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Expectancy Modulation of Opioid Neurotransmission

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Abstract

Expectancies are powerful modulators of cognitive and emotional experiences, as well as the neurobiological responses linked to these processes. In medicine, placebo effects are a clear example of how expectancies activate opioid neurotransmission in a treatment context, leading to the experience of analgesia and the improvement of emotional states, among other symptoms. Molecular neuroimaging techniques using positron emission tomography (PET) and the selective **μ**-opioid receptor tracer [^{11}C] carfentanil have significantly contributed to our understanding of the neurobiological systems involved in the formation of placebo effects. This line of research has described neural and neurotransmitter networks implicated in placebo effects and provided the technical tools to examine inter-individual differences in the function of placebo responsive mechanisms. As a consequence, the capacity to activate endogenous opioid networks during the administration of placebos has been linked to the concept of resiliency mechanisms, partially determined by genetic factors, and uncovered by the cognitive emotional integration of the expectations created by the therapeutic environment and its maintenance through learning mechanisms. This evidence has contributed to the understanding of the biological bases of the cognitive and psychological mechanisms implicated in the response to treatments, and opened up new opportunities for drug development and the enhancement of treatment responses. Further, delineation of these processes within and across diseases is critical to understand neural systems that could be enhanced to promote symptomatic improvement and modify disease progression.

1. EXPECTATION MODULATION OF OPIOID NEUROTRANSMISSION

Positive expectations of improvement—the so-called placebo effect—are powerful modulators of clinical outcomes. This effect has been particularly well described during the treatment of clinical and experimental pain and depression, although it extends to a large number of other conditions, such as Parkinson disease and functional bowel disorders (Benedetti, 2008; Weimer, Colloca, & Enck, 2015). Work in this area has demonstrated that responses to positive expectations are associated with the activation of specific brain regions and neurotransmitter systems (Scott et al., 2008; Wager et al., 2004; Wager, Scott, & Zubieta, 2007; Zubieta et al., 2005), which seem to overlap with those affected by the pathology and treatments under study (de la Fuente-Fernandez et al., 2001; de la Fuente-

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Fernandez et al., 2002; Kennedy et al., 2006; Mayberg et al., 2002; Scott et al., 2008; Volkow et al., 2003).

Over three decades of research have linked placebo analgesia to the activation of endogenous opioid system. The first demonstration of the effects of positive expectations of improvement on changes in neurotransmitter systems showed that placebo analgesic effects could be blocked after the administration of the μ-opioid receptor (MOPR) antagonist naloxone (Levine, Gordon, & Fields, 1978). Placebo effects were then understood as a mechanism of pain transmission inhibition through the descending pain modulating system that originates in the cerebral cortex. Further research demonstrated the activation of several cortical areas in response to placebos, including the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC) (Petrovic et al., 2002; Wager et al., 2004). This activation then extends into the descending pain modulating system, involving the hypothalamus, the periaqueductal gray (PAG), and the rostroventromedial medulla (Eippert et al., 2009a), and reaches down to the spinal cord, where inhibition of dorsal horn neurons are likely to occur (Eippert et al., 2009b). Neuropharmacological studies further confirmed the role of the opioid system in placebo analgesia using opioid antagonists blockade (Amanzio & Benedetti, 1999; Benedetti, 1996; Eippert et al., 2009a, 2009b; Levine et al., 1978), and in vivo receptor binding of MOPRs (Wager, Scott, & Zubieta, 2007; Zubieta et al., 2005).

In addition, substantial evidence has supported the activation of reward-related networks in the context of placebo administration, both in (Scott et al., 2007) and outside the pain field (e.g., Parkinson's disease) (de la Fuente-Fernandez et al., 2001). It has been argued that the placebo effects represent a form of reward expectation which activates the same circuitry that is involved in the expectation of rewards in general (de la Fuente-Fernandez et al., 2001). This hypothesis essentially states that a person's expectations about their subsequent response to a placebo are central to the placebo effect (Kirsch, 1997). More recently, and along similar lines, it has been shown that individual positive or negative beliefs regarding the efficacy of a particular treatment modality influenced the formation of placebo effects (Watkinson, Chapman, & Horne, 2017).

This dual neural representation of placebo analgesia in pain and reward-related regions is consistent with the notion that positive expectations might have a twofold effect: the reduction of negative outcomes (e.g., pain, depression) and/or the increase likelihood of positive outcomes (e.g., therapeutic benefit) (Benedetti, 2014). Not surprisingly, placebo-induced increased opioid neurotransmission has been demonstrated in both pain- and reward-related networks as well as across disorders (e.g., pain, depression), consistently with the role of the opioid system in the regulation of stress and reward responses, as it will be pointed out later.

This review examines some of the findings we just summarized, in the context of a broader understanding of the role of the opioid receptor system and its function in regulating stress and reward responses, as a way to understand the neurobiology of placebo effects.

2. OPIOID NEUROTRANSMISSION AND FUNCTION

The opioid system consists of a large number of opioid peptides (β-endorphin, the endomorphins, enkephalins, and dynorphins) and their opioid receptor sites (μ: β-endorphin, the endomorphins, and enkephalins; δ: enkephalins; K: dynorphins). In particular, the MOPRs are broadly distributed and are critically involved in the induction of endogenous and exogenous analgesia, reward and stress responsiveness (Kreek & Koob, 1998; Vaccarino & Kastin, 2000), as well as the regulation of emotion (Zubieta et al., 2003), hedonic responses to natural rewards (Pecina & Berridge, 2005), and social interactions (Herman & Panksepp, 1978; Hsu et al., 2013). MOPRs are widely distributed in the brain and attain their highest concentrations in the thalamus and PAG, where they regulate pain and stress responses, and in the amygdala, nucleus accumbens, and the cingulate cortex, where these receptors modulate reward, emotion, and in the case of the amygdala, also sensory processing (Oroszi & Goldman, 2004).

While opioids are best recognized for their ability to modulate pain processing, this effect might be, in fact, an expression of a broader function to counteract stress responses. Pain, as any other stressor, signals physical threat and elicits many of the same responses as nonnoxious stressors, including increased arousal, changes in autonomic activity, avoidance behaviors, and negative affect (Ribeiro et al., 2005). This “antistress” activity of endogenous opioids seems to be specifically mediated by MOPRs, whereas a stress-like aversion has been associated with the dynorphin–κ-opioid receptor (KOPR) system (Chavkin, 2013). These studies suggest that opioids mediate responses to stress broadly, providing biological mechanisms of susceptibility or resilience to physical or emotional stressors.

Emerging evidence from the human and animal literatures also points to the possibility that opioids contribute to the processing of social information. According to the brain opioid theory of social attachment (Panksepp et al., 1978), endogenous opioids are released by experiences of social bonding and mediate the pleasant feelings stemming from social bonding and affiliation (Ikemoto & Panksepp, 1992; Panksepp, 2003; Panksepp & Beatty, 1980). Furthermore, social isolation decreases the expression of proenkephalin in the nucleus accumbens, caudate, and putamen, regions known to be involved in reward and motivational processing (Angulo et al., 1991), and patients with depression show reduced endogenous opioid release in response to social rejection in brain regions implicated in stress, mood, and motivation (Hsu et al., 2015).

There is also a large body of evidence demonstrating the key role of the endogenous opioid system regulating reward and addictive behaviors. In this context, it is generally accepted that systemic and local region-specific administration of MOPR agonists, and to a lesser extent δ-opioid receptor (DOPR) agonists, stimulate positive reinforcement and euphoria, whereas KOPR agonists inhibit positive reinforcement and induce aversion and dysphoria. In fact, MOPR and DOPR antagonists have direct aversive–anxiogenic effects and can also suppress the positive reinforcing properties of natural rewards (Colasanti et al., 2011), whereas KOPR antagonists have been shown to facilitate these effects (Van Ree et al., 2000).

This ubiquitous role of the endogenous opioid system and opioid receptors modulating the adaptation of the organism to physical or emotional challenges which threaten its internal homeostasis, as well as the ability to regulate reward responses, place this system at the core of how positive expectations in the context of a "psychosocial" therapeutic encounter under stressful conditions (e.g., illness), might result in a cascade of neurobiological responses that promote the recovery of an organism undergoing allostatic challenges.

3. OPIOID PHARMACOLOGICAL AND NEUROIMAGING STUDIES OF PLACEBO EFFECTS

As briefly described earlier, pharmacological (Amanzio & Benedetti, 1999; Gracely et al., 1983; Levine et al., 1978) and neuroimaging studies (Petrovic et al., 2002; Scott et al., 2008; Zubieta et al., 2005) have extensively demonstrated the role of the opioid system in placebo analgesia. The first study that confirmed this relationship showed that placebo analgesic effects could be blocked by the administration of the MOPR antagonist naloxone (Levine et al., 1978). In a subsequent study Amanzio and Benedetti (1999) extended these findings investigating the role of opioid and nonopioid mechanisms in the formation of placebo analgesic effects. The contribution of the opioid system to the formation of placebo analgesic effects was further studied using blood flow measures and a pharmacological challenge (Petrovic et al., 2002). This study compared the effects of the short-acting MOPR agonist remifentanil on regional cerebral blood flow (rCBF) as measured with positron emission tomography (PET), with the effects of a placebo under expectations of analgesia. The results of this study demonstrated overlapping brain activity in the rostral ACC under the placebo and remifentanil conditions. Placebo administration also increased the correlation between the activity of this region and that of the midbrain PAG, a region known to exert modulatory effects on pain transmission. Individuals with high placebo analgesic responses showed greater rCBF responses to remifentanil, suggesting that individual differences in placebo analgesia may involve differences in the concentration or functionality of MOPRs (Petrovic et al., 2002). Soon after, Wager et al. (2004) and Eippert, Bingel, Schoell, Yacubian, Büchel (2008) confirmed the role of the rACC in the formation of placebo responses. Furthermore, on the basis of previous experiments on the blockade of placebo analgesia by the opioid antagonist naloxone (Amanzio & Benedetti, 1999), Eippert et al. (2009a) conducted a study to investigate the location of naloxone action in the brain. Using a pharmaco-fMRI intervention, they found that naloxone reduced behavioral placebo effects as well as placebo-induced responses in pain-modulatory cortical structures, such as the DLPFC and the rostral ACC. They also found a similar naloxone modulation of placebo-induced responses in key structures of the descending pain control system, including the hypothalamus, the PAG, and the rostral ventromedial medulla. Most importantly, naloxone abolished the increase in coupling between the rostral ACC and the PAG that was induced by the placebo. Finally, the same group demonstrated the first direct evidence that psychological factors can influence nociceptive processing at the earliest stage of the central nervous system, namely the dorsal horn of the spinal cord and that one mechanism of placebo analgesia is inhibition of spinal cord nociceptive processing.

4. PLACEBO EFFECTS AND μ-OPIOID NEUROTRANSMISSION

Among the different approaches to investigate the role of the opioid system in the neurobiology of placebo effects in humans, the use of selective radioligands and PET has resulted in major contributions to the field. Cerebral MOPRs availability and endogenous opioid release can be quantified in vivo using PET and the MOPR selective radiotracer [^{11}C]carfentanil (Fig. 1), or the nonselective opioid receptor radioligands, such as [^{11}C]buprenorphine, [^{11}C]−/[^{18}F]diprenorphine (DPN), or the μ- and K-antagonist ^{11}C-cyclofoxy. In these types of functional molecular assays, acute reductions in the in vivo receptor availability (binding potential) from a pain to a pain with placebo condition reflect placebo-induced activation of endogenous opioid neurotransmission; however, the sensitivity of these radiotracers to displacement by the endogenous ligands is quite variable, and greater for the agonist [^{11}C] carfentanil among the available agents.

The first direct evidence of the administration of a placebo with expectations of analgesia was associated with the activation of the endogenous opioid system and MOPRs in vivo was published in 2005 (Zubieta et al., 2005). Here, the administration of the placebo was associated with increased endogenous opioid release in the rostral and subgenual ACC, the DLPFC, anterior insular cortex, and the nucleus accumbens. This activation was also associated with quantifiable reductions in physical and emotional elements of the pain experience. The regions implicated in this phenomenon included some involved in cognitive and emotional integration (DLPFC, rostral ACC); the representation and modulation of pain and emotionally salient stimuli (insula); and reward and saliency assessments (nucleus accumbens). The DLPFC was not found to be related to changes in the psychophysical properties of the pain challenge, but instead was negatively associated with the expected analgesic effect of the placebo, suggesting that the reduction in the inhibitory effect of MOPRs in this cognitive and anti-nociceptive region was allowing the top-down engagement of subcortical pain regulatory regions through changes in the activation of MORs. These findings were replicated in a follow-up study (Scott et al., 2008), where the administration of the placebo was also associated with significant endogenous opioid activation in the pre- and subgenual ACC, orbitofrontal cortex, anterior and posterior insula, medial thalamus, nucleus accumbens, amygdala, and PAG. There was a notable lack of involvement of the DLPFC in this particular study. Regional magnitudes of activation correlated with the expected level of subjects expected analgesia (nucleus accumbens, PAG), the update of these verbally induced expectations by the subjectively perceived efficacy of the placebo (the ratio between observed and expected efficacy) (nucleus accumbens, amygdala), as well as with placebo-induced changes in pain intensity (rostral ACC, nucleus accumbens, orbitofrontal cortex) and positive affect (nucleus accumbens).

Further studies examined the contribution of expectations and of learning processes, the latter defined as the differential between initial expectations and self-assessed effectiveness (prediction error) on the activity of the endogenous opioid system during placebo administration. These analyses incorporated 48 healthy subjects (20 of them were previously studied; Scott et al., 2008) using PET and the MOPR selective radiotracer [^{11}C] carfentanil (Pecina, Stohler, & Zubieta, 2014), during the same challenge. In order to create a measure of expectations and expectations/outcomes comparisons, subjects were assigned to a Low

(≤50) or High (>50) expectations or effectiveness groups based on their expected analgesic effects (0–100 VAS) before the experiment and their perceived effectiveness of the placebo (0–100 VAS) after the experiment. When the two variables were combined, these resulted in four groups: a High Expectation/Low Effectiveness group, Low Expectations/Low Effectiveness group, High Expectations/High Effectiveness group, and Low Expectations/High Effectiveness group. This study showed a lack of significant relationships between the subjects expected analgesic effects and placebo-associated reductions in pain ratings. Instead, individuals with high expectations showed greater μ-opioid system activation in the DLPFC which were not associated with placebo analgesic effects. Conversely, a learning mechanism defined by the discrepancy between expected analgesia and subjectively perceived effectiveness, a prediction error signal was associated with placebo analgesic responses, and with the activation of regional μ-opioid neurotransmission in a substantial number of regions implicated in opioid-mediated antinociception (ACC, orbitofrontal cortex, amygdala, thalamus, and insula; Fig. 2A). The largest placebo responses were observed in those with low expectations and high subjective effectiveness (positive prediction error signal), whereas “nocebo” hyperalgesic responses were observed in those reporting high expectations and low reported effectiveness (negative prediction error signal). The magnitude of μ-opioid system activation in the dorsal ACC mediated the effect of prediction error on placebo analgesia.

In an attempt to investigate the role of the opioid system in the maintenance of placebo analgesia, a subsequent study examined whether the magnitude of regional opioid activation would also be associated with the strength of the recall of the placebo-induced analgesic responses (e.g., the persistence of a memory of placebo-induced analgesia) (Pecina, Stohler, & Zubieta, 2013). In this study, participants were asked to recall their pain experience by completing the McGill Pain Questionnaire (MPQ) in a phone interview 24h after the study completion using the same scanning protocol used in previous studies (Scott et al., 2008). Subjects were further assigned to a positive placebo effect recall or a negative placebo effect recall based on their responses to the MPQ 24h after each scanning procedure.

This data showed that in addition to its immediate placebo analgesic effects, the MOPR system is involved in the subsequent recall of the anal-gesic experience. This is consistent with animal models showing an effect of the enkephalinergic system and MOPRs in learning and memory when activated at the time of conditioning (Rigter, 1978). Specifically, the accurate or enhanced recall of analgesic effects 24h after the studies (the recall of the placebo effect) was associated with μ-opioid system activation during placebo administration in the ventral tegmental area and the Papez circuit, implicated in reward-motivated learning and memory processing, respectively (Adcock et al., 2006). This report highlighted a novel role of this system in the formation of memories and potentially the sustainability of placebo analgesic effects through reinforcement learning (Au Yeung et al., 2014; Colloca & Miller, 2011; Lui et al., 2010).

5. OPIOID-MEDIATED PERSONALITY PREDICTORS OF PLACEBO EFFECTS

Neurobiological systems implicated in cognitive and psychological responses are likely to be influenced by more stable layers of neurobiology (e.g., personality traits), which ultimately affect those same cognitive and psychological responses. These endophenotypes can therefore be used to predict these behavioral responses.

To address this question, we examined the contribution of personality traits to the variability in placebo analgesic responses in a sample of 50 healthy volunteers using the sustained pain paradigm described earlier (Pecina et al., 2013b). Our primary hypothesis was that placebo analgesia would be associated with stress resiliency personality-related traits, an effect likely mediated, at least in part, by the endogenous opioid system, given the role of the MOPR-mediated neurotransmission in the maintenance of homeostasis during various forms of stress, including sustained pain (Ribeiro et al., 2005). We examined the predictive value of a variety of scales assessing emotional, psychological, and social well-being, dispositional optimism, satisfaction with life, and ego-resiliency. We also evaluated overall personality traits (NEO Personality Inventory Revised; Costa & McRae, 1992) and traits specifically related to the trait anxiety and reward processing.

Using the change in average VAS score of pain intensity as the dependent variable, the most predictive traits of placebo analgesia in a univariate model were Ego-Resiliency, NEO-Agreeableness, and NEO-Neuroticism, which, respectively, explained 16%, 14%, and 12% of the variance in placebo response. The former two were positive predictors, while the latter was a negative predictor. A multivariate model, which decomposed the Agreeableness and Neuroticism NEO-domains into their respective facets, showed that a composite measure of Ego-Resiliency, and the NEO facets Altruism, Straightforwardness (positive predictors), and Angry Hostility (negative predictor) accounted for 25% of the variation in placebo analgesic responses and had a predictive ability of 18%. Subjects scoring above the median in the composite of those trait measures also presented greater placebo-induced activation of μ-opioid neurotransmission in the subgenual and dorsal ACC, orbitofrontal cortex, insula, nucleus accumbens, amygdala, and PAG (Fig. 2B). Additionally, we found significant reductions in cortisol plasma levels during placebo administration, which were correlated with reductions in subjective pain reports and μ-opioid system activation in the dorsal ACC and PAG. These results and others (for a review, see Jaksic, Aukst-Margetic, & Jakovljevic, 2013) suggest that stable personality traits related to stress resiliency and interpersonal relationships have a substantial impact on the capacity to develop placebo effects and could be employed to stratify analysis and reduce variability in treatment trials where placebo effects can be particularly prominent, obscuring the effects of potentially active treatments.

6. GENETIC MODULATION OF PLACEBO EFFECTS: *A118G* ASN40ASP AND *FAAH* PRO129THR

Given the involvement of the endogenous opioid system and MOPRs in the formation of placebo effects, it would be expected that genetic variation impacting this neurotransmitter

system would influence placebo-activated processes. A candidate genetic variant examined by our group was the *OPRM1* A118G variant (Asn40Asp, rs1799971; (Bergen et al., 1997), whereby the 118G variant (Asp40) is thought to be expressed at lower levels (Zhang et al., 2005). Consistent with findings in animal models, we found that *OPRM1* G carriers, compared with AA homozygotes, showed an overall reduction of baseline MOPR availability in regions implicated in pain and affective regulation (Fig. 3). In response to a sustained painful stimulus, we found no effect of A118G on pain-induced endogenous opioid release. G carriers showed lower placebo-induced μ-opioid system activation in the anterior insula, the amygdala, the nucleus accumbens, the thalamus, and the brainstem. At a trait level, G carriers reported higher NEO-Neuroticism scores, a personality trait previously associated with increased pain and lower placebo responses, which were negatively correlated with baseline MOPR availability in the anterior insula and subgenual ACC. These results demonstrated that the A118G *OPRM1* polymorphism contributes to interindividual variations in the function of neurotransmitters responsive to pain, as well as their regulation through cognitive–emotional influences in the context of placebo effects.

In addition, genetic variation within neural systems, known to colocalize and interact with the endogenous opioid system, has the potential to discover targets that would allow for the modulation (e.g., enhancement in clinical practice, reduction in clinical trials) of placebo-activated processes. One such systemistheendocannabinoid, comprised of cannabinoid CB1 and CB2 receptors and their endogenous ligands, including *N*-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) (Kogan & Mechoulam, 2006). This system is thought to be involved in analgesia (Hohmann, 2002) and reward/reinforcement (Gardner & Vorel, 1998) mechanisms, both of which are thought to be engaged during the development of placebo effects (Colloca, Sigaudo, & Benedetti, 2008). Previous work had shown that in the context of a conditioning paradigm, the cannabinoid receptor 1 (CBR1) antagonist SR 141716A (Rimonabant) blocked nonopioid, ketorolac-conditioned placebo analgesia, but not opioid placebo responses after morphine conditioning (Benedetti et al., 2011). However, our study showed that genetic variation in the functional missense variant Pro129Thr of the gene coding *fatty acid amide hydrolase (FAAH)*, the major degrading enzyme of endocannabinoids, modulated opioid neurotransmission measures during a placebo analgesia experiment (Pecina et al., 2014b), independent of other aspects of pain. Surprisingly, Pro129/Pro129 homozygotes, which have increased activity of the *FAAH* and therefore lower cannabinoid levels (Chiang et al., 2004), showed significantly greater psychophysical placebo responses, a more positive internal affective state during the placebo condition and greater recall of the placebo experience 24h after the pain challenge compared to Thr129 carriers. The neuroimaging data showed that during placebo administration *FAAH* Pro129/Pro129 homozygotes had greater placebo-induced endogenous opioid system activation, but not DA, in areas of the prefrontal cortex, including the DLFPC; the dorsal and ventromedial PFC; the lateral and medial orbitofrontal cortex; the inferior frontal gyrus; the dorsal, rostral, and subgenual ACC; the anterior and posterior insula; and the hippocampus and parahippocampal gyrus. Subcortically, regions where *FAAH* Pro129/Pro129 homozygotes had greater endogenous opioid release included the nucleus accumbens/mammillary region, the dorsal and ventral putamen, and the anterior and posterior thalamus (Fig. 2. The effects of *FAAH* on placebo-induced regional activation of μ-opioid

neurotransmission were significantly correlated with psychophysical responses to placebo and with an enhancement of the recall of placebo effects 24h after the pain challenge.

These results suggested that functional *FAAH* genotype variation selectively influenced psychophysical placebo effects and placebo-induced activation of MOPR-mediated neurotransmission in a network of regions previously involved in placebo-induced analgesia (Scott et al., 2008; Zubieta et al., 2005). *FAAH* Thr129 carriers, despite their chronic greater tonic eCB concentrations, showed lower psychophysical placebo responses and regional μ-opioid activation during placebo administration, compared with Pro129/Pro129 homozygotes, which suggest a downregulation of CBR1 sites as potentially mediating these reduced placebo responses. These results demonstrated an interaction between eCB and μ-opioid neurotransmission in the formation of placebo responses in the absence of previous conditioning and provided new insights into the neurobiology of placebo effects in conditions where these interactions play a critical role, such as substance use disorders (Belcher et al., 2017; Fattore et al., 2005, 2007; Navarro et al., 2001).

7. OPIOID-MEDIATED PREDICTORS OF PLACEBO EFFECTS IN MAJOR DEPRESSION

As briefly described in Section 1, the opioid system has a significant role in the neurobiology of emotion, stress responses, and memory. This system has been involved in the physiological regulation of affective experiences in healthy humans as well as in cognitive mechanisms of treatment response in patients diagnosed with major depression.

In a study that examined the effects of a sadness-induction challenge on the changes in μ-opioid neurotransmission using [^{11}C]carfentanil in 14 healthy female volunteers (Zubieta et al., 2003), the sustained sadness condition was associated with reduced endogenous opioid activity in the rostral ACC, ventral pallidum, amygdala, and inferior temporal cortex. Deactivation of μ-opioid neurotransmission in the rACC, ventral pallidum, and amygdala was correlated with increases in negative affect ratings and reductions in positive affect ratings during the sustained sadness state, confirming the role of the MOPR system in the physiological regulation of affective experiences in humans. In a follow-up study in 14 patients with major depressive disorder (MDD) (Kennedy et al., 2006), patients with depression showed significantly greater opioid release in the left inferior temporal cortex, which correlated with increased negative affect ratings experienced during the condition. MDD patients, compared to controls, showed significantly lower baseline MOPR binding in the posterior thalamus, which also associated with poorer treatment responses. Healthy controls instead showed larger sadness-induced opioid release in the ACC, temporal cortex, ventral basal ganglia, hypothalamus, amygdala, and periamygdalar cortex. These two pieces of literature represented the first human evidence implicating the μ-opioid system in the response to an emotional challenge in the absence of a painful stimuli both in healthy controls and patients with depression, and suggested a dysregulation of emotional stress regulatory mechanisms. In a separate sample, and using a peer rejection and acceptance paradigm, patients with major depression, compared to healthy controls, demonstrated lower levels of endogenous opioid release and μ-receptor activation in response to both acceptance

and rejection, which was associated with lower levels of stress tolerance, as measures with standardized scales (Hsu et al., 2013, 2015).

A recent novel study directly tested the contribution of the opioid system to the formation of placebo effects in unmedicated patients with moderate–severe major depression (Pecina et al., 2015). The rationale of this study followed the well-described role of opioid neurotransmission in placebo analgesic effects (Pecina & Zubieta, 2015; Zubieta et al., 2005), as well as the role of this system in the biology of depression, as summarized earlier. The study design incorporated a commonly used placebo lead-in phase with the administration of two identical placebos: one described as potentially having fast-acting antidepressant effects (active) and the other described as being a placebo with no antidepressant effects (inactive). In addition to evaluating the effects of sustained placebo pills, an intravenous (IV) placebo administration followed the 1-week active placebo to investigate the effects of acute placebo administration on μ-opioid neurotransmission. Following each placebo intervention, patients underwent a 10-week open-label trial with a common SSRI antidepressant.

In this study, higher baseline MOPR binding in the nucleus accumbens was associated with better response to 10 weeks of open-label antidepressant treatment. Reductions in depressive symptoms after 1 week of placebo treatment were associated with increased placebo-induced opioid release in the subgenual ACC, nucleus accumbens, midline thalamus, and amygdala (Fig. 2C). Importantly, placebo-induced activation of the opioid system in these stress and emotion regulatory regions predicted 43% of the variance in the response to antidepressant treatment after 10 weeks. Similarly, subjective clinical placebo effects predicted 46% of the response to antidepressant treatment, while the combination of both predicted 57% of the total antidepressant response. Still, by weeks 8 and 10, depression severity scores were roughly twice as high among placebo nonresponders compared with placebo responders. Furthermore, achievement of remission was also significantly higher among placebo responders compared with nonresponders, an observation that potentially challenged a common tenant that eliminating placebo responders in clinical trials with placebo lead-in phases or novel sequential parallel comparison designs would help to more clearly interpret RCT results.

This study demonstrated that opioid neurotransmission is not only relevant to the formation of placebo analgesia responses but also to the formation of placebo responses in other conditions, such as depression. Furthermore, interindividual differences in opioid neurotransmission explained a substantial amount of the variance in response to common antidepressant treatments, by its role in the placebo response inherent in any treatment or by its interaction with common antidepressants.

8. FUTURE DIRECTIONS

Many questions remain to apply this knowledge to therapeutic interventions.

Are there processes that may enhance placebo effects in clinical practice? The available information points to various genetic polymorphisms that could be targeted, directly or

indirectly, to promote the engagement of these internal processes of recovery. For example, and as noted earlier, lesser functional variants of the *FAAH* and the *OPRM1* genes were associated with lower endogenous opioid-mediated placebo analgesic responses, while those of the catechol-*O*-methyltransferase (COMT) enzyme were linked to higher placebo responses in patients diagnosed with irritable bowel syndrome. The latter effect was particularly prominent in a treatment arm enhanced by increased patient–clinician interaction (Hall et al., 2012). While the field of placebo genetics is still in its infancy, this information provides targets that could be modulated in practice to enhance clinical responses (a desirable effect in unblinded clinical treatments). In RCTs, genetic information can be utilized for the opposite effect, the stratification of study participants as more or less likely to respond to the placebo arms, hence aiding in the separation of active and "inactive" effects and in the separation of placebo (or sham) and study drug (or procedure)-associated treatment outcomes.

Does the modulation of placebo-activated mechanisms change outcomes in chronic conditions, such as persistent pain syndromes or major depression, for example? In clinical trials, the placebo responses invariably parallel those of active treatments, suggesting that perhaps through processes related to reward learning (Pecina, Stohler, & Zubieta, 2014a), placebo-activated mechanisms can improve the clinical status of patients with illnesses such as major depression, Parkinson's disease, or various forms of persistent pain, which register high placebo response rates in RCTs. At the present time, however, there is no neurobiological data showing that pathophysiological processes present in, for example, major depression, or persistent pain, can be reversed by continued placebo treatment in placebo responders. For example, while reductions in MOPR concentrations have been observed in fibromyalgia (Harris et al., 2007), and the capacity to activate endogenous opioid neurotransmission has been shown reduced in chronic low back pain (Martikainen et al., 2013)and major depression (Hsu et al., 2015; Pecina et al., 2015), it is presently unknown whether placebo administration, while known to affect those mechanisms, can reverse the observed deficits.

Does placebo responsiveness predict better responses to psychosocial interventions, such as cognitive behavioral or other therapies, as opposed to traditional drug-based approaches? MOPR-mediated neurotransmission is centrally implicated in prosocial, affiliative behaviors and, as noted earlier, is one of the neurotransmitter systems known to mediate placebo responses in humans, an effect clearly shown in the absence of conditioning procedures. Social processes that form part of patient–clinician interactions have been shown to enhance the responsiveness to treatment. A study of patients with irritable bowel syndrome showed that nonspecific effects could produce statistically and clinically significant improvement in outcomes, and that the patient–practitioner relationship was the most important component of those nonspecific effects (Kaptchuk et al., 2008). While it makes logical sense that placebo responsiveness and the expectations created by a positive patient–clinician relationship may be mediated by similar neurobiological processes, it remains to be determined whether the capacity to respond to placebo administration would also be linked to a higher likelihood of response to psychosocial or cognitive (e.g., cognitive behavioral therapy) interventions, hence reducing the need for more invasive or medication-based treatments.

Do interindividual variations in placebo responsiveness at the neurobiological or psychophysical levels interact or promote responses to standard therapeutic approaches? It has been shown that placebo responders also demonstrate a greater response to open antidepressant administration in major depression, an effect that was largely accounted for by the activation of endogenous opioid neurotransmission (Pecina et al., 2015). As noted by Enck et al. (2013) this suggests that neurobiological processes activated by placebo administration could be additive, or even interactive, with those impacted by active drugs or procedures. For example, antidepressants are known to act on neurotransmitter systems such as the serotonergic, noradrenergic, and dopaminergic systems, but also indirectly modulate endogenous opioid neurotransmission. A number of studies have shown that the analgesic effects of antidepressants are at least partly mediated by their modulation of the endogenous opioid system, while in animal models of depression, their antidepressant effects can also be antagonized by opioid receptor blockade. In this manner, the additive or interactive effects of placebo-activated processes with those of various treatments could in fact enhance or potentiate positive outcomes in clinical studies.

How can this information clarify the analysis of outcomes in clinical trials of novel interventions? At the very least, the study of placebo neurobiology points to specific mechanisms of resiliency that should not be disregarded as noise, but as processes that when engaged or enhanced, could impact the recovery from common chronic and highly impactful disorders.

9. CONCLUSIONS

The studies reviewed in this chapter point to the involvement of specific neurotransmitter systems and neural networks in the formation of placebo analgesic and antidepressant responses, with the endogenous opioid system and MOPRs playing a central role in these processes. In the absence of conditioning, interindividual variation in neurobiological and psychophysical placebo effects is associated with expectations (a result of the interaction between the individual and the “treatment” environment and potential preexisting biases) and maintained by learning processes (driven by the relationship between initial expectations and subjectively experienced outcomes (Pecina et al., 2014b)). They are also determined by the individual neurobiology, in particular genetic variations in common polymorphisms that modulate endogenous opioid system function. As would be expected for genetically modulated traits, specific personality characteristics associated with stress tolerance and the capacity to respond favorably (or unfavorably) to changes in the environment, also predicted a substantial proportion of the variance in the development of both, subjective and objectively measured placebo responses.

Largely disregarded as measurement “noise” in clinical trials, placebo neurobiology rather points at mechanisms that can be activated by cognitive–emotional processes that take place in the therapeutic environment to reduce illness burden by the engagement of stress regulatory mechanisms (either physical, such as pain, or emotional, as in the case of depression), where the endogenous opioid system plays a central role.

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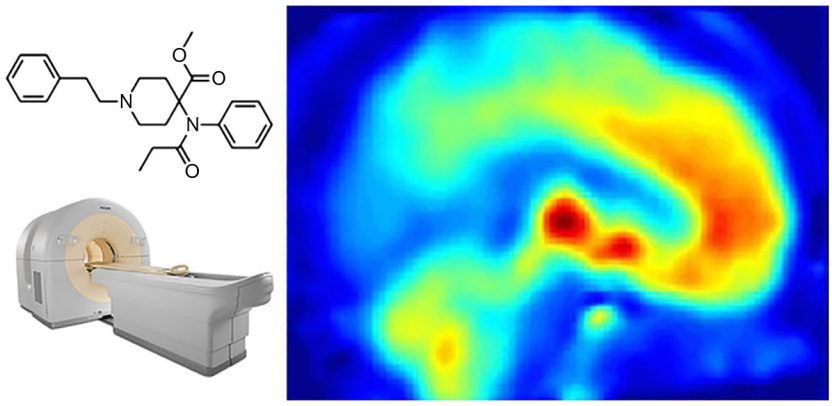

Fig. 1.

Brain regions with high density of μ-opioid receptors and high affinity for the radioligand [^{11}C]carfentanil during positron emission tomography. *Credit: Data from Dr. Jon-Kar Zubieta's Lab.*

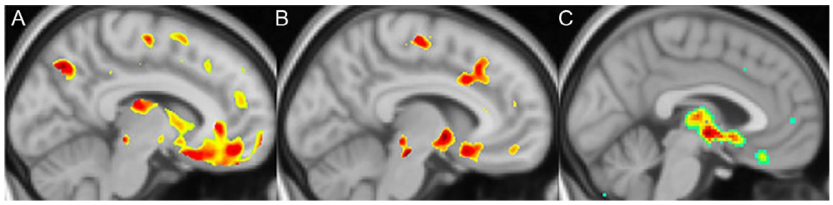

Fig. 2.

Placebo-induced changes in μ-opioid neurotransmission in the ventromedial prefrontal cortex in response to different placebo manipulations. (A) Activation of regional μ-opioid neurotransmission during a pain challenge in patients with low expectancies of improvement and high effectiveness. (B) Activation of regional μ-opioid neurotransmission during a pain challenge in patients high levels of Ego-Resiliency, NEO Altruism, NEO Straightforwardness, and low levels of NEO Angry Hostility. (C) Activation of regional μ-opioid neurotransmission in patients with major depression after the administration of intravenous and oral placebos with expectations of fast-acting anti-depressant effects. *Credit: Data from Dr. Jon-Kar Zubieta's Lab*.

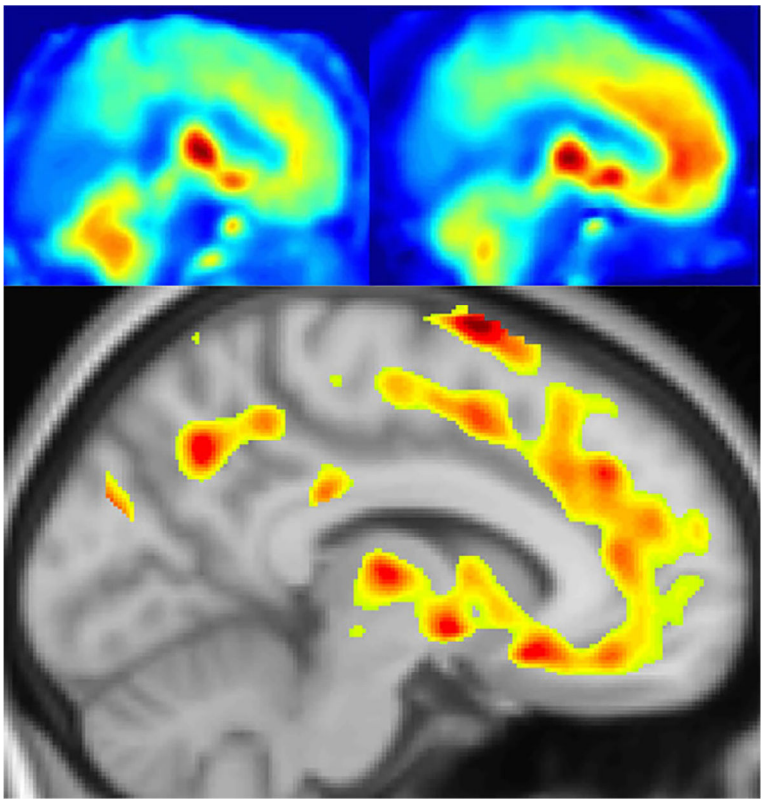

Fig. 3.

Effects of the mu opioid receptor polymorphism (*OPRM1* A118G) on μ-opioid receptor binding potential. *Top left*: μ-opioid receptor binding potential in G carriers. *Top right*: μ-opioid receptor binding potential in AA homozygotes. *Bottom*: AA homozygotes, compared to G carriers, had greater μ-opioid receptor binding at baseline in the anterior cingulate cortex, nucleus accumbens, and thalamus. *Credit: Data from Dr. Jon-Kar Zubieta's Lab*.