[Frontiers in Bioscience S2, 106-111, January 1, 2010]

The placebo response in pain and depression: in search of a common pathway

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1. ABSTRACT

The placebo effect has been extensively studied in many disease states, some of the most notable being pain and depression. Utilizing a Medline search, studies were identified that reported on areas of the brain shown to be involved in either placebo analgesia or mood response. This paper presents a distillation of this research, in an effort to identify a common "placebo pathway" between mood and pain. Placebo-related responses to both analgesia and relief from depression were reported to be associated with an increase in activity in the frontal cortex and a decrease in activity in the thalamus.

2. INTRODUCTION

Although the very existence of the placebo effect has been questioned (1), alleviation of pain and depression, as well as many other disorders, may be achieved through administration of placebo in some patients (2). The contribution of placebo to treatment response can complicate the development of therapies when it occurs in clinical trials (3), but in clinical practice, placebo response may, in fact, have practical use (4).

Understanding the neurobiology of the placebo response may lead to development of more effective

treatments for many disease states. Targeting the "placebo mechanism" rather than the underlying disorder could provide an alternative approach, or a supplemental treatment, to relieve pain, depression, and other disorders. For disorders of unknown mechanism or those not amenable to direct treatment, exploitation of the placebo effect may be of special utility. Harnessing the power of placebo could lead to therapies devoid of pharmacological side effects, although most patients would still experience adverse events, as shown in every placebo-controlled clinical trial.

Through imaging and biochemical studies, mechanisms of the placebo response are being elucidated, and numerous excellent reviews have been published (5-7). The basic approach has been to measure regional cerebral blood flow (rCBF) directly by positron emission tomography (PET) or by measuring blood oxygen-level dependent changes in rCBF using functional magnetic resonance imaging. Understandably, use of different approaches has introduced its own challenges (8). The intent of this paper, however, is not to provide another review; rather, it is to explore the possibility of a common pathway between the placebo response involved in pain and that involved in depression. It should not be assumed that there is a single "placebo pathway," which is the mechanism responsible for a placebo response in all disorders. Indeed, several researchers have concluded that there is no common pathway and that the placebo response is specific to the disease state (6, 9).

This paper will focus on anatomic regions of the brain involved with the placebo response in pain and depression, with the goal of identifying an anatomical "final common pathway." Certainly, placebo responses in other disorders could have been chosen, but pain and depression appear to be so closely linked that the possibility of finding a common pathway may be greater with pain and depression. Although appealing in its simplicity, it is clear that brain function can not be reduced to simple common pathways. The placebo response does not exist in isolation. It is influenced by expectations (9-10) and cognitive processes, especially memory (11). Individual differences, largely explained by past experiences, especially the affective components of pain, greatly influence the placebo analgesic response (12). Individual differences in the anticipation of analgesia, mediated via the nucleus accumbens, have been reported as an explanation for differences in the placebo response (13), and a unifying theory, the "Psychoneural Translation Hypothesis," has been proposed (14). The fact that placebo responses can be demonstrated in numerous disorders has been well established, however, and that literature will not be reviewed here. Rather, the goal of this paper is to search for a "common anatomical thread," at least for pain and depression.

Although not covered in this review, it must be acknowledged that some processing appears to occur at the spinal cord level (15). In addition, the immune system appears to be involved in response to placebo (16-17).

3. METHODS

Most research on the neurobiology of the placebo response focuses on the brain, and undoubtedly this is where most of the activity takes place. For this review, papers which identified anatomical brain regions involved in the placebo response were chosen. Medline searches were conducted with search terms such as "placebo," "placebo effect," "depression AND placebo," "pain AND placebo," "placebo pathways," and "placebo AND imaging."

Data identifying anatomical brain regions involved in the placebo response were compiled and condensed. Some literature reports were very specific in describing the localization of the placebo response. In an effort to find a "common thread," these areas were collapsed. For instance, some papers identified the rostral anterior cingulate, others the anterior cingulate, and others the cingulate gyrus as areas of placebo response. In our review, the collapsed area was considered to be the cingulate cortex. As not all readers will agree with this approach, both "as reported" and "condensed" areas are provided.

4. REVIEW OF THE LITERATURE

4.1. Placebo and pain

Bingel and colleagues confirmed that the rostral anterior cingulate cortex (rACC) is involved in the placebo analgesic response, and further demonstrated that the bilateral amygdalae and periaqueductal gray (PAG) are also involved (18). Preceding this study, there was a report that the anterior cingulate cortex (ACC) was activated by placebo, and the authors of that report stated that, "Placebo analgesia seems to activate a more rostral part of the orbitofrontal cortex as compared with the general opioid effect" (19). In contrast, Wager *et al.* found that placebo analgesia was related to decreased activity in pain sensitive brain regions, including the thalamus, insula, and ACC (20-21). Reductions in brain activation in pain-related regions (thalamus, somatosensory cortex, insula, ACC) were also found by other researchers (22).

In another study, placebo analgesia was found to be mediated by mu-opioid receptor transmission in the pregenual rostral anterior cingulate, subgenual rostral anterior cingulate, dorsolateral prefrontal cortex, insular cortex, and nucleus accumbens (23). A subsequent pain study demonstrated placebo-induced activation of the mesolimbic dopaminergic system involving the nucleus accumbens, ventral putamen, and right ventral caudate nucleus, and again showed increased mu-opioid receptor transmission in the rostral and subgenual anterior cingulate, orbitofrontal cortex, anterior and posterior insulae, nucleus accumbens, amygdala, and PAG (24). Additionally, Nemoto and colleagues found that PET scans showed decreased rCBF in the medial prefrontal cortex (MPFC), the posterior parietal cortex, and the inferior parietal lobe in placebo responders, both with pain stimulus and at rest (25). They also found decreased rCBF in the ACC, supplemental motor area, and left inferior temporal lobe, in responders to placebo.

Table 1. Brain regions involved in placebo response, by study

	References - Pain							References - Depression		
Brain Region	Bingel 2006	Petrovic 2002	Wager 2004, 2005	Price 2008	Zubieta 2005	Scott 2008	Nemoto 2007	Mayberg 2002	Leuchter 2002	Vallance 2007
Somatosensory cortex				D [1]						
Insula			D [1]	D [1]	I [2]					
Posterior insula						I [2]		I [2]		
Cingulate cortex										I [2]
Pregenual rostral anterior cingulate					I [2]					
Subgenual rostral anterior cingulate					I [2]					
Subgenual cingulate						I [2]		D [1]		
Dorsolateral prefrontal cortex					I [2]					
Medial prefrontal cortex							I [2]			
Orbitofrontal cortex		I [2]				I [2]				
Prefrontal cortex								I [2]	I [2]	
Frontal cortex										I [2]
Premotor cortex								I [2]		
Supplemental motor area							D [1]			
Anterior cingulate		D [1]	D [1]				D [1]	I [2]		
Posterior cingulate								I [2]		
Rostral anterior cingulate		I [2]				I [2]				
Nucleus acumbens					I [2]	I [2]				
Inferior temporal lobe							D [1]			
Posterior parietal cortex							I [2]			
Parietal cortex								I [2]		
Inferior parietal lobe							I [2]			
Parahippocampus								D [1]		
Amygdala	I [2]					I [2]				
Periaqueductal gray	I [2]					I [2]				
Thalamus		D [1]	D [1]							
Ventral putamen						I [2]				
Right ventral caudal nucleus						I [2]				

Abbreviations: [1]Decreases, [2]Increases

Finally, in a review of the literature regarding placebo and pain, Lidstone and Stoessl concluded that the superior MPFC, midrostral dorsal anterior cingulate, and the dorsolateral, ventrolateral, and orbitofrontal cortices are consistently involved in placebo analgesia (26).

4.2. Placebo and depression

Although the placebo response in treatment of depression is well known (27-28), identification of the brain regions involved has been more challenging, and the literature on this topic is sparse. This is understandable given that depression can not be measured by delivering a discreet stimulus. Furthermore, onset and resolution of depression are not discreet phenomena, but rather, develop over time. However, more immediate effects have been elicited by using mood challenges (29). In addition, considerable progress has been made in understanding the neuroanatomical substrate of the placebo response in depression.

Recovery from depression associated with placebo has been related to increased activity in the prefrontal cortex, premotor cortex, posterior insula, posterior cingulate, and anterior cingulate, and with decreased activity in the hypothalamus, parahippocampus, and subgenual cingulate (30). Cordance, a measure of quantitative electroencephalogram associated with cerebral blood flow, was found to be increased in the prefrontal area of placebo responders (31). In a recent review, Vallance and colleagues concluded that recovery from depression, either after placebo or no treatment was associated with increased activity in the cingulate cortex and frontal cortex (32).

4.3. Findings

Data reviewed above are summarized in Table 1, which was then collapsed into Table 2, as described in the Methods section. Where described, increases (I) and decreases (D) in activity are indicated. Clearly, results from different studies vary widely, even when regions are collapsed. Nevertheless, 2 regions, the prefrontal cortex and the parietal cortex, were reported to have increased activity associated with the placebo response in analgesia and relief from depression. The thalamus, on the other hand, was associated with a decrease in activity. These 3 regions are indicated in bold in Table 2.

5. PERSPECTIVE

Although there is much yet to be learned, great strides have been made in understanding the neurobiology of pain and depression. Because it is more discreet, acute pain is easier to study than chronic pain from a neuroanatomical perspective. The complexity of chronic pain, and the wide range of nervous system structures involved, has made the understanding of the neurobiology of such pain illusive. The brain pathways involved in mood modulation appear to be equally, if not more complicated than those involved in chronic pain, thus, the elucidation of the neurobiology of mood has been difficult, as well.

Table 2. Brain regions involved in placebo response: condensed

	References - Pain							References - Depression		
Brain Region	Bingel 2006	Petrovic 2002	Wager 2004, 2005	Price 2008	Zubieta 2005	Scott 2008	Nemoto 2007	Mayberg 2002	Leuchter 2002	Vallance 2007
Prefrontal cortex		**I [1]**			**I [1]**	**I [1]**	**I [1]**	**I [1]**	**I [1]**	
Frontal cortex										I [1]
Premotor cortex							D [2]	I [1]		
Somatosensory cortex				D [2]						
Parietal cortex							**I [1]**	**I [1]**		
Insula			D [2]	D [2]		I [1]		I [1]		
Cingulate cortex	I [1]	I [1]	D [2]	D [2]	I [1]	I [1]	D [2]	I [1]		I [1]
Inferior temporal lobe										
Parahippocampus								D [2]		
Amygdala	I [1]					I [1]				
Thalamus			**D [2]**	**D [2]**				**D [2]**		
Periaqueductal gray	I [1]					I [1]				
Nucleus acumbens					I [1]	I [1]				
Putamen						I [1]				
Caudal nucleus						I [1]				

Abbreviations: [1]Increases, [2]Decrease

Further challenging our understanding of the neurobiology of mood and pain is the fact that both of these conditions are subject to a placebo response. It has long been understood that these and other disorders respond to placebo, but only since the development of functional neuroimaging techniques has insight been gained into the biological mechanisms associated with the placebo response.

The goal of this review was to find a common pathway which might mediate the placebo response in both pain and mood. Given the relative newness of the field and the complexities of these conditions and the central nervous system, it is not surprising that different groups have identified various brain regions responsible for the placebo response in both pain conditions and mood abnormalities. However, among the literature reports reviewed, placebo-related responses to both analgesia and relief from depression were reported to be associated with an increase in activity in the frontal cortex and a decrease in activity in the thalamus.

If the frontal cortex and thalamus are involved in a placebo-related antidepressant effect and placebo-induced analgesia, one would expect that these regions would also be involved in the disorders relieved by placebo, suggesting that activity in the frontal cortex would be decreased, and activity in the thalamus increased, in depression and pain. Although the situation is complex, with some conflicting evidence, it appears that in both pain and depression, there is, indeed, decreased activity in the prefrontal cortex and increased activity in the thalamus.

With regard to pain, many studies have been conducted attempting to identify the brain regions involved, and numerous regions have been identified as participating in the perception and processing of pain. Results have varied, but the cingulate cortex has been consistently found to be involved in the perception of pain (33). The increase of activity in the frontal cortex associated with the placebo response would predict that activity might be decreased with pain. However, although the prefrontal cortex was often found to be involved in pain sensation and processing, findings suggest both increased activity associated with pain (34-36) and distraction from pain (37). Some of the discrepant findings may be related to resolution of available methods. Indeed, different regions of the prefrontal cortex have been found to be activated by painful and pleasant stimuli (38). It may be that the placebo effect has more to do with the processing of pain than actual reduction in intensity. This would be consistent with studies suggesting that the prefrontal cortex is involved in the cognitive aspects of painful experiences (39). Although data are sparser, increase in thalamic activity was found in association with pain (33), and thalamic stimulation was reported with the placebo response, as described in Section 4, above.

In the case of depression, although the cingulate cortex was identified as the region most consistently abnormal, hypoperfusion was found in the dorsolateral prefrontal cortex (40). Baseline rCBF of depressed patients tended to be lower than those of normal subjects with significant reductions being observed in the frontal region of the left hemisphere and in some areas of the frontal region of the right hemisphere (41). This group also reported that chronic treatment with amitriptyline induced a significant increase in rCBF in the left frontal region. In a review of the literature, Soares and Mann stated that: "Decreased prefrontal cortex blood flow and metabolism in depressed unipolar and bipolar patients are the most consistently replicated findings, and correlate with severity of illness. Antidepressant medications, but not ECT (electroconvulsive therapy), seem to reverse some of the identified functional brain changes in the depressed state" (42).

Thus, decreased activity in the prefrontal cortex appears to be a fairly consistent finding with depression, and as described above, the placebo response was often found to increase activity in this area. More difficult to understand is the situation with the thalamus. A decrease in activity appears to be associated with the placebo response. However, compared with controls, moderately depressed patients showed reduced activation in the thalamus bilaterally (43).

In summary, if the frontal cortex and thalamus continue to be identified as being involved in the placebo response, it will be important to consider other conditions amenable to placebo treatment (for example, Parkinson's disease, anxiety, attention defecit disorder) to determine if this "common pathway" is also operative in disorders beyond pain and mood. Granted, this approach vastly oversimplifies a complex and often conflicting body of knowledge, but the search for simple common pathways may provide a fresh perspective in trying to understand the processes and structures involved in pain and depression.

6. ACKNOWLEDGEMENTS

Both authors are employees of Eli Lilly and Company.

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Abbreviations: ACC = anterior cingulate cortex, MPFC = medial prefrontal cortex, PAG = periaqueductal gray, PET = positron emission tomography, rACC = rostral anterior cingulate cortex, rCBF = regional cerebral blood flow.

Key Words: Placebo, Pain, Depression, Neurobiology, Imaging, Review

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