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Review article

A new perspective on the anterior cingulate cortex and affective pain

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ABSTRACT

Pain is a complex experience including sensory-discriminative and emotional-affective components. Base on the intensity and chronification of pain, pain is divided into physiological and pathological pain. Anterior cingulate cortex (ACC), which is activated by noxious and contextual stimuli, is involved in pain processing, especially affective pain, the neural mechanisms of the ACC involvement in affective pain have yet to be elaborated. This review summarizes the main progresses and recent findings from our and other laboratories regarding the ACC and affective pain. Most evidence provided new insights into the neural mechanisms underlying affective pain. Excitation of ACC pyramidal neurons is necessary and sufficient for the pain-related negative emotion. We also sketched other brain regions associated with the ACC and discussed the role of these brain regions in affective pain. Actually, it is likely that the neural network between these brain regions is critical for the negative affect of pain. In particular, the important advances within the optogenetic filed provide new opportunities to deepen and expand our understanding of the affective pain.

1. Introduction

As a complex experience, pain is not only an important health problem, a worldwide burden in terms of patient suffering, but also a topic of enduring interest. Anatomical and physiological studies in animals, as well as functional imaging studies in humans have shown that multiple cortical areas are activated by painful stimuli, including primary (SI) and secondary (SII) somatosensory cortices of the lateral pain system (Fig. 1A), the insular cortex (IC) and the anterior cingulate cortex (ACC) of the medial pain system (Fig. 1B) (Schnitzler and Ploner, 2000). The ACC is a part of the brain's limbic system, and located in the frontal part of the cingulate cortex in the inner side of the cerebral hemispheres. The ACC is a complex and heterogeneous cortex, receives afferent inputs mainly from the medial thalamic nuclei (midline and intralaminar nuclei) that contain nociceptive neurons that receive input from the spinothalamic tract (Vogt et al., 1987; Craig and Serrano, 1994; Shi and Apkarian, 1995). Classically, the ACC has been related to affect, and has been most frequently linked to the experience of pain. The earliest conclusion on ACC function in pain is from Schaffer and his colleagues in a monkey model in 1888 (See Vannemreddy and Stone, 2017). They demonstrated that cingulate lesions decreased pain sensitivity. After 100 years, Lenz et al. found the human anterior cingulate gyrus directly responds to nociceptive input (Lenz et al., 1998). Davis and colleagues showed a series of fMRI studies on physiological pain in humans. They demonstrated that transcutaneous electrical nerve stimulation (TENS) of the median nerve evoked different intensities of pain and activated the ACC. Cingulotomy disinhibited both pain intensity and pain affect, and neurons in the ACC of awake human subjects responded to painful somatic thermal and mechanical stimuli (Davis et al., 1994; Davis et al., 1997; 2000). However, more groups reported that cingulotomy mostly occludes pain-related emotions, but does not affect the patient's ability to identify the intensity and localization of the noxious stimulus (Ballantine et al., 1967; Sherman and Mitchell, 1973; Hurt and Ballantine et al., 1974; Hassenbusch et al., 1990; Santo et al., 1990; Devinsky et al., 1995; Wong et al., 1997; Wilkinson et al., 1999). Despite most pioneer clinical studies help us to identify the ACC in the pain processing, human functional studies are often simply the correlation studies of brain activity with different testing conditions and many conclusions of these studies can be easily switched to the opposite way (Zhuo, 2005; 2011). To elucidate the complexity of the phenomenon of pain processing in the ACC, experimental conditions, control measures, drug efficacy and different pain assays have to be considered. Preclinical animal studies on the ACC and pain have achieved great progress in past decades. Nociceptive specific neurons in the ACC were proved to encode the integration of nociception, the anticipation of pain that precedes avoidance, and reward behaviors resulting from cutaneous electric stimulation (Koyama et al., 1998; 2000, 2001). Zhuo group have also been devoting their efforts

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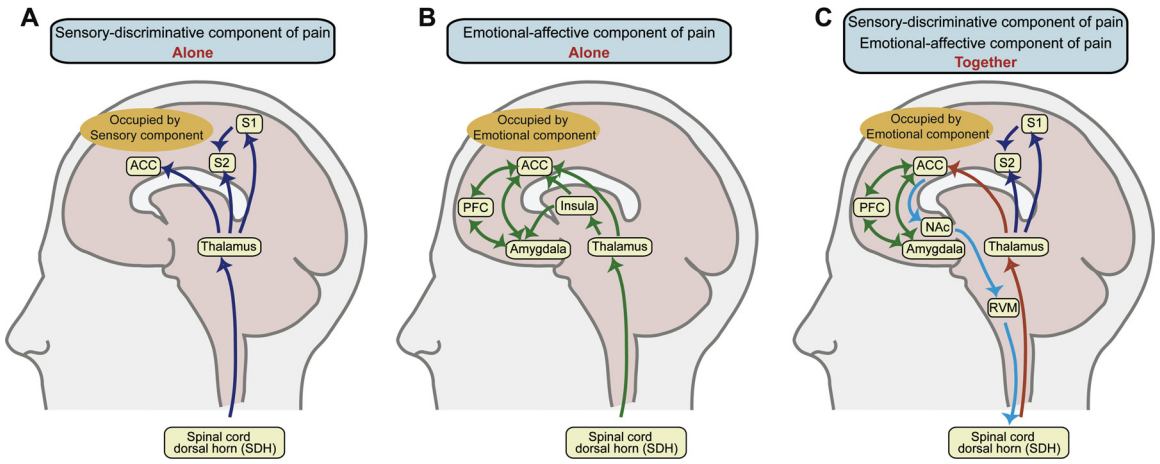

Fig. 1. The ACC encodes pain processing in priority levels.
(A) The sensory-discriminative component of pain has been ascribed to the lateral nociceptive system.
(B) The affective-motivation component of pain is mediated by the medial nociceptive system.
(C) The sensory-discriminative component of pain (blue arrow) and the emotional-affective component of pain (green arrow) may be considered the two levels in pain processing. The emotional-affective component is preferentially processed in the ACC (green arrow). This priority of pain processing in the ACC causes descending facilitation (light blue arrow) in the downstream brain areas, which then facilitate spinal nociception.

towards understanding the neuronal mechanisms of the ACC involved in chronic pain and anxiety (Wei and Zhuo, 2001; Wu et al., 2008; Toyoda et al., 2009; Li et al., 2010; Kim et al., 2011; Koga et al., 2015a; Tsuda et al., 2017).

There are a number of excellent reviews on *ACC and pain*, especially sensory pain and human imaging (Vogt, 2005; Vogt et al., 2006; Vogt, 2016; Zhuo, 2008, 2011, 2017). In this review we attempt to offer a comprehensive view on the *ACC and affective pain* with special focus on the preclinical animal studies. In particular, we present a dual role of the ACC on both necessary and sufficient for pain-related negative emotion. In addition to the ACC, we discuss other brain regions associated with the ACC and their roles in affective pain, which suggest that the neural network between the ACC and these brain structures is critical for the affective pain. The research advances in the optogenetic field help us to understand the neural circuit for affective pain between the ACC and other brain areas.

2. Role of the ACC in affective pain

The ACC appears to play a role in the rational cognitive and pain-related functions, such as empathy and emotion, especially pain-related unpleasantness and aversion (Devinsky et al., 1995; Bush et al., 2000; Wiech and Tracey, 2009). Most of landmark reports and reviews from functional imaging, electrophysiology, and anatomy studies on the human ACC have indicated that the ACC interacts with other cortical structures as part of the circuits specialized for affective processes. In the 1960s, Drs. Brown and Lighthill first reported 110 patients with severe emotional imbalance who were treated via selective anterior cingulotomy (ACC lesion) (Brown and Lighthil, 1968). Dr. Gol also demonstrated that electrical stimulation of the limbic system, including the ACC, did not affect some of the patients' headaches and backaches, but the patients stated that they felt more cheerful and alert (Gol, 1967). Furthermore, Bushnell and colleagues showed direct evidence that in hypnotic situations, the specific manipulation of pain unpleasantness induced significant changes in the ACC, while the manipulation of pain intensity primarily changes the S1 cortex (Bushnell and Duncan, 1989; Rainville et al., 1997; Hofbauer et al., 2001).

Pain-related emotion could also be detected in animal models based on the motivational priming theory (Lang, 1995). Pain-related emotion is controlled by defensive systems and activated by harmful or potential harmful stimuli, resulting in negative emotions. Conditioning procedures normally used to measure pain-related aversion and fear include the conditioned place preference (CPP), conditioned place aversion (CPA), the place escape/avoidance paradigm (PEAP), the passive avoidance test, and the operant escape test, among others. In addition to pain-related aversion and fear, studies of animal models have shown that the ACC is also essential for anxiety (Zhuo, 2016) and depression (Bissiere et al., 2006). Based on the different types of pain, different noxious stimuli (thermal, mechanical, electrical, inflammatory, and neuropathic) have been studied concerning affective responses exposed by more complicated behavioral models. These more sophisticated models provide a basis to explore underlying cellular mechanisms of the ACC in different types of pain processing.

2.1. Physiological pain and unpleasantness

As described above, there are two general types of pain, physiological pain and pathological/clinical pain. The former is acute and has a protective role that warns of potential tissue damage in response to noxious stimuli. Physiological pain is normally elicited by electrical, mechanical, or thermal stimulation to activate nociceptive transducers in skin or viscus. Rainville and colleagues discovered that tonic stimulation (ischemic exercise or thermal pressor) evokes a higher estimation of unpleasantness at any given level of pain intensity (Rainville et al., 1992). While selectively altering the unpleasantness of painful stimulation without changing the perceived stimulus intensity by hypnotic suggestions, PET scans revealed a correlation between perceived unpleasantness and ACC activity (Rainville et al., 1997). Additionally, hypnotic suggestions for increases and decreases in pain affect have impacted the estimates of the affective component of pain changes, whereas the estimated intensity of pain remains constant. However, subjects under hypnotic suggestions for increases and decreases in pain sensation intensity estimate that both pain intensity and pain affect change in parallel (Rainville et al., 1999). These results provide evidence for the separate dimensions of pain (Fields, 1999; Price, 2000). Clinically, cingulotomy (including the ACC and surrounding cortex) reduces pain-related unpleasantness/dysphoria and inhibits painful stimuli avoidance without influencing the patient's ability to identify intensity and location of painful stimuli (Ballantine et al., 1967; Hurt and Ballantine et al., 1974; Devinsky et al., 1995).

Unlike clinical studies in humans, experimental animals are unable to self-report, but their behaviors in response to noxious stimuli can be assessed objectively with high reliability (Mogil, 2009). A noxious electrical foot shock-induced conditioned avoidance was first used in