muscle weakness could be a passive adaptive response, where facilitation of pain might promote protection from new injury and vasodilatation and immobilization might help the healing process of the injured region. Persistent sympathoinhibition has been implicated for developing posttraumatic complex regional pain syndrome (CRPS). However, there is little known about the underlying neuroanatomical pathways involved in persistent sympathoinhibition in CRPS patients.

Anatomical substrate for explaining different patterns of autonomic response

Periaqueductal gray (PAG) has been seen as a center for defensive reactions that is capable of coordinating the sensory, motor, and autonomic outputs of the stress response. According to Vianna [1], four main longitudinal cell-rich subdivisions exist in the PAG, namely the dorsomedial (dmPAG), dorsolateral (dlPAG), lateral, and ventrolateral (vlPAG) subdivisions. Activation of neurons in the lateral/dorsolateral column of the PAG (l/dlPAG) results in sympathoexcitation that accompany the fight-or-flight response [2,3]. Activation of neurons in the vlPAG results in the sympathoinhibition that can accompany deep pain [2,3]. These PAG columns have extensive, viscerotopically organized, descending projections to sympathetic premotor neurons in the rostroventral medulla (RVM) [4]. Differential activation of l/dlPAG columns and vlPAG columns could provide a substrate for the parallel activation or inhibition of premotor neurons in the RVM and Locus Coeruleus thus explaining different patterns of autonomic activity supporting active and passive coping behaviors.

The Spino-Parabrachial Circuits

Afferent signals from the autonomic nervous system terminating in lamina I and the nucleus tractus solitarius (NTS) are conveyed to higher brain centers via two main pathways. The phylogenetically older pathway connects to the parabrachial nucleus (PB), and the new pathway connects to the lateral thalamus (Spinothalamic Tract pathway) [5]. Gauriau et al. [6] studied the ascending projections of lamina I in the rat through the contralateral and lateral funiculus of the spinal cord, and they found extensive projections terminate in lateral and external medial parabrachial (PB) area. Nociceptive neurons of the PB area have two main targets in the forebrain, the amygdala and the hypothalamus, and two significant targets in the brainstem, the PAG and the VLM. In the amygdala, the nociceptive neurons from the PB area target primarily the central nucleus (CeA) [6]. In the PAG, the PB area sends projections to the ventrolateral, lateral, and dorsomedial columns (Figure 1). In primates, however, the newer pathway omits the PB and projects directly from lamina I and the NTS to a pair of specific subnuclei in the thalamus [7,8].

Forebrain and Midbrain Involvement

The amygdala consists of an evolutionarily primitive division associated with the olfactory system (central nuclei CeA) and an evolutionarily newer division associated with the neocortex (basolateral complex BLA). The CeA is the main output from the amygdala for the physiological expression of emotions and it has multiple connections with the hypothalamus and the brainstem. According to Langevin [9], the function of the amygdala is to link sensory inputs with psychological and physiological processes. For instance, the amygdala plays a critical role in fear conditioning where it links innocuous stimuli with aversive ones through initial pairing of the stimuli. By linking specific autonomic and psychological processes to sensory stimuli, the amygdala establishes the basis of emotional responses to events and situations [9]. Rizvi et al. [10] demonstrated that PAG receives heavy, highly organized projections from the CeA, and in turn, PAG has reciprocal connections with the CeA. Freezing is the typical behavioral response seen in fear conditioning to painful stimuli, a response that depends on the integrity of the CeA [11]. Lesions of the vlPAG reduce freezing responses to neutral stimuli associated with footshock [12]. Kalin et al. [13] found that bilaterally lesioning the CeA region resulted in a reduction in freezing behavior occurring in the human intruder paradigm. Diminished freezing was not observed following complete neurotoxic lesions of the amygdala. Kong et al. [14] have found that compared with low intensity pain, high intensity heat pain stimuli applied to the right forearm can produce significantly stronger activation at the vlPAG. Quirk et al. [15]

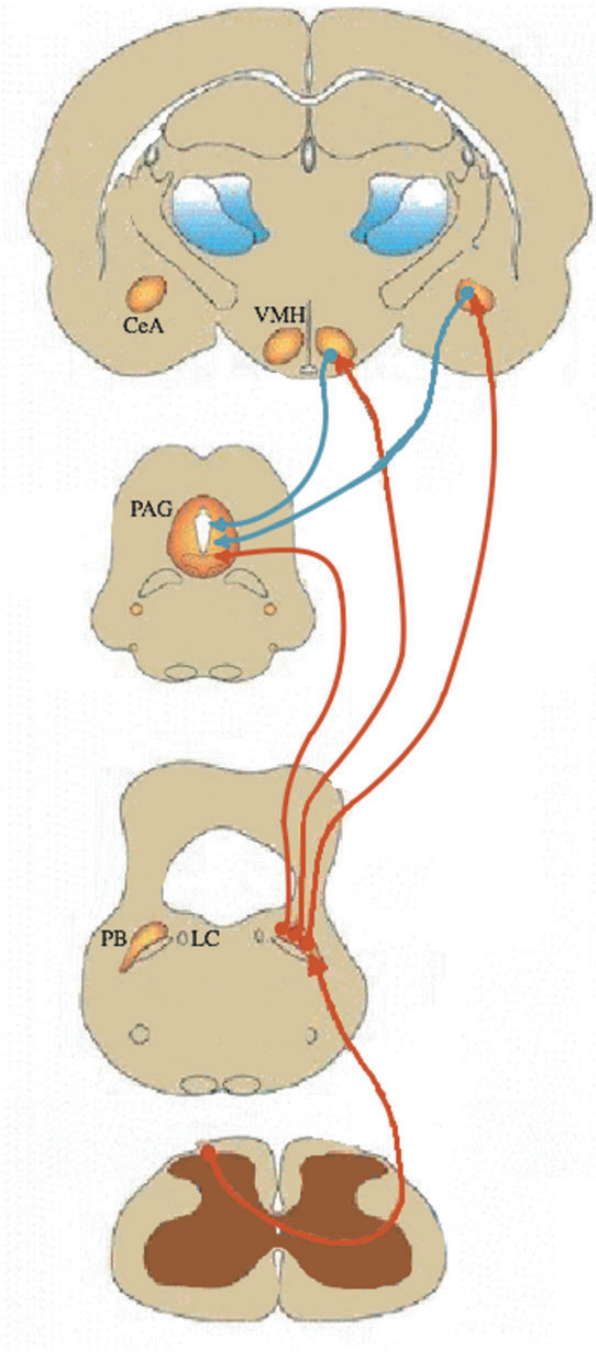

Figure 1 Phylogenetically older pathways of autonomic nervous system. Afferent signals from the autonomic nervous system terminating in lamina I ascend through the contralateral funiculus to terminate in parabrachial (PB) area. Nociceptive neurons of the PB area target the periaqueductal grey (PAG) in the brainstem and the amygdala and the hypothalamus (VMH) in the forebrain. In the amygdala, the nociceptive neurons from the PB area target primarily the central nucleus (CeA). CeA and VMH send projections to PAG columns thus explaining different patterns of autonomic response.

observed that stimulation of the medial prefrontal cortex (mPFC) dramatically reduced the responsiveness of CeA neurons, and they stated that their findings provide direct physiological support for the hypothesis that mPFC reduces fear responses by reducing amygdala output. Authors propose that the inhibitory effect of mPFC stimulation is mediated by GABAergic intercalated cells (ITC cells) that send GABAergic projections to the CeA [15] and receive a robust projection from mPFC [16,17]. Inhibition of fear expression via ITC cells could explain how fear behavior might be extinguished, despite the persistence of conditioned tone responses in lateral amygdala neurons throughout extinction. Geha et al. [18] investigated gray matter morphometry and white matter anisotropy in CRPS patients and matched controls, and they showed that CRPS patients exhibited gray matter atrophy in the right vmPFC regardless of whether the pain was localized in right, left, or bilateral body regions.

A Model of Dysfunctional PFC-Amygdala-PAG Circuitry

We speculate that CRPS patients are unable to reverse sympathoinhibition and restore sympathetic reflexes after initial trauma has healed. Since CRPS patients exhibit vmPFC gray matter atrophy, we propose a dysfunctional relationship between the vmPFC and the amygdala, implicating less inhibition of sympathoinhibition expression from vmPFC and maintaining sympathoinhibition despite initial trauma having been healed. Maintained sympathoinhibition maintains both peripheral neuroinflammation and pain [19]. The persistence of nociceptive afferent stimuli from PB area to CeA output neurons could reinforce sympathoinhibition driven by vlPAG (Figure 2).

Clinical Implications and Future Directions

Damage to the amygdala [20] or areas of temporal lobe including the amygdala [21] produces deficits in fear conditioning in humans. The impairment reported is related to the ability of a neutral stimulus to come to elicit an autonomic response through repeated pairings with an aversive unconditioned stimulus. Knight et al. [22] indicated that the amygdala is not only involved in the formation of conditioned stimulus-unconditioned stimulus associations, but is also crucial for the autonomic response of conditional fear. If sympathoinhibition could be assimilated to a behavioral (conditioned) response seen in fear conditioning to painful stimuli, then damage to the amygdala could produce extinction of the autonomic response, offering an explanation for the case report presented by Shibata et al. [23], and supporting our hypothesis. Shibata et al. [23] presented a case report of refractory CRPS whose symptoms were resolved after the patient suffered a traumatic cerebral contusion in the left temporal lobe, which caused no neurological deficit. In a similar vein, the use of mirror visual feedback (MVF) to convey the visual illusion to the patient that his "painful" arm moving (painlessly) in response to motor commands may result in an extinction of the conditioned

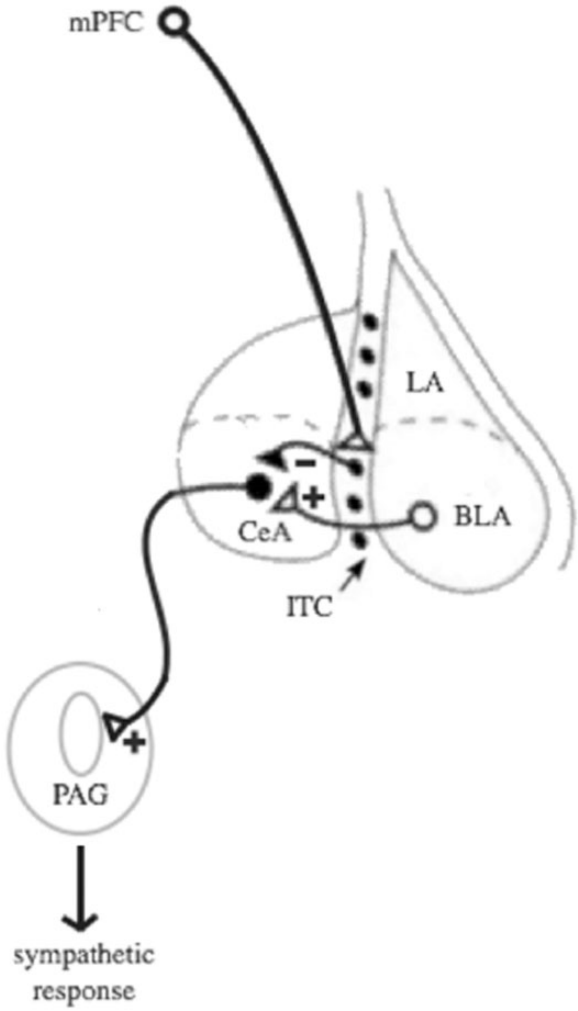

Figure 2 Relationship between medial prefrontal cortex and amygdala.
The central nucleus of the amygdala (CeA) via projections to the periaqueductal grey (PAG), drives the posttraumatic conditioned sympathoinhibition response to nociceptive inputs from the parabrachial (PB) area and basolateral amygdala (BLA). After healing, the medial prefrontal cortex (mPFC) reduces the responsiveness of CeA neurons via intercalated (ITC) cells. Thus mPFC reduces autonomic responses by reducing amygdala output. CRPS patients exhibit less inhibition of sympathoinhibition because mPFC atrophy, explaining how sympathoinhibition is not extinguished despite initial trauma having been healed.

response of freezing (immobilization). McCabe et al. [24] showed at six weeks of MVF in early CRPS a reversal of sympathoinhibition, a return to normal function, and no pain at rest or during movement [24]. On the other hand, if mPFC activity is relevant to extinction of sympathoinhibition response, then therapies that restore reduced cerebral gray matter showing clinical improvement, do that by reinforcing the inhibition of sympathoinhibition from vmPFC [25]. If persistent sympathoinhibition is a hyperalgesic state showed by CRPS patients but not by posttraumatic patients who do not develop CRPS, then our hypothesis could also explain the findings of Moseley et al. [26]. Authors conducted a multicenter, prospective cohort study of patients with wrist fracture, and they found that no patient with a pain score of three or lower went on to develop CRPS, but 46% of the patients with scores of five or higher in the first week after fracture went on to develop CRPS [26].

CRPS type II develops after trauma that is associated with a lesion of a large nerve, and nociceptive afferent stimuli secondary to abnormal ectopic activity also could reinforce conditioned sympathoinhibition response and could share a similar mechanism like CRPS I.

The proposed hypothesis can offer new insights for detecting earlier posttraumatic patients who are at risk for developing CRPS, and designing new therapies suggesting that "injury signaling" couldn't be interpreted that healing process is still ongoing and the passive adaptive response must be maintained.

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