Opioid and Placebo Analgesia Share the Same Network
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The relationship between the endogenous opioid system and placebo analgesia has fascinated the research community for decades. Using functional imaging methods, it is now possible to study the underlying opioid and placebo processes in the brain. Such studies have shown overlapping activity in the anterior cingulate cortex (ACC) and the insula stretching into the orbitofrontal cortex. Because the ACC is involved in top-down attentional regulation, this region may mediate the interaction between higher cognitive processes and the endogenous opioid network. Moreover, data also indicate that the ACC may exert its modulation through the brainstem opioid network. The orbitofrontal cortex also shows placebo-dependent activation, but it does not have similar access to the opioid network. Thus, this region may be involved in other aspects of the placebo response such as processing treatment expectations.

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Placebo analgesia research had the first major scientific breakthrough when it was discovered that the placebo effect depended on the endogenous opioid system, a finding that has been replicated in several studies (eg, refs. 2-4). Since this discovery, complex and well-designed behavioral designs have shown strong relationships between placebo analgesia and treatment expectation,2,5-8 drug conditioning,2 autonomic correlates, and somatotopic dependence.3 Recently, a third important step has been taken in placebo research, that is, unraveling the underlying neuronal correlates involved in the placebo analgesia response using positron emission tomography (PET) or functional MRI (fMRI).9-12

Placebo analgesia is a unique phenomenon because it is one of few higher cognitive top-down processes in which a known specific neuromodulatory system operates, ie, the opioid system. However, the endogenous opioid system is also involved in a broad range of emotional processes shown both in animals and in humans.13-15 This knowledge makes the placebo effect interesting not only for understanding pain regulation but emotional regulation in general. This review article will try to relate the described placebo network9-12 to the endogenous opioid system in the cortex and the brainstem.

The Opioid System in the Brain

Opioid receptors in the central nervous system (CNS) are found in the entire neuroaxis, eg, in the cortex, brainstem, and spinal cord.16-21 Although these receptors are widespread throughout the CNS, the localization is not diffuse but highly regional. It has been proposed that networks containing opioid receptors may exert analgesic effects through several different mechanisms.22 These include modulation of spinal noxious input (in the dorsal horn and in the ascending pathways), direct control of cortical and brainstem structures that are involved in pain processing, or regulation of the ascending forebrain systems. At present, the modulation of the spinal cord has been best described.17,18

The brainstem opioid system consists of a network of regions, including the periaqueductal gray (PAG), the parabrachial nucleus, and the rostral ventromedial medulla, which are critically involved in descending opioid dependent analgesia (for a complete review, see refs. 17,18).

The opioid receptor network is less characterized in the cortex, especially in the more developed human brain. However, autoradiographic studies of postmortem human and primate brains and PET studies of opioid receptors in the human subjects have started to reveal a cortical opioid sys-
The autoradiographic studies indicate high concentrations of opioid receptors not only in the brainstem, eg, the PAG, the intralaminar, and medial thalamic nuclei, but also in the cingulate cortex and prefrontal cortex. These and other animal studies have suggested that the anterior cingulate cortex (ACC) has one of the highest levels of opioid receptor bindings in the cortex.

PET studies using radioactive opioid [11C]-diprenorphine, which indicates the mu-, delta-, and kappa-opioid receptor availability, have confirmed previous animal and human autoradiography findings. Although no quantitative analysis of the entire brain has been presented, the opioid receptor images from these PET studies suggest a high opioid receptor concentration in the insula and the frontal cortex. Raw data indicate that the binding potential is highest in the rostral parts of the anterior cingulate cortex (rACC). The receptor imaging studies have also indicated high opioid receptor binding potential in basal ganglia and thalamus.

A similar network has showed increased neuronal activity (using PET and measuring the regional blood flow as an index of the underlying neuronal activity) during treatment with opioid-receptor agonists, such as remifentanil and fentanyl. In 2 of the studies, it was shown that remifentanil, a mu-opioid compound with a short half life, increases the activity in several regions known to be involved in pain-processing and containing a high concentrations of opioid receptors. Opioid-dependent increases were observed in the caudal and rostral ACC, midanterior insula, stretching into the orbitofrontal/temporopolar cortex, and in the brainstem. Common for all previously presented functional imaging studies was an observed activity increase in the rostral ACC in response to opioid treatment. Thus, it may be suggested that a relationship exists between the opioid system and the rACC. In summary, autoradiographic studies, opioid-receptor imaging studies, and functional imaging studies all indicate that a specific opioid-rich network exists in the cortex that includes the ACC and the anterior insula.

**Conditions That Activate the Endogenous Opioid System**

The complexity of the endogenous opioid network indicates that it is an important regulatory system for the organism. However, it is less elaborated in which natural situations these systems are active and their role for increasing the chances of the survival of the organism.

In animal studies, contexts that induce fear and stress have been described as important for the activation of the endogenous opioid system, ie, fear- or stress-related analgesia. This state has been induced either using noxious shocks, conditioning a noxious shock with an neutral stimulation (ie, conditioned stress induced analgesia) or setting up a context in which fear is thought to be induced in the animal, eg, putting an animal in the same cage as its predator (see ref. for details). These triggers will activate an opioid system mediated via the amygdala, which then activates the brainstem opioid system via the PAG.
duction of analgesia in humans, although a great deal of variability exists in these studies. The placebo response is probably the best-described experimental situation in which the endogenous opioid system in humans is naturally activated and, thus, research on the placebo response is of general importance also for understanding the endogenous opioid system.

Apart from the analgesic function the opioid subsystems may be specifically involved in different motivational and mood regulations. Emotional responses in rats have been suggested to be dependent on the opioid system. Even more intriguing, it has been suggested that the mu-opioid system may be involved in emotional processing and regulation in humans. Thus, its role is not just to regulate pain perception but to modulate the general state of the organism, which also includes a change of the perceived pain. This role implies that the opioid effect can be understood only in relation to the external context and the internal state (eg, motivation and emotion).

**Placebo and Cognition**

Although opioid conditioning is one possible mechanism inducing analgesia, the placebo effect also must be accessible via higher cognitive processes because it is clearly affected by beliefs, attitudes, and conscious expectations. Nonspecific stimuli in the context, which are coded in higher cognitive networks, may both induce and modulate placebo analgesia. An impressing and well-studied higher cognitive process that influences placebo response is expectations of a treatment outcome. Thus, the belief that a treatment is effective directly correlates with the degree of placebo analgesia.

Apart from containing a large concentration of opioid receptors, the ACC is involved in higher cognitive attentional tasks. Modern theories of attention suggest that the ACC is involved in conflict monitoring or conflict resolution. A conflict implies that two different processes compete for the attentional space in the brain and therefore must be controlled. The meta-analysis by Bush and coworkers suggested that the ACC also is involved attentional processing on the pain experience.

**Placebo Analgesia and the Opioid Network**

We have suggested that the rACC is involved in the interaction between attention and the opioid system in placebo analgesia because of the dense concentration of opioid receptors found in the ACC and its involvement in tasks requiring conflict resolution (as mentioned previously). Thus, rACC may be viewed as the region in which higher cognitive attentional processes have access to a specific neuromodulatory system. In line with this suggestion, we performed a PET study in which an increased neuronal activity was observed during placebo analgesia in the same region of rostral ACC as maximally activated when the same subjects were treated with opioids (Fig. 1). Another activation observed in the placebo condition encompassed the orbitofrontal cortex (Obfc) stretching in to the anterior insula.

Figure 2 Placebo-dependent increases and decreases in the ACC. Increased activity is indicated with gray, and decreased activity is indicated with white circles. In the studies by Wager and coworkers, the activity increases were observed in the anticipation phase (gray circles), whereas the decreases were observed in the stimulation phase (white circles). In the study by Lieberman and coworkers, only decreases were observed in the ACC (white circle). (The image is presented on an SPM-template at www.fil.ion.ucl.ac.uk/spm.)

Platebo-dependent activation of the rACC has been replicated recently (Fig. 2). A similar ACC activation was described by Bingel and coworkers in placebo-induced analgesia. In the article by Wager and coworkers, placebo studies were performed while the underlying neuronal activity was studied using functional MRI in both the anticipation and the induction phase of a painful stimulus. Both studies showed placebo-dependent activations of the rACC as well as in the lateral Obfc in the anticipation phase. However, these activations were not observed during the pain stimulation itself. Instead, decreased activations in the ACC were observed in the placebo pain phase. The authors suggest that when there is a preparatory phase, the placebo-dependent modulatory effect may be induced before the actual painful stimulation, leading to a decreased pain processing during the stimulation. This is a fascinating suggestion, indicating that we are able to activate the endogenous system in a preperceptual manner. The decreased activation observed some-
what later would then indicate an attenuated processing of pain unpleasantness processed in the ACC.40

In the study by Lieberman and coworkers11 no increased placebo-dependent activation was observed in the rACC; instead, a negative correlation was observed between the placebo degree and the activity in mid-caudal ACC (a more posterior region of the ACC). However, in this study the placebo effect was induced during a 2-week period and acute modulatory effects were not studied. The 2 last described articles10,11 point to some of the difficulties in the study of higher cognitive modulations of pain, that is, similar regions in the ACC are involved in processing perception of pain unpleasantness (possibly inducing relative decrease of ACC activity during placebo treatment) as well as in pain regulation (possibly inducing relative increases of ACC activity during placebo treatment). Although the pain regulatory activations seem to be somewhat more rostral10 the 2 areas of activity may partly overlap and the pain-related decreases may attenuate placebo induced increase in activity. Nevertheless, 4 of the 5 presented placebo experiments9,10,12 indicate the involvement of the rACC in placebo effect (Fig. 2).

When it comes to the orbitofrontal cortex, 4 of the presented functional imaging experiments indicate a placebo-dependent activation of this region9-11 (Fig. 3) with a preference for the right Obfc.9,11 Few functional imaging studies on the opioid effect have described extensive or any opioid-related activations of the Obfc, which may indicate that other processing components of the placebo response are computed in this region. As an example, we observed placebo-dependent increases in the Obfc that were clearly more extensive than the opioid-dependent increases (Fig. 1).9 The opioid-induced Obfc activation was present only on the border between the temporopolar/insular activations. In fact, the activations observed in the Obfc may more represent a smoothing effect of the data. A key function of the Obfc is to monitor and modulate the motivational value of external stimuli based on their coupling to primary re-enforcers41-44 to perform a goal-directed behavior.45 Because the Obfc is involved in attributing external stimuli a relative value depending on the internal states and external contexts it is tempting to suggest that this region is involved in inducing the expectation of treatment and how the expectation should affect the pain experience, which may be a process preceding the opioid-dependent modulation of pain perception. Such a bias signal may be used by the ACC that is in a position to interact with the endogenous opioid system (Fig. 4).

The placebo-induced activity in the Obfc also stretched into the temporopolar region/anterior insula, which is interesting because the insula has a high concentration of opioid receptors indicated by both receptor imaging and functional imaging studies (as mentioned previously) and also has been suggested to be involved in a meta-representation of the state of the body associated with emotional awareness.38

**Interaction Between rACC and Brainstem Opioid Systems**

It has previously been proposed that the opioid system in the ACC has access to the powerful opioid system in the brainstem (Fig. 4).18,23 We suggested that this is one of the mechanisms by which the higher cognitive systems in the ACC may influence nociceptive input to the brain and thereby pain perception.9 We performed a regression analysis and observed that both in placebo analgesia and opioid analgesia the rACC activity correlated with the brainstem, a finding that was not observed for the pain condition without treatment. Although no causality can be shown, the data indicate that such a mechanism may exist. A similar regression has been replicated in the placebo analgesia study by Bingel and coworkers.12 Moreover, a similar functional connection has been shown in pain-distraction46 and prolonged tonic pain,47 suggesting that other pain regulatory conditions may involve ACC-mediated opioid-dependent control of the brainstem opioid system. Wager and coworkers did not supply such an analysis with the rACC but showed that also the orbitofrontal cortex has a similar functional connectivity with the brainstem.10 This supports the conclusion that both regions work in the same modulatory network.

**Placebo Responders and the Opioid System**

Several studies have indicated that there is a large variability between individual subjects in the placebo response. The reason for this is probably multifactorial. One factor that may crucially affect the placebo analgesic response is the under-
lying opioid system, that is, it would not possible to induce opioid-dependent placebo analgesia in a subject who is lacking an endogenous opioid system. Of course, there are no opioid-knockout subjects to test whether they respond to placebo or not. However, data indicate that the opioid system possibly vary in different subjects. Although this finding may have different causes, genetic factors are probably highly involved. In line with this suggestion one recent study has indicated that the COMT gene is directly involved in regulating the opioid system and the functionality of the opioid system in human subjects. In our placebo study, we crudely divided the subjects in placebo responders and placebo non-responders. We then compared the activations elicited by the opioids (ie, remifentanil) and observed that the placebo responders activated the rACC whereas the nonresponders did not. This analysis was powerful because we specifically studied the opioid response (and not placebo response) in placebo responders versus. nonresponders. The results are in line with a more effective opioid system in the placebo responders. However, this subject sample was very small and should be repeated in a larger subject sample.

**Conclusion**

Recent imaging studies have started to disclose a functional-anatomical relationship between the opioid and placebo processes in the human brain. An emerging view suggests that a complex network in the brain is underlying the placebo response (Fig. 4), consisting of both opioid rich regions in ACC and insula (involved in subprocesses of the placebo effect such as attentional modulation and emotional awareness), but also regions not activated by opioids such as the orbitofrontal cortex (involved in the processing of expectation). This network induces top-down control of a powerful opioid network in the brainstem. Of course, other regions also may be involved in the placebo process, eg, the dorsolateral prefrontal cortex is probably involved in short-term memory holding the nonemotional context supporting the placebo response on-line. Another region possibly belonging to this network is the amygdala because it is involved in a similar opioid-dependent control of the brainstem in the fear response. In a near future, displacement studies of the opioid receptor system will further show whether the opioid network may be directly involved in the placebo response. Moreover a combination between genetic and imaging studies may indicate whether different genotypes affecting the opioid system also affects the opioid phenotype and thereby the placebo response.

**References**


**Figure 4** The opioid network in the cortex and the brainstem and its interaction with the orbitofrontal cortex. There is an opioid-rich network in the brainstem, including the periaqueductal gray (PAG), the parabracial nucleus (PBN), and the rostral ventrolateral medulla (RVM). This network may be controlled by the opioid-dependent processes in the amygdala in fear-induced analgesia. We suggest that the ACC, as a part of an opioid-rich network also including the anterior insula and the Obfc, is similarly involved in brainstem regulation in placebo analgesia. Given that the Obfc is not highly activated by opioids, it may be involved processing other components in the placebo response, such as treatment expectations. (The image is presented on an SPM-template at www.fil.ion.ucl.ac.uk/spm.)
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