Neuroimaging study of placebo analgesia in humans

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Abstract: Placebo has been reported to exert beneficial effects in patients regarding the treatment of pain. Human functional neuroimaging technology can study the intact human brain to elucidate its functional neuroanatomy and the neurobiological mechanism of the placebo effect. Blood flow measurement using functional magnetic resonance imaging and positron emission tomography (PET) has revealed that analgesia is related to decreased neural activities in pain-modulatory brain regions, such as the rostral anterior cingulate cortex (rACC), insula, thalamus, and brainstem including periaqueductal gray (PAG) and ventromedial medulla. The endogenous opioid system and its activation of μ -opioid receptors are thought to mediate the observed effects of placebo. The μ -opioid receptor-selective radiotracer-labeled PET studies show that the placebo effects are accompanied by reduction in activation of opioid neural transmission in pain-sensitive brain regions, including rACC, prefrontal cortex, insula, thalamus, amygdala, nucleus accumbens (NAC) and PAG. Further PET studies with dopamine D2/D3 receptor-labeling radiotracer demonstrate that basal ganglia including NAC are related to placebo analgesic responses. NAC dopamine release induced by placebo analgesia is related to expectation of analgesia. These data indicate that the aforementioned brain regions and neurotransmitters such as endogenous opioid and dopamine systems contribute to placebo analgesia.

Keywords: placebo; pain; functional magnetic resonance imaging; positron emission tomography; opioid; dopamine

1 Introduction

The beneficial effects of placebo in the perception of pain are widely known. A considerable proportion of the research has been conducted in the fields of pain and analgesia, and the placebo analgesia appears to be the best understood model of placebo mechanisms. The 44 clinical trials' review show that placebo has analgesic beneficial effect including the treatment of pain^[1-3]. Subjective assessments such as

McGill Pain Questionnaire (MPQ)^[4] including visual analog scale, are frequently used to assess pain perception. Although significance of placebo analgesic effects compared to neutral condition is greater than using only placebo as a control condition^[5], the subjective outcome of placebo analgesic effects is indicated by the reduction in the pain intensity of 6 on 100 VAS in 44 clinical trials^[2]. There emerges literature examining the functional neuroanatomical and neurobiologic features of placebo-induced analgesia. Through the use of blood oxygen level-dependent signal (BOLD) with functional magnetic resonance imaging (fMRI) or molecular imaging positron emission tomography (PET), neural activity changes in both sensory and affective dimensions of pain-modulatory brain regions have been detected on placebo administration condition. In addition, the placebo analgesia has been

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involved in opioid-mediated antinociception and dopamine-related reward expectation^[6-8]. In this review, we mainly focus on the neuroimaging studies of the mechanism of placebo-induced analgesia in humans.

2 Functional neuroanatomic imaging study of placebo analgesia

fMRI study can provide neuroanatomic evidence supporting that brain regions are affected by placebo-induced analgesia. Identifying placebo effects in brain activity may provide insight into components of pain perception in regions associated with sensory, affective, and cognitive pain processing. A recent fMRI study with BOLD has investigated the effects of placebo analgesia in a thermal model of pain processing^[9]. The placebo manipulations could reduce the experience of pain, and the pain-responsive regions of the brain show a reduced fMRI BOLD signal (measurement of the related neural activity, which is thought to reflect the summation of local field potentials^[10]). Also, the pain-related neural activity is reduced within thalamus, rostral anterior cingulate cortex (rACC), and insular cortex during the placebo condition, compared to the baseline. In addition, the magnitudes of these decreases are correlated with the subjectively rated pain relief afforded by the placebo. Another important aspect of their study is the investigation on the effects on expectation of placebo analgesia in the period of anticipation of pain. fMRI activities in the lateral prefrontal cortex and orbitofrontal cortex (OFC) could be improved by placebo. The magnitude of the prefrontal activation is correlated with an increase in the periaqueductal gray (PAG) area. Furthermore, the increases in these brain activities in the anticipation of the pain period are also correlated positively with decreases in pain and pain-sensitive neural activity during stimulation of the placebo. Using a similar experimental approach in fMRI study, it has been revealed that the rACC displays a greater activation during the placebo condition compared to the control. A connectivity analysis has identified that the placebo analgesia depends on the increase in functional connectivity between the rACC with amygdala and the PAG^[11]. The finding that rACC activation is related to placebo analgesia is based on a previous study by using

PET. Petrovic *et al.*^[12] have compared the effects between placebo and a μ -opioid receptor remifentanyl during pain stimulation. The results have demonstrated that both placebo and opioid are associated with increased activity in the rACC and confirmed a covariation between the activities in rACC and the brainstem. In a recent fMRI study investigating the activation of the opioidergic descending pain control system in placebo analgesia, Eippert *et al.*^[13] have found that the opioid antagonist naloxone could reduce placebo-induced effects in pain-modulatory cortical areas such as rACC and brainstem, including hypothalamus, PAG, and rostral ventromedial medulla (RVM). Furthermore, naloxone could abolish placebo-induced functional connectivity between rACC and PAG as well as RVM activation.

Combining the above studies, brain regions such as prefrontal cortex, rACC, insula, thalamus, and brainstem, including PAG and RVM, play important roles in modulation of neural circuit under placebo analgesic response. The prefrontal cortex, especially dorsolateral prefrontal cortex (DLPFC), has been consistently proved to be associated with cognitive control of representation and maintenance of information, consistent with a role in expectation^[14]. Since both DLPFC and OFC activations are correlated with brainstem activation^[9] in placebo expectation, the prefrontal cortex may trigger placebo analgesia responses through co-activation with other pain modulation regions such as rACC, insula, thalamus and brainstem such as PAG and RVM. PAG plays a key role in descending pain modulation and is under the control of the rACC through direct or indirect projections^[15,16]. The above studies have consistently demonstrated the co-activation and correlation between rACC and PAG activations, which suggests the recruitment of the PAG through rACC for descending pain modulation in placebo analgesia.

3 Molecular imaging study of endogenous opioid mechanisms in placebo analgesia

Levine *et al.*^[17] have reported that placebo analgesia could be abolished by μ -opioid antagonist naloxone, an important step in understanding the proposition that the placebo analgesia is mediated by endogenous opioid systems. A number of studies have shown that placebo administra-

tion with expectation of analgesia is associated with a pain-rating reduction that is reserved by either the open or the hidden administration of naloxone in both clinical and experimental pain studies^[18-21]. Molecular imaging technique PET can directly study the activity of the endogenous opioid system on μ -opioid receptor in humans. Petrovic *et al.*^[12] have revealed a similar role of brain regions between intravenous opioid analgesia and placebo analgesic responses induced by a fake analgesic i.v. injection, to test the hypothesis that placebo involves both higher order cognitive networks and endogenous opioid systems in humans. They have also demonstrated that both μ -opioid receptor agonist remifentanyl administration and placebo analgesia can increase rACC blood flow responses. Using PET with a μ -opioid receptor-selective radiotracer [¹¹C] carfentanyl, Zubieta *et al.*^[22-25] have demonstrated that the activations of the endogenous opioid system and μ -opioid receptors would be observed *in vivo* as reductions in the capability of μ -opioid receptor to bind the radiolabeled tracer as measured with PET during the sustained pain condition compared with baseline. Besides, the activation of the μ -opioid receptor system is associated with reductions in the sensory and affective ratings of the pain experience^[22]. Recent PET studies on the opioidergic mechanisms of placebo analgesia in humans with sustained jaw muscle pain^[26,27] have demonstrated the placebo-induced endogenous opioid activation on μ -opioid receptor in pain-modulatory brain regions, including DLPFC, OFC, rACC, amygdala, NAC, insula, thalamus, hypothalamus, and PAG. The endogenous opioid activation on μ -opioid receptor is further associated with reduction in subjective pain rating. These endogenous opioid activation on μ -opioid receptor in the brain regions is correlated with lower ratings of pain intensity (rACC, insula, and NAC), pain unpleasantness (rACC), reductions in MPQ sensory (rACC, insula), affective (NAC) and total (rACC, insula) scores, as well as negative emotional state (NAC)^[8]. When subjects are divided into equal groups of high and low placebo responders based on the median change (50%) in pain intensity ratings after placebo administration, the opioid activation in NAC is significantly different between the 2 groups. Furthermore, placebo and nocebo effects are associated with

opposite response of endogenous opioid neurotransmission in a distributed network of brain regions^[27]. The NAC lies at the interface of sensorimotor and limbic systems, in connections with regions such as OFC and amygdala. This circuit is involved in the integration of cognitive, affective, and motor responses in animal models. In addition, this circuit and other brain regions such as insula and medial thalamus are heavily modulated by the endogenous opioid system and μ -opioid receptors.

4 Molecular imaging study of endogenous dopaminergic mechanisms in placebo analgesia

Placebo analgesic responses have been found to be mediated by mechanisms other than opioids in other circumstances. For example, placebo effects in irritable bowel syndrome patients were found to be naloxone-insensitive, suggesting the mediation by non-opioid mechanisms^[28]. Although other neurochemical mechanisms have not yet been identified, it is worth noting that the possible involvement of some neurotransmitters has been found in some conditions. For instance, a possible role of dopaminergic mechanisms in the placebo effect is initially postulated following the investigations that basal ganglia dopamine release took place in the placebo arm of a randomized and controlled trial in Parkinson's disease. Besides, dorsal basal ganglia dopamine activity is related to the improvement in motor control, while NAC dopamine is associated with the expectations of improvement reported by the subjects^[29,30]. Using molecular imaging PET with dopamine D2/D3 receptor radiotracer [¹¹C] raclopride, Scott *et al.*^[27] have investigated endogenous dopaminergic mechanisms under a 20-min standardized pain challenge in the absence and the presence of a placebo with expected analgesic properties. Placebo-induced activation of dopaminergic neurotransmission was observed in mesolimbic dopaminergic terminal regions in ventral caudate, ventral putamen, and NAC. The positive correlation has been found between placebo-induced dopamine D2/D3 activation and reduction in intensity of pain in the NAC. Furthermore, the placebo-induced activation of dopamine D2/D3 is positively correlated with opioid activation on μ -opioid receptor in response to placebo administration in the NAC. When

both dopamine and opioid activation in response to placebo administration were examined in their contributions to placebo analgesia, the most significant predictor was the activation of dopamine neurotransmission in the NAC, accounting for 25% of the variance in placebo analgesia. Consistent with the hypothesis that NAC dopamine response to placebo constitutes a “trigger”, response to the saliency and reward value of the placebo would allow for the activations of downstream adaptive (e.g., opioid) responses^[8]. It is hypothesized that the inter-individual variations in placebo-induced NAC dopamine activity and in the synaptic activity of this region may be related to the differences in the processing of reward expectation^[31]. The molecular imaging PET with dopamine D2/D3 receptor-labeled [¹¹C] raclopride and fMRI were employed to test this hypothesis. The results show that activation of NAC dopamine release could be observed during placebo administration and is related to its anticipated effects. In addition, expectation of monetary gain could increase NAC synaptic activity during anticipation of a monetary reward in fMRI study. The positive correlation is found between NAC fMRI BOLD signal from null to high reward trials and placebo-induced NAC dopamine D2/D3 activation of dopamine neurotransmission during pain expectation. In NAC, responses to reward expectation account for 28% of the variance in the formation of placebo analgesia.

5 Conclusion

Our understanding and conceptualization of the placebo effects on pain has changed nowadays by using neuroimaging studies. An emerging literature demonstrates that neural activity changes in both sensory and affective dimensions of pain-modulatory brain regions have been detected under placebo administration conditions. These brain regions with opioid-mediated activation include DLPFC, OFC, rACC, amygdala, NAC, insula, thalamus and brainstem including PAG and RVM, and that with dopamine-mediated activation is ventral basal ganglia including NAC (Fig. 1). The fact that the magnitudes of the activations in prefrontal cortex and rACC are correlated with an increase in activation in the PAG area^[9,12,13] suggests the prefrontal cortex and rACC recruit-

Fig. 1 Placebo-induced neural activity in pain-modulatory brain regions. Schematic representation shows some of the connectivity between the regions in both μ -opioid and dopamine system (only ventral basal ganglia including NAC) activation during placebo administration. The dashed line represents prefrontal cortex and rACC recruitment of the brainstem including PAG for opioidergic descending pain control systems under placebo analgesic responses, while solid line indicates both opioid- and dopamine-mediated activations to placebo administration, especially the role of NAC in the reward expectation in the formation of placebo analgesia. OFC: orbitofrontal cortex; DLPFC: dorsolateral prefrontal cortex; rACC: rostral anterior cingulate cortex; Hypothalamus: hypothalamus; PAG: periaqueductal gray; RVM: rostral ventromedial medulla.

ment of the PAG in descending pain modulation of mechanisms in placebo analgesia. In addition, NAC synaptic activation and its dopamine release are linked to the reward expectation during placebo analgesia, and this area is considered to have the capacity to activate other brain regions in response to reward^[27,31]. Finally, although the neuroimaging studies have discovered that the placebo has neurobiological effects on brain and body in both experimental and clinical pain, further experimental and clinical studies are also required to improve the understanding of neurobiological mechanisms of placebo analgesia for the advancement of clinical practice in the future.

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安慰剂镇痛的神影影像学研究

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摘要: 许多文献资料报道了安慰剂对疼痛的镇痛效果。人体大脑功能影像技术可以在无创伤条件下研究安慰剂镇痛的大脑功能解剖结构及其神经生物学机制。功能磁共振成像和正电子发射断层扫描(PET)的脑血流测定表明大脑前扣带回喙部(rACC)、脑岛、丘脑和脑干的中脑导水管周围灰质(PAG)及延髓头端腹侧部的神经兴奋性降低与安慰剂镇痛调节有关。内源性吗啡肽系统及激活吗啡肽 μ 受体参与安慰剂的镇痛作用。吗啡肽 μ 受体标记的PET影像研究提示安慰剂镇痛伴随着疼痛相关大脑部位(如rACC、前额叶皮层、脑岛、丘脑、杏仁核、伏隔核、PAG等)中内源性吗啡肽活性的降低。此外, 标记多巴胺D2/D3受体的PET实验证明基底核包括伏隔核的多巴胺活性与安慰剂镇痛相关。安慰剂镇痛引起的伏隔核的多巴胺释放与安慰剂期待相关。以上结果提示上述大脑区域和内源性吗啡肽及多巴胺在安慰剂镇痛方面有重要作用。

关键词: 安慰剂; 疼痛; 功能磁共振成像; 正电子发射断层扫描术; 吗啡肽; 多巴胺