Int J Clin Exp Med 2016;9(12):22976-22984
www.ijcem.com /ISSN:1940-5901/IJCEM0031078

Review Article

Neural circuits of pain and itch processing involved in anterior cingulate cortex

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Received April 2, 2016; Accepted September 2, 2016; Epub December 15, 2016; Published December 30, 2016

Abstract: Anterior cingulate cortex (ACC) is widely considered to be the most important part of the brain's limbic system. Previous researches have shown that ACC plays a significant role in consciousness and behavior, including emotion, sensory, motor, memory, nociceptive processing, etc. Among these connections, nociceptive processing, especially pain and itch, has always been one of the prior research programs for the field of medicine. In recent years, the development of new techniques and advance in neurobiology has led to our new understanding on the link between ACC and nociceptive processing. In addition, neurophysiologic research has revealed that multiple peptides and neurotransmitters, including opioid peptides, glutamate, serotonin and dopamine, are involved in the mechanisms of modulation of nociception by ACC. In this review, we examine a wealth of recent neuroanatomical and neurobiological research that involves ACC and nociceptive processing, and provide a comprehensive review of the neural circuits of pain and itch processing in ACC, and the glutaminergic and opioidergic circuits are especially discussed.

Keywords: Anterior cingulate cortex, pain, itch, neural circuits, opioidergic circuits

Introduction

Anterior cingulate cortex (ACC) is widely considered to be the complex heterogeneous structure of the brain's limbic system. Anatomically, ACC is a distinct subregion of ventromedial frontal cortex consisting of the cingulate sulcus and gyrus that lie dorsal to the corpus collosum and ventral to the superior frontal gyrus. Based upon cytoarchitecture and functional connectivities, ACC is further dichotomized into a more rostral/ventral affective/emotional division comprising pregenual (pgACC) and subgenual ACC (sgACC), which equivalent to Brodmann area (BA) 24a, 24b, 24c, 25, 32 and 33. And a more dorsal cognitive division comprises anterior and posterior portions of the dorsal ACC (adACC and pdACC), equivalent to BA 24a', 24b', 24c', 24d, 32' and 33 (**Figure 1**) [1-3]. Etkin et al. pointed out that between dorsal-caudal and ventral-rostral subdivisions of the ACC had regulatory roles in emotional processing, and the former was involved in negative emotion whereas the latter was with respect to generating emotional responses [2]. Hsieha et al. indicated that BA24 of caudal ACC and BA9/32 (medial prefrontal cortex/rostral ACC, mPFC/rACC) were preferentially involved in the affective/evaluative processing of pain [4]. Early ablation studies from patients and animals have shown that ACC plays a significant role in consciousness and behavior [5, 6]. Subsequent functional studies using a variety of approaches, including electrical stimulation, microelectrode recording, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), provided us a further understanding of the link between ACC and emotion, sensory, motor, memory, nociceptive

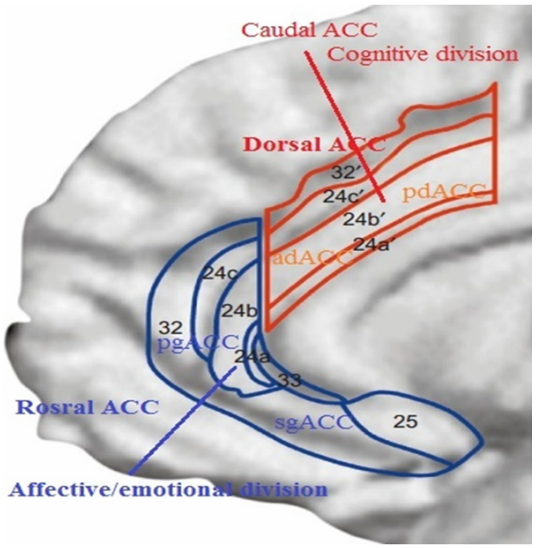

Figure 1. Parcellation of ACC subregions. Abbreviations: sgACC, subgenual ACC; pgACC, pregenual ACC; adACC, anterior dorsal ACC; pdACC, posterior dorsal ACC.

processing [3, 7-10]. Among these connections, nociceptive processing, especially pain and itch, has always been the focus of the research area. Previous reports demonstrated that although pain and itch have some differences, the neural processing of pain has some similarities to that of itch [11-14]. In addition, neurophysiological research has revealed that multiple peptides and neurotransmitters, including opioid peptides, glutamate, serotonin and dopamine, are involved in the modulation of nociception by ACC [15-17]. In this review, we provide a comprehensive review of the neural circuits of pain and itch processing in ACC, and the glutaminergic and opioidergic circuits are especially discussed.

Neural circuit of pain processing in ACC

It has long been known that pain processing is mediated by a neural network consisting of both cortical and subcortical structures. ACC is a key component of the cortical circuit which also includes the primary and secondary somatosensory cortex (SI and SII), the insula and prefrontal regions, whereas the subcortical components of the pain matrix includes the thalamus, amygdala and hippocampus, etc [18, 19]. However, our knowledge about the neural mechanisms of pain processing inside ACC is limited, nor is the neuroanatomical and neurobiological connections between ACC and these cortical and subcortical cerebral areas. It is generally assumed that the ACC involves the descending pain modulatory system [20]. Study from Freund W et al. indicated that painful electrical stimulation activates ventral posterior ACC more, but during thermal stimulation, there was more activation in dorsal posterior ACC [21]. A research about links between nociception and projections to cortical and motor systems from Bai-Chuang Shyu et al. found that nociceptive responses are generated directly by pyramidal projection neurons in all layers [22]. Davis et al. reported in patients with chronic pain by a positron emission tomography study that there were two distinct ACC areas activated after thalamic stimulation, one in the anterior (aACC) and the other in the posterior portion of the ACC (pACC) [23]. These results suggest that pain processing probably owns a common signaling channel as well as specific neural circuit corresponding to different kinds of pain inside ACC.

The functional connectivity between ACC and other cerebral structures in pain processing is the focus of neuroscience field. It is now believed that the periaqueductal gray (PAG, known as one of the central pain descending modulation systems [24]) receives direct projections from ACC [25]. The neuroanatomical connection between the ACC and PAG has been revealed by iontophoretic injections of horseradish peroxidase in dorsal, lateral and medial areas of PAG [26]. By a fMRI study about the response to an onset (aversion) and offset (reward) of a noxious heat stimulus of humans and rats, Becerra et al. demonstrated the relevance between rACC and the nucleus accumbens (NAc) in affective and motivational aspects of pain [27], suggesting that rACC-NAc circuit is involved in modulating affective and motivational aspects of pain. A series of research indicates that ACC and the insula subserve the affective-motivational component of pain processing [28-30]. Orbitofrontal cortex, insula, NAc, amygdala and PAG are connected together with ACC through the opioid system [31, 32]. Furthermore, the pathophysiology of chronic visceral pain involved the link between ACC and PAG, insula, amygdala, anterior cingulate cortex, orbitofrontal cortex, medial and dorsolateral prefrontal cortex, and parietal cortex [33]. The thalamus is also one of the most frequently activated regions in human pain research [34]. The retrograde tracing study

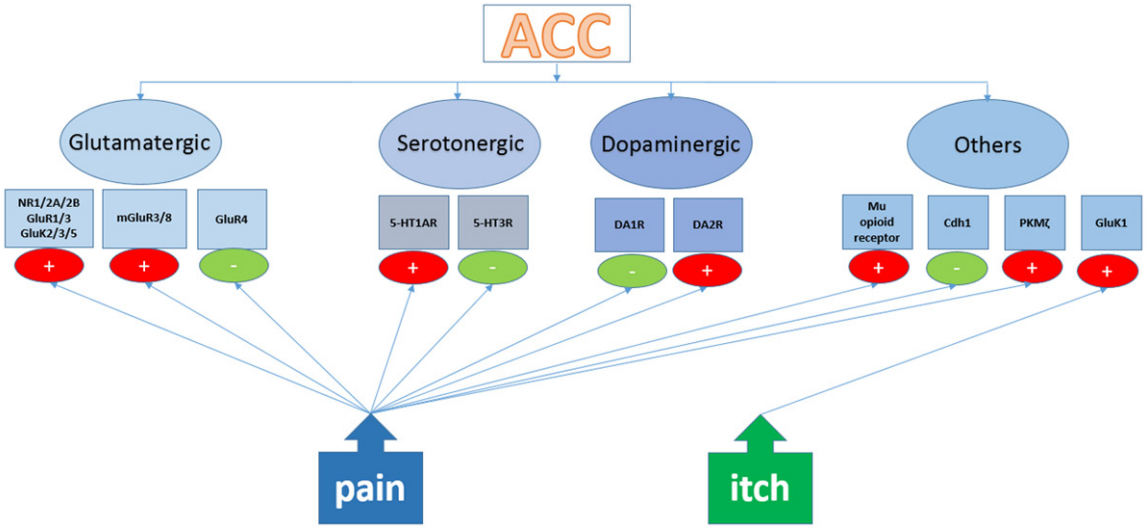

Figure 2. Schematic representation of the signal pathways activated by pain and itch. The expression of mGluR3, mGluR8, GluR1, GluR3, NR1, NR2A, NR2B, 5-HT1AR and mu-opioid receptor in ACC was up-regulated (red oval) whereas GluR4, 5-HT3R, DA1R, DA2R and Cdh1 were down-regulated (blue oval)under pain condition. The expression of PKMζ in ACC was also up-regulated (red oval). The expression of GluK1 in ACC was up-regulated under itch condition (red oval). "+" and "-" stand for up-regulation and down-regulation, respectively.

from Abrahamson EE et al. demonstrated that the descending projections to the PHA arise from the cingulate cortex and the medial and lateral hypothalamus [35]. Functional tracing of medial nociceptive pathways using MRI observed that noxious stimulation induced enhancement of manganese ion transportation from medial thalamus to cingulate cortex [36]. Neurobiological study indicated that the likely thalamic source of nociceptive inputs to ACC is from the midline, mediodorsal and intralaminar thalamic nuclei (MITN) [37]. These findings suggest that the significance of thalamic-anterior cingulate pathway in pain conditions. In addition, transneuronal tracing with neurotropic pseudorabies viruses (PRV) demonstrated a pathway from ACC to the dorsal hippocampus [38].

The dorsal ACC (dACC) has been shown to be a heterogeneous brain region, which includes two parts, one is a more rostral part of dACC which plays a role in affective processing, and the other is a more caudal region which involves in cognitional and motor processing with projections to the red nucleus and spinal cord [8, 39, 40].

Neurotransmitter and receptor mechanisms underlying ACC

The involvement of the ACC in nociception modulation may be associated with the activities of a variety of neurotransmitters and peptides, including opioid, glutamate, dopamine and serotonin (**Figure 2**). Among the three ionotropic glutamate receptor subtypes, researchers have focused their attention most strongly on NMDA receptors. The research about the relationship between endogenous D-serine in the rACC and pain-related negative affect suggested that activation of NMDA receptors in the rACC is necessary for the acquisition of specific pain-related negative emotion [41]. It was reported that painful stimuli potentiate the prefrontal synaptic transmission and induce glutamate NMDA NR2B receptor expression in the ACC and inhibition of NR2B receptors by administering selective NR2B receptor antagonists locally into the ACC or systemically inhibits inflammation-related allodynia [42-44]. Immunoblot analysis from Yang JX et al. also revealed that chronic constriction injury (CCI) increased the expression of NR2B protein in the ACC and microinjection of NR2B inhibitor ifenprodil into contralateral ACC significantly inhibited CCI-induced thermal hyperalgesia and mechanical allodynia [45]. On the contrary, data from mice with bone cancer pain revealed a significant decrease in the levels of NR1, NR2A, and NR2B subunits of NMDA receptors in the rACC and the results indicated that tumor-induced injury may cause a persistent decrease in NMDA receptor expression in rACC

neurons [46]. Xu H et al. found that both the presynaptic release probability of glutamate and postsynaptic glutamate AMPA receptor-mediated responses were enhanced after injury using the mouse peripheral nerve injury mode, but western blot analysis indicated there was no difference in the expression levels of both GluR1 and GluR2/3 receptors in ACC between the control mice and mice with nerve ligation. Under paclitaxel-induced neuropathic pain (PINP) condition, GluR1, GluR3, GLuK2, GLuK3, GLuK5, NR1 and mGLuR8 were significantly up-regulated, whereas GluR2, GLuK1, GLuK4, NR2A and NR2B were not significantly altered and GluR4 was lowly expressed [47]. Recently, Gao SH et al. reported that intra-ACC microinjection of mGluR1-shRNA suppressed the CCI-induced behavioral hypersensitivity, particularly thermal hyperalgesia [48]. Further studies are needed to clarify the effects of various subtypes glutamate receptors in pain processing. The ACC glutamate receptor-based modulation of pain is also associated with other neurotransmitters. The study of López-Avila A et al. suggests an interaction between dopaminergic and glutamatergic systems within the ACC in the genesis and maintenance of long-term nociception [16]. Ortega-Legaspi JM et al. provided evidence of an increase of inhibitory dopaminergic receptor (D2R) mRNA and protein in cg1 in correlation with nociceptive behavior in a neuropathic model of pain in the rat [49]. Ikeda H et al. reported that antagonize of dopamine D1 receptor in the ACC prevented to the analgesic effect of lemon oil [50]. Serotonin (5-HT) and 5-HT receptor are highly involved in pathogenesis of pain [51-62]. Koeppe C et al. found that the activation was significantly reduced after treatment of the 5-HT3 receptor antagonist tropisetron in ACC [63]. Martikainen IK et al. performed psychophysical testing in eleven healthy males who had participated in a positron emission tomography study with [carbonyl-(11)C]WAY-100635 ligand for the assessment of 5-HT(1A) receptor binding potential (BP) and demonstrated that 5-HT(1A) receptors in the brain influence pain [17]. Tan W et al. employed spared nerve injury (SNI) model in rat and found down-regulation of Cdh1 protein level as well as up-regulation of AMPA receptor GluR1 subunit protein level in the ACC after SNI surgery and intra-ACC treatment with Cdh1-expressing lentivirus vectors elevated Cdh1 levels and alleviated established mechanical allodynia in SNI rats [64]. In addition, some research data indicated that PKMζ in the ACC acts to maintain neuropathic pain [65-67].

The opioidergic circuit in ACC

The ACC is a key region in the processing of pain and the opioid system is bound up with pain. In the early 1990s, it was reported that ACC has one of the highest densities of opioid receptors in the CNS and it has been implicated in acute and chronic pain responses [68]. And there is already growing evidence, on the basis of recent research [69, 70], that the ACC opioid system probably take center stage in processing negative pain affect. However, little is known about opioid system organization and actions.

Different division corresponds to different opioid architectures inside ACC. A rodent study about opioid architecture in the perigenual and midcingulate divisions of ACC from Vogt LJ et al. indicated that perigenual and midcingulate cortices have different opioid architectures due to a higher proportion of mu-opioid receptors expressed by afferent axons in areas 24 and 32 [15]. Further study identified the pgACC as one brain region with a major impact on opioidergic pain modulation [71]. Bruehl S et al. reported that inadequate endogenous opioid inhibitory activity in the rostral anterior cingulate (rACC) contributes to the links between trait anger-out and pain [72]. Interestingly, study on placebo analgesia suggested that the endogenous opioid system is closely linked with it and provides evidence that the rACC represents a crucial cortical area for this type of endogenous pain control [73-76]. A recent research about asymmetry of the endogenous opioid system in ACC suggested that region-specific lateralization of neuronal networks expressing opioid peptides underlies in part lateralization of higher functions, including positive and negative emotions and pain in the human brain [77].

Neural mechanisms of itch processing in ACC

Itch is the most prevalent symptom of allergic and inflammatory skin disease [78, 79]. Although it is known that itch induces activation of a neural network in the brain, the neuroanatomical pathway of the network as well as

the pathophysiology and neurobiology are not well understood. As a key component of pain processing, ACC also involves itch processing. Imaging study of central itch modulation using PET found that the significant increases of regional cerebral blood flow caused by histamine stimuli were observed in ACC [80, 81]. A series of fMRI study about histamine-mediated and non-histaminergic forms of itch observed signal intensity changes of ACC [82-87]. As with pain experience, the affective and emotional aspects of itch processing are also significantly represented in the activation of ACC, amygdala, and NAc [88-90]. In the field of molecular biology, Descalzi G et al. combined pharmacological, genetic, and electrophysiological approaches and showed that cortical GluK1-containing kainate (KA) receptors are involved in scratching induced by histamine and non-histamine-dependent itching stimuli [91]. Further neuroanatomical and neurobiological studies elucidating the nature of the neural circuits are needed.

Summary

Neuroimaging, neuropathological, and lesion analysis data show that the anterior cingulate cortex is an important cortex region whose central role is to regulate the neural circuits of pain and itch processes. Further in-depth studies are required to explore the an extended anatomical network formed by the neural projections of the ACC in the regulation of the emotional expression and experience of pain or itch.

Acknowledgements

This project was supported by a grant from a Project of China National Natural Science Foundation of PR China (81072152, 81670240), Natural Science Foundation of Hubei Province (2015CFA027), Research Foundation of Health and Family Planning Commission of Hubei Province (WJ2015M), Hebei Province Higher Educational Science and Technology Program, and Health and Family Planning Commission of Hubei Province (No. WJ2015MB008). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure of conflict of interest

None.

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