Bachelor Degree Project

UNIVERSITY OF SKÖVDE

THINK YOUR PAIN AWAY

The neurochemistry of placebo analgesia

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Abstract

Placebo treatments are inert but are known to alleviate symptoms across numerous clinical conditions. One of the most studied placebo effects is placebo analgesia, which is a placebo effect limited to pain relief. This thesis aims to introduce the current state of research regarding the neuroscience of placebo analgesia and specifically to present research findings regarding the neurotransmission. Studies have demonstrated that placebo analgesia can be elicited through two separate processes interacting with each other; manipulation of expectations and through conditioning. These processes seem to affect neurotransmission in different ways. Many brain areas have been found to be correlated to placebo analgesia. Besides the pain-processing brain areas, studies point to that the prefrontal cortex can have a vital role in the placebo analgesic effect. Known neurotransmitters that have shown to be involved in placebo analgesia are endogenous opioids, cholecystokinin (CCK), and endocannabinoids. Studies point to that endogenous opioids are involved in the placebo analgesic effect when elicited by expectation or conditioned by an opioid drug. CCK act on placebo analgesia by affecting the release of endogenous opioids and endocannabinoids seem to be involved in placebo analgesia while it occurs due to conditioning with non-opioid drugs. Getting a better understanding of placebo analgesia and find ways to apply this knowledge in the clinical context could powerfully develop the whole medical society.

Keywords: placebo analgesia, neuroscience, neurotransmission, endogenous opioids, cholecystokinin, endocannabinoids

Table of contents

Introduction

Ordinary lotion producing powerful pain relief (Nakamura et al., 2012) and sugar pills giving pain relief to patients with chronic pain (Schafer, Geuter, & Wager, 2018) does sound too good to be true. Still, these remarkable outcomes are real and caused by something we today refer to as 'the placebo effect' (Benedetti, 2014; Schafer et al., 2018).

The first placebo-controlled trial was made by John Haygarth in 1801. At this time a common way to alleviate symptoms of different diseases was to use what was known as 'Perkins tractors' (Benedetti, 2013; De Craen, Kaptchuk, Tijssen, & Kleijnen, 1999). Perkins tractors were tiny rods of metal which were said to relieve symptoms through the electromagnetic influence of metal when touching the body. Haygarth decided to test the effectiveness of these metallic rods by treating five patients with 'fake' tractors made out of wood. In this trial, four of five patients expressed pain relief after being treated. It is clear that Haygarth had a placebo effect in mind during this trial even if he did not use that very word. He described the experiment as 'clearly proving the wonderful effects of the passions of hope and faith, excited by mere imagination' (De Craen et al., 1999). Although there was nearly any literature using the word 'placebo' at this time, there were many cases where one can interpret that the main intention of the physician was to please rather than to cure the patient (Benedetti, 2013; Colloca, Flaten, & Meissner, 2013).

The biggest upswing for placebo was made in 1955 thanks to Henry Beecher who published the article 'The powerful placebo'. In this paper, Beecher analyzed 15 controlled trials, of nearly 1000 patients in total, and collected the results to prove that the placebo effect can produce a great physical change in the body (Beecher, 1955; Kaptchuk, 1998). With the growing use of placebo as controls in medical and surgical treatments, more people became interested in challenging the current practice of medicine (Colloca et al., 2013).

Because of placebos beneficial influence in various clinical and physiological outcomes, the placebo research has grown exponentially during the last few years (Colloca et al., 2013). It is now stated that placebos are not one treatment alone but are made up of many things such as words, rituals, and symbols which creates a set of sensory and social stimuli. These stimuli together as a whole ritual of therapeutic actions are creating the placebo effect (Ashar, Chang, & Wager, 2017; Benedetti, 2014; Colloca et al., 2013). Further, there is no longer talked about one, but many, different types off placebo effects (Benedetti, 2014). The most studied placebo effect is 'placebo analgesia,' which is a placebo effect limited to pain relief (i.e., analgesia)(Eippert et al., 2009a; Schafer et al., 2018). It is also now demonstrated that placebos do not only have an effect during the prescription of placebo treatments but can modulate the effectiveness and tolerability of active

treatments (Frisaldi, Shaibani, & Benedetti, 2018). In other words, even if a clinician is not purposely prescribing placebo pills, beneficial placebo effects and harmful nocebo effects (i.e., the opposite of placebo) occurs continuously in the clinical context. The magnitude of these effects depends on numerous aspects such as the way a treatment is delivered or previous experiences of treatment success (Price, Finniss, & Benedetti, 2008).

Since placebo and nocebo effects occur during all treatments, it is crucial to determine the underlying brain mechanisms of these effects to be able to fully understand all kinds of treatments (Price et al., 2008). This thesis aims to investigate the underlying brain mechanisms of placebo analgesia, and specifically the involved neurotransmitters. Numerous studies have confirmed that several cortical areas are activated in response to placebo analgesia (Peciña & Zubieta, 2018; Petrovic, Kalso, Petersson, & Ingvar, 2002; Wager et al., 2004). Besides the involvement of numerous pain-relevant brain areas such as anterior cingulate cortex (ACC), thalamus, and the insula (Colagiuri, Schenk, Kessler, Dorsey, & Colloca, 2015), the prefrontal cortex (PFC) seem to play an important role in the placebo analgesic effect (Benedetti & Frisaldi, 2014). However, there are researchers claiming that placebo analgesia can occur even without higher order cognitions like the PFC (Jensen, 2018). Placebo analgesia further engages a variety of neurobiological mechanisms such as endogenous opioids, CCK, and endocannabinoids, still, what role these neurotransmitters play are still quite unclear (Colloca, 2019; Colloca et al., 2013).

Aim and structure

This thesis aims to introduce the current state of research regarding the neuroscience of placebo analgesia and specifically to present research findings regarding the neurotransmission. To be able to provide an answer to the research questions a literature review has been made. The literature review has been based on the latest and most relevant research in the field of cognitive neuroscience of placebo analgesia. Literature from 2015-2019 was searched for on the Web of Science and on Google Scholar using keywords like ’neuroscience of placebo’ and ’placebo analgesia’ filtered to focus on cognitive neuroscience. Some articles from earlier years written by important researchers in the field (e.g., Fabrizio Benedetti) have also been added to this thesis to get a more comprehensive review. After collecting as many articles on the subject as possible, the most relevant high-quality articles have been chosen for this review. This was based on, for example, the effect size of the studies, the citation rates on the articles, and on the impact factor (IF) of the journals publishing the articles. I have compared and contrast the presented results on the chosen

articles in order to find out if they contradict in any important ways or if they all point in the same direction. The findings of this review are presented in this thesis.

To get a better understanding of how pain research works this thesis will start off with a description of pain modulation and pain measurements. This will be followed by an overview of studies regarding placebo analgesia, including how it is studied, what influences the magnitude of the effect, and the role of expectation and conditioning in placebo analgesia. A brief introduction of two perspectives on placebo analgesia (’the predictive coding perspective’ and ’the dual-process model’) will also be given. These are followed by recent findings regarding neural correlates of placebo and of placebo analgesia, and further of the neurotransmission of placebo analgesia including endogenous opioids, CCK, and endocannabinoids. After presenting the most relevant research in the field of cognitive neuroscience of placebo analgesia, a discussion of the gathered results will be made with a main focus on the neurotransmission. This is followed by a discussion of limitations and of a presentation of gaps in the scientific literature regarding placebo analgesia. The thesis ends up with a conclusion of what has been said.

Pain

Pain modulation

As Benedetti (2014) claims, there is not one single placebo effect, but many. These placebo effects all have different neurobiological bases and all work across different conditions and systems (Benedetti, 2014; Eippert et al., 2009a). One of the most studied placebo effects is ’placebo analgesia,’ which is a placebo effect limited to pain relief (Eippert et al., 2009a). The International Association for the Study of Pain (IASP) describes the word ’analgesia’ as; ”Absence of pain in response to stimulation which would normally be painful” (International Association for the Study of Pain, 2019). As mentioned, the placebo analgesic effect will be the main focus of this thesis.

To be able to understand how analgesia (i.e., pain relief) works it is crucial to have a good understanding of what pain is and how it is modulated. The IASP defines pain as; ”An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (International Association for the Study of Pain, 2019). According to Tracey and Mantyh (2007), pain is a conscious, subjective experience interpreted by the nociceptive input and influenced by both emotions, memories, genetic factors, cognitive factors, and medical factors. With other words, the resultant pain is not necessarily linearly related to the nociceptive input (Tracey & Mantyh, 2007).

Büchel, Geuter, Sprenger, and Eippert (2014) explain that the nociceptive system (i.e., the sensory nervous system) includes the primary sensory nociceptors found mainly in the skin, joints or in the walls of organs. These nociceptors send signals to the dorsal horn, located in the spinal cord, where other neurons (i.e., second-order neurons) are activated. These second-order neurons send the received information to the brain through bottom-up routes where the signals, at last, are perceived as pain. The bottom-up routes are complemented by a ’top-down’-system from the brain to the body. This means that the brain can exert its influence on the incoming pain signals and either decrease or increase the pain sensation (Büchel et al., 2014). The brain areas involved in the processing of pain is commonly called the ’pain matrix’ and involves brain regions such as the ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), insula, periaqueductal gray matter (PAG), secondary somatosensory cortex (S2), supplementary motor area (SMA), and supramarginal gyrus (SMG)(Wager et al., 2013). These top-down influences of pain likely involve the brains attentional system in interaction with the pain matrix (Tracey & Mantyh, 2007). However, the modulation of pain by attention is not the only way to reduce or increase pain. As will be discussed below, placebo analgesia can be formed in various ways, involving non-attentional brain systems (Carvalho et al., 2016) and various neurotransmitters (Colloca et al., 2013).

Pain measurement

Since placebo analgesic studies involve measuring pain experience, it is crucial to have a clear picture of how pain can be measured to understand these studies. As described above, pain is a complex phenomenon. Even though there are a variety of ways to measure pain (Huskisson, 1974) making an accurate evaluation of pain is a major challenge even for health care professionals. It is especially difficult when it comes to children considering both the subjectivity of pain experiences and the limitation of children’s social and cognitive development (Le May et al., 2018).

One of the most widely used measurements is self-reports. Among these, some of the most known are the Visual Analogue Scale (VAS), the Colour Analogue Scale (CAS), and the Face Pain Scale-Revised (FPS-R). These scales vary in appearance, but all consist of some type of pain rating where you are asked how much pain you feel from ’no pain’ to ’worst pain possible’ (Le May et al., 2018). However, these self-report scales have been criticized for being too simple while trying to give a single value to the complex multidimensional experience of pain. Additionally, the patient might not know what the ’worst pain imaginable’ feels like. A more complex measurement is the Multidimensional Affect and Pain Survey (MAPS). This survey is made up of an extensive list of

descriptive adjectives that encompass the pain and emotional experience. However, one disadvantage of this measurement is that it is very time consuming (Waldman, 2009).

Some objective measurements are also used to measure pain. These are especially useful to measure pain in infants and young children who are not capable of describing pain themselves. For example, the ’Neonatal Facial Coding System’ (NFCS) is used to tell the pain-level in infants and children by looking at their facial responses (Kappesser, De Laffolie, Faas, Ehrhardt, & Hermann, 2019). Another objective pain measure is the ’Modified Behavior Pain Scale’ (MBPS), which measures three separate pain-behaviors to decide the level of pain (DiLorenzo, Riddell, Flora, & Craig, 2018).

At last, brain imaging techniques like ’positron emission tomography’ (PET) and ’functional magnetic resonance imaging’ (fMRI) can be used to determine activity increase in pain-sensitive brain regions in the pain matrix during painful experiences (Wager et al., 2004).

Placebo analgesia in humans

Although many studies have been made on placebo analgesia in animals (Colloca et al., 2013), this thesis will focus only on studies made on humans. This section will begin with a brief explanation of how these placebo analgesic studies are conducted, continue with presenting what has been shown to affect the magnitude of placebo analgesia, and finally present two different perspectives on how placebo analgesia occurs.

Placebo analgesic studies

Many studies on placebo analgesia have used what is called an open-hidden model meaning that the treatment is given in an open or in a hidden way. When the treatment is given in an open way it is given by a clinician in sight of the patient. When the treatment is given in a hidden way it can, for example, be given by a programmed infusion pump instead of by a clinician so that the patient is not aware that he or she receives treatment. In this way, the experimenter can determine if suggestions of pain relief are affecting the analgesic outcome (Price et al., 2008).

It has been shown that open administration of treatment is much more effective than hidden administration (Amanzio, Pollo, Maggi, & Benedetti, 2001; Colloca, Lopiano, Lanotte, & Benedetti, 2004). For example, in a study by Amanzio et al. (2001) analgesic medication was given either openly by a clinician together with verbal suggestions of pain relief or administered by a ”hidden” machine (without verbal suggestions). The results of their study showed that the reduction of pain was significantly greater when given by the clinician than by the machine. In another study

with an open-hidden model, the patients who received medicine from a doctor needed a significantly smaller dose of medicine to reach post-operative analgesia compared to the patients receiving a hidden administration of the medicine (Price et al., 2008). These results point to the importance of the clinician-patient relationship in the eliciting of a placebo analgesic effect (Colloca et al., 2004), which will be discussed further later on in the section called: ’The role of expectation in placebo analgesia’.

Another type of placebo studies is ’open-label studies’. In these studies, the patients are aware that they are receiving placebos (Schaefer, Sahin, & Berstecher, 2018). Studies have demonstrated that placebo analgesia works even if the patient is aware that he or she is given a placebo treatment (Carvalho et al., 2016). For example, Carvalho et al. (2016) demonstrated that open-labeled placebos could cause analgesia in people with chronic low-back pain (Carvalho et al., 2016). However, the mechanisms underlying this effect are still unclear (Schaefer et al., 2018). Further, while some individuals can respond to placebos while knowing that they are receiving inert treatment, there are others who never respond to placebos at all (Wager & Atlas, 2015).

Placebo responders and non-responders

Individuals who are responding to placebos (i.e., are showing an improvement in symptoms after receiving a placebo treatment) are called ’placebo responders’ and individuals who are not responding to placebos are for that reason referred to as ’placebo non-responders’. In some cases, the individuals who show the largest response to placebos also show the largest response to drugs (Peciña et al., 2015).

The reason why people respond so differently are just beginning to be understood (Wager & Atlas, 2015) and an established percentage of placebo responders and placebo non-responders has not yet been set (Price et al., 2008). However, there are different individual aspects that have been shown to affect the likelihood of eliciting a placebo analgesic effect (Price et al., 2008). Studies have also shown that personality traits can explain parts of the differences in responding to placebo analgesia (Peciña et al., 2013a). It has, for example, been demonstrated that individuals with personality traits like; extraversion (Kelley et al., 2009), optimism (Geers, Wellman, Fowler, Helfer, & France, 2010; Morton, Watson, El-Deredy, & Jones, 2009), and stress resiliency are more likely to elicit placebo analgesic effects (Peciña & Zubieta, 2018). While personality traits like; anxiety (Geers et al., 2010; Morton et al., 2009) and neuroticism are less likely to elicit placebo analgesic effects (Peciña & Zubieta, 2018). According to Colagiuri et al. (2015) genetics might also play a role regarding who becomes a placebo-responder and who does not (Colagiuri et al., 2015).

Some fMRI studies have demonstrated that individual differences in nucleus accumbens (NAC) and in the ventral striatum (VS) might be important for identifying placebo responders and placebo non-responders. These brain areas seem to have increased grey matter volume and stronger placebo-related opioid and fMRI activity responses during pain (Frisaldi et al., 2018). It has further been demonstrated that difference in individuals opioids systems seem to be an important factor in the response variability (Aslaksen, Forsberg, & Gjerstad, 2018; Klinger, Kothe, Schmitz, Kamping, & Flor, 2017; Vambheim & Flaten, 2017).

Benedetti and Frisaldi (2014) claims that it seems like the non-responders can sometimes answer to placebo analgesia if it is preconditioned with analgesic treatment, but rarely while they are given placebo for the first time. This means that it is to some extent possible to make non-responders become placebo responders if the effect is elicited without conscious expectation of pain relief (Benedetti & Frisaldi, 2014).

The role of expectation in placebo analgesia

Because of the presumed role of expectations in placebo analgesia many studies have been made on this subject (Peciña & Zubieta, 2018). It has been demonstrated that verbal suggestions inducing a certain expectation of analgesia create a significantly larger placebo analgesic response than an uncertain suggestion (Price et al., 2008). This was for example demonstrated in a study on postoperative patients who were treated with strong pain killers (buprenorphine) for three days in a row together with a basal infusion of saline solution (i.e., an inert liquid). The pain killers and the saline solution was exactly the same for all patients. Nevertheless, the symbolic meaning of the saline solution was changed in three groups of patients. The first group was the ’no-treatment’-group and was therefore not told anything about the saline solution. The second group was told that the saline solution could be either a placebo liquid or a powerful analgesic (i.e., uncertain suggestions). And the last group was told that the saline solution was a powerful analgesic. The results of this study showed that the third group (the one told that the infusion was a powerful analgesic) chose to take a significantly smaller amount of ’buprenorphine’ (7.65 mg) than both the second group (the one with uncertain suggestions) (9.15 mg), and the first group (the ’no-treatment’ group) (11.55 mg). Interestingly enough, the same analgesic effect was obtained with different doses of ’buprenorphine’ (Pollo et al., 2001). This study illustrated that even a small change in the verbal context of the clinician can have a huge impact on the magnitude of the placebo analgesic response (Price et al., 2008).

In an attempt to further investigate the role of expectation in placebo analgesia, Nakamura et al. (2012) wanted to investigate if the placebo analgesic effect could appear in a dose-dependent way. The goal of this experiment was to see if greater expectancy for pain relief produced a greater level of placebo analgesia. In their study, 84 participants received three identical, inert creams which were told to vary in analgesic strength. To create different levels of expectations of pain relief a training phase was made where the intensity of the painful stimuli was reduced depending on which cream they were treated with. The participants treated with the ”strong cream” received low pain stimuli, the participants treated with the ”weak cream” received medium pain stimuli, and the participants treated with the control-cream did not receive reduced pain-stimuli at all (e.g., strong pain stimuli). In the following phase, the intensity of the painful stimuli was made identical no matter which creams the participant received. Despite that, the researchers found a significant reduction in noxious stimulus-evoked skin conductance, pupil diameter and EEG (i.e., electroencephalogram) in proportion to the magnitude of the induced placebo. These results revealed that placebo analgesia can appear in a ’dose’-dependent way, mediated by the levels of expectancy for pain relief (Nakamura et al., 2012).

Furthermore, social processes that create parts of the patient-clinician relationships have been shown to enhance the responsiveness to placebo analgesic treatment (Peciña & Zubieta, 2018). It has been shown that components like empathy, warmth, length of time, and communication of positive expectation could significantly affect the clinical outcome (Kaptchuk et al., 2008). Kelley et al. (2009) argue that good patient-clinician relationships can enhance the placebo analgesic response is because it will increase the level of expectation in the patient (Kelley et al., 2009).

Kessner, Wiech, Forkmann, Ploner, and Bingel (2013) demonstrated that success or failure from previous treatment effects the expectancy and further the outcome of the current treatment. This was later confirmed by Watkinson, Chapman, and Horne (2017) who concluded that individual positive or negative expectancies regarding the effectiveness of treatment affected the formation of a placebo analgesic effect (Watkinson et al., 2017).

We have seen that placebo analgesia can be formed through manipulation of expectations. It is shown that the placebo analgesic effect formed by expectation is stronger after certain suggestions and can appear in a ’dose-dependent’ manner. Furthermore, the social process surrounding a clinical setting is another way of manipulating expectations. Finally, as current expectations are often formed by previous experiences of similar situations, treatment history also affects the placebo analgesic response. Next, a different way to form a placebo analgesic response is presented involving associative learning.

The role of conditioning in placebo analgesia

Some placebo studies point out that a placebo analgesic effect can result from unconscious processes like; conditioning (Amanzio & Benedetti, 1999; Price et al., 2008). De Houwer (2018) describes conditioning as a form of learning where the change in behavior is due to the conditioned association of two events. An example of conditioning is the ’classical conditioning’ made by Pavlov (i.e., Pavlovian conditioning). In ’classical conditioning’ behavior changes as a function of the pairing between two stimuli, called a conditioned stimulus and an unconditioned stimulus. Pavlov made an experiment of this with dogs where he paired the sound of a bell with bringing of food. When the conditioning was done, the bell itself could make the dogs salivate even in the absence of food (Pavlov, 2010). In the case of placebo analgesia, contextual cues (e.g., the shape and color of pills and the environment of the hospital) would represent the conditioned stimuli and the unconditioned stimuli would be the active treatment (Benedetti et al., 2003).

There are different opinions concerning the role of conditioning in placebo analgesia. While some claim that conditioning is crucial for eliciting a placebo analgesic effect (De Houwer, 2018) others claim that all placebo effects are mediated by expectation (Montgomery & Kirsch, 1997; Stewart-Williams & Podd, 2004).

Benedetti (2013) studied the effect of different verbal suggestions on motor performance in patients with Parkinson’s disease and on ischemic arm pain in healthy individuals. The results of this study showed that verbally induced expectations on motor improvement/worsening and on analgesia/hyperalgesia canceled the effect of conditioning. Benedetti (2013) further, investigated the effects of different verbal suggestions on the release of the growth hormone and on cortisol. The results from this trial showed that if the clinician told the patient that they would have an increase (or decrease) of cortisol and of the growth hormone (i.e., verbally increased their expectation) there were no changes in the release. Yet, if they made a preconditioning phase were made where they stimulated the growth hormone and inhibited cortisol release a significant decrease in cortisol and an increase of the growth hormone were found after placebo administration. Interestingly enough, this effect occurred even when opposite verbal suggestions were made. These findings say that even if a conditioning process is made, placebo effects are elicited by expectation when it comes to conscious mental systems like motor movement and pain. However, when it comes to unconscious physiological functions like hormonal secretion, placebo effects are elicited by conditioning (Benedetti, 2013).

Another study on conditioning was made by Colloca, Petrovic, Wager, Ingvar, and Benedetti (2010) who wanted to examine if the degree of the placebo analgesic effect would differ in a long (four sessions) comparing to a short (one session) conditioning period (i.e., learning phase). This was made with modulating both painful and non-painful stimuli to the foot of the participants. The placebo and nocebo manipulation were made by pairing red or green light to a series of stimuli that were made higher or lower. Yellow light was also associated with a series of control stimuli. The results of their study showed that the longer the conditioning period the larger the placebo analgesic effect (Colloca et al., 2010).

It has been demonstrated that live observation of a successful treatment generates placebo analgesia (Colagiuri et al., 2015). Hunter, Siess, and Colloca (2014) investigated this even further and made a study where they compared live and video-based observation of induced placebo analgesia. The results showed that video-based observation induced significant placebo analgesic responses that were of similar magnitude to live observation (Hunter et al., 2014). In other words, it is not crucial to undergo a successful first-person treatment in order to become a good placebo responder. An observation of positive outcome in another person is enough to trigger the same analgesic response (Benedetti & Frisaldi, 2014) which further support that the placebo effect represents a learning phenomenon (Price et al., 2008).

Studies also suggest that placebo effects can be modulated by subliminal cues (i.e., a stimulus below the threshold of sensation and consciousness)(Jensen, 2018). For example, in a study by Jensen et al. (2012) conditioned responses to pain stimuli were activated by subliminal cues. The experiment was made by first creating a conditioning phase (i.e., learning phase) where placebo effects were settled by connecting two visual cues with high or low intensity of pain. Later on, during the test phase, moderate pain was rated more or less painful depending on which visual cue the participant saw. Interestingly enough, when repeating the study with another group using subliminal cues instead of visible, the same conditioned responses to pain stimuli was activated. This study demonstrated significant differences in pain ratings in response to conditioned subliminal cues, establishing that conditional placebo analgesic effects can be activated by non-conscious mechanisms (Jensen, 2018; Jensen et al., 2012). Still, the claims about learning without awareness have been criticized. Lovibond and Shanks (2002) argue that conditioning might depend on the operation of a system correlating with consciousness rather than a separate, lower level system.

Putting this together, it seems like placebo analgesia can be elicited through two separate processes interacting with each other; conditioning and manipulation of expectations. There are

different perspectives on how this works. This thesis is presenting two of them; the predictive coding perspective and the dual-process model.

A predictive coding perspective of placebo analgesia

Studies have shown that the brain is creating a model of the world which it repeatedly tries to optimize by using sensory inputs. This model is over and over again refined over the lifespan through neurodevelopment learning and associative plasticity. As the brain learns the structure and consistency underlying different sensations this model allows more and more adequate predictions (Büchel et al., 2014).

According to the ’predictive coding perspective’ on brain functions, the brain is not passively waiting for nociceptive stimuli to affect it but rather actively makes conclusions based on prior experience (Büchel et al., 2014). In the case of placebo analgesia, this means that previous experiences about a treatment outcome can form the very sensory perception itself as a way to try to combine the mismatch between ’what is expected’ and ’what is felt’ (Jensen, 2018; Piedimonte, Guerra, Vighetti, & Carlino, 2017). Expectations, therefore, play a crucial role when a mismatch (i.e., a prediction error) between the actual pain and the expectation of pain occurs (Piedimonte et al., 2017). The comparisons between ’what is expected’ and ’what is felt’ can also impact expectations in the future. In that case, past experiences of pain relief increase the expectation of future pain relief, which can lead to a higher possibility of eliciting a placebo analgesic effect again (Nakamura et al., 2012).

In sum, the predictive coding framework describes placebo analgesia as being the connecting effect between top-down (i.e., signals from the brain to the body) expectations of pain relief with bottom-up sensory signals (i.e., signals from sensory neurons to the brain). In a different view, the brain is explained to contain two sub-systems, attempting to explain expectancy modulated placebo effects and placebo effects arising as a result of conditioning.

A dual-process model of placebo analgesia

The dual-process theory is a say that our reaction to environmental information occurs through two separate systems which are working in parallel to help us operate throughout our surroundings. ’System 1’ includes both reasoning and decision making, and rely on conscious awareness. In contrast, ’System 2’ are generally more automatic and deep-rooted, needing no conscious effort to get activated (Sowden, Pringle, & Gabora, 2015).

Schafer et al. (2018) claim that since both expectation and conditioning are important in placebo analgesia, the dual-process model is the most adequate perspective. The dual-process model of placebo analgesia is described as consisting of two systems which when combined form the most powerful placebo effect. System 1 can change quite easily during the process of learning new things, which can further affect the degree of the placebo analgesic effect. This dynamic system alone cannot elicit a placebo analgesic effect in the absence of expectations. System 2 slowly adds information over time, which results in conditioning. Conscious thoughts are therefore not required for this system to activate. Within this system, specific circumstantial aspects are associated with experienced outcomes (i.e., a conditioning process) which, later on, cause adaptive associative responses that can lead to placebo analgesia (Schafer et al., 2018).

In sum, the dual-process model says that placebo analgesia consists of two separate systems which if combined form the most powerful placebo effect. Further, research has demonstrated that several brain areas are activated in response to placebo, these neural correlates will be presented next (Peciña & Zubieta, 2018; Petrovic et al., 2002; Wager et al., 2004).

Neural correlates of placebo

To better understand the neurobiological mechanisms of placebo responses patients with Parkinson's disease have been studied (Price et al., 2008). Parkinson's disease is a disease affecting the neurons producing dopamine, leading to symptoms like disturbed motor skills (Benedetti et al., 2004). It has been showed that patients with Parkinson's disease respond well to placebos (Goetz, Leurgans, Raman, & Stebbins, 2000). De la Fuente-Fernández et al. (2001) made a study with positron emission tomography (PET) in patients with Parkinson's disease showing that placebo-induced expectation of motor improvement activated the damaged dopamine system in the striatum. Further, Benedetti et al. (2004) made an experiment studying single neurons in patients with Parkinson's disease who had implanted electrodes for deep brain stimulation (DBS). In this study, single neurons in the subthalamic nucleus (i.e., in the thalamus) were recorded before and after receiving a saline solution told to be powerful medicine for motor-improvement (i.e., a placebo medicine for Parkinson's disease). The results of the study demonstrated that the placebo responders had a significant decrease of frequency in neural discharge and a disappearance of bursting activity of sub-thalamic neurons, which was tightly correlated with clinical improvement (Benedetti et al., 2004).

The neural mechanisms of placebo treatments have also been studied in patients with major depressive disorder (MDD). In one study made by Leuchter, Cook, Witte, Morgan, and Abrams

(2002), it was found that placebos induced changes in the PFC of patients with MDD. In another study by Mayberg et al. (2002), changes in glucose metabolism in the brain was measured with PET in patients with MDD. The results of this study showed that placebo treatments were associated with regional metabolic increases in the PFC, the ACC, the premotor cortex (PMC), the parietal lobe, the posterior insula, and in the posterior cingulate cortex (PCC). Placebo treatments were also associated with a metabolic decrease in the subgenual cingulate cortex, the para-hippocampus, and in the thalamus (Mayberg et al., 2002). A study by Lieberman et al. (2004) showed that, beyond the mentioned brain areas, the amygdala also seems to be involved in the placebo effect.

Neural correlates of placebo analgesia

If narrowing it down to placebo analgesia, numerous studies have confirmed that several cortical areas are correlated to this effect as well (Peciña & Zubieta, 2018; Petrovic et al., 2002; Wager et al., 2004). Using PET Petrovic et al. (2002) demonstrated that both opioid analgesia and placebo analgesia are associated with increased activity in the rostral ACC. These findings suggest a related neural mechanism in the placebo analgesia and opioid analgesia. Recent fMRI studies have also connected placebo analgesia to activity in the NAC and the VS (Frisaldi et al., 2018). Further, a covariation between the rostral ACC and the brainstem during placebo analgesia have been found (Colagiuri et al., 2015).

Several studies have demonstrated that placebo analgesia decreases the fMRI activity in pain-responsive brain areas (Colagiuri et al., 2015). For example, a decrease in pain-relevant brain areas such as the amygdala, the primary somatosensory cortex (S1), the secondary somatosensory cortex (S2), and basal ganglia during placebo analgesic effects have been found (Colagiuri et al., 2015). Besides the cortical areas, the activation has also been shown to go into the pain adjusting system, including the periaqueductal gray (PAG), hypothalamus, and the rostral ventromedial medulla (RVM)(Eippert et al., 2009a) and further down to the spinal cord where inhibition of dorsal horn neurons probably take place (Eippert, Finsterbusch, Bingel, & Büchel, 2009b).

Wager et al. (2004) observed that placebo analgesia was not only associated with decreased brain activity in pain-processing areas like ACC, thalamus, and insula, but also with increased activity in the PFC (Wager et al., 2004). By using repetitive transcranial magnetic stimulation (TMS) to inactivate the PFC, it has been found that this inactivation disrupts placebo analgesia (Benedetti & Frisaldi, 2014). However, as mentioned earlier, it has also been suggested that placebo analgesic effects can occur even without higher-order cognitions like PFC (Jensen, 2018).

Neurotransmission of placebo analgesia

Placebo effects engage various neurobiological mechanisms such as endogenous opioids, CCK, endocannabinoids, oxytocin, vasopressin, and dopamine systems. In this thesis, I have chosen to focus on endogenous opioids, CCK, and endocannabinoids (Colloca, 2019). The reason for this is because these three neurotransmitters have all been found to powerfully modulate placebo analgesia (Colloca, 2019; Colloca et al., 2013). In this section, these three substances will be presented, including research findings regarding their role in the placebo analgesic effect.

Neurotransmission and function of endogenous opioids

Endogenous opioids are molecules part of a large, complex system of neurons in the central and peripheral nervous system. They act as neurotransmitters to elicit effects such as analgesia. As with all ligands, the opioids work by acting on receptors. The three main opioid receptors, which are found in a variety of brain regions, are called; μ (MOR), δ (DOR), and ϰ (KOR) (Colloca et al., 2013; Holden, Jeong, & Forrest, 2005). These three receptors can all produce an analgesic effect on incoming painful stimuli (Holden et al., 2005). Most studied and discussed receptor regarding placebo analgesia is the MOR-receptor (Peciña & Zubieta, 2018), which attains in highest concentration in the thalamus, in PAG, and in components of the limbic system such as the amygdala, the NAC, and the cingulate cortex (Oroszi & Goldman, 2004). As mentioned earlier, thalamus, ACC (Wager et al., 2004), and amygdala have also been found to play a role in the placebo analgesic effect (Colagiuri et al., 2015).

The role of endogenous opioids in placebo analgesia

The first study trying to understand the underlying biologic mechanisms of placebo analgesia was made in 1978 by Levine, Gordon, and Fields. The aim of their study was to block opioid receptors with the opioid antagonist naloxone to test if endorphins (i.e., endogenous opioid peptides) mediated placebo analgesia. The results of the study showed a disturbance of placebo analgesia after inducing naloxone, which supported the hypothesis that endogenous opioids are involved in the effect of placebo analgesia (Büchel et al., 2014; Colagiuri et al., 2015; Levine et al., 1978; Zubieta, Yau, Scott, & Stohler, 2006). However, Gracely, Dubner, Wolskee, and Deeter (1983) later demonstrated that placebo analgesia can occur even after blocking opioid mechanisms with naloxone (Büchel et al., 2014; Colagiuri et al., 2015; Gracely et al., 1983; Zubieta et al., 2006).

Benedetti (1996) managed to establish that at least a part of placebo analgesia must be due to endogenous opioids. In this study, they investigated the effect of naloxone and proglumide (i.e., a

CCK antagonist) on placebo analgesia. The study was made with experimental ischemic pain in the arm on 340 healthy men and women. Before beginning the mentioned process, a needle was inserted into a vein of the forearm of the participants. The needle was linked to a line reaching a room where hidden injections could be performed. In that way, both injections in full view and hidden injections could be administered through the process. The participants rated pain intensity on a scale from 1-10 making it possible for the experimenters to see if naloxone and proglumide affected the ratings. The results of this study demonstrated that placebo analgesic responses could be reduced by naloxone, confirming that at least parts of placebo analgesia are mediated by endogenous opioids (Benedetti, 1996; Berna et al., 2018; Büchel et al., 2014; Colagiuri et al., 2015; Petrovic et al., 2002).

It is argued that various environments and situations might affect the endogenous opioid system in different ways (Berna et al., 2018; Fields & Levine, 1984; Zubieta et al., 2006). A study by Benedetti and Amanzio (1997) demonstrated that placebo analgesia seems to be either completely blocked, unaffected or reduced by naloxone depending on what procedure was used to activate the placebo analgesic response (Benedetti & Amanzio, 1997; Berna et al., 2018). It was shown that, if the placebo response was induced with expectation cues, it could be blocked by naloxone but if it was induced with prior conditioning with a non-opioid drug, it could not be blocked by naloxone. This leads to the suggestion that endogenous opioids might have a role in placebo analgesia when it is induced by expectation, but not when it is induced by conditioning with a non-opioid drug (Benedetti & Amanzio, 1997).

It has been found that conditioning and cognitive factors are balanced in various ways in placebo analgesia (Amanzio & Benedetti, 1999; Zubieta et al., 2006). Some researchers further add that this balance is essential for the activation of either opioid or non-opioid systems (Amanzio & Benedetti, 1999; Berna et al., 2018). In a study by Amanzio and Benedetti (1999), different types of placebo analgesic effects were induced through drug-conditioning, expectation cues, or through a combination of both. The non-opioid drug that was used in this study was ketorolac, a non-steroidal anti-inflammatory drug (NSAID). The results of this study demonstrated that all expectation cues produced placebo responses that could be blocked by naloxone, meaning that they were elicited by endogenous opioids. Opioid-conditioning alone (without expectation cues) could also be reversed by naloxone. However, after a conditioning process with ketorolac, the placebo analgesic effect could not be blocked by naloxone (i.e., was not elicited by endogenous opioids). This suggests that different pharmacological mechanisms are involved in learned (i.e., conditioned) placebo responses, depending on previous exposure to an opioid or a non-opioid substance (Amanzio & Benedetti,

1999). An additional example of placebo analgesia being elicited by a non-opioid mechanism was made by Vase, Robinson, Verne, and Price (2005). In this study, they wanted to determine if placebo analgesic effects of patients with irritable bowel syndrome (IBS) are related to other mechanisms than the endogenous opioid systems. The results showed that the placebo analgesic responses elicited in the patients with IBS could not be blocked by naloxone, suggesting that these had been mediated by non-opioid mechanisms (Vase et al., 2005).

Benedetti, Arduino, and Amanzio (1999) wanted to see if it was possible to get a somatotopic activation of endogenous opioid systems by target-directed expectations of analgesia. This was tested by creating an experiment where four noxious stimuli were applied to the feet and hands of the participants. It was shown that if an inert cream, said to be a powerful anesthetic, was applied to one of these body parts (while the noxious stimuli were applied to both feet and hands) pain decreased only where the cream was applied. This effect could be blocked by naloxone which suggests that placebo activated endogenous opioids have a somatotopic organization (i.e., a point-for-point correspondence)(Benedetti et al., 1999). Later on, many studies have demonstrated that placebo analgesic effects due to expectation can occur in specific body regions and that this specificity can be reversed by naloxone. This suggests that placebo analgesic effects probably involve a very specific opioid release, rather than a general release of opioids (like an increased opioid concentration in the cerebral fluid)(Finniss, Kaptchuk, Miller, & Benedetti, 2010) which had previously been suggested by Lipman et al. (1990).

One brain imaging study confirming placebo analgesia being mediated by opioids was published by Zubieta et al. (2005) and was later confirmed by Wager, Scott, and Zubieta (2007). Both these studies where made focusing on the opioid receptor MOR using brain imaging techniques such as PET and MRI. Their studies showed an increase in MOR-activity during placebo analgesia (Benedetti, Piedimonte, & Frisaldi, 2018; Wager et al., 2007; Wager & Atlas, 2015). Eippert et al. (2009a) further demonstrated that placebo-induced reductions in pain-related fMRI activity are reversible by naloxone (Benedetti et al., 2018; Eippert et al., 2009a; Peciña, Stohler, & Zubieta, 2013b). Another brain imaging study was made by Scott et al. (2008) using PET in an attempt to investigate the role of expectation in endogenous opioid neurotransmission in placebo analgesia. In this experiment, the participants went through a 20-minutes regulated pain challenge, in the presence and in the absence of a placebo with expected analgesic effect. The results of their study showed that endogenous opioid activity was associated with the expected effectiveness of the placebo treatment, where the stronger expectation was associated with a higher opioid activity (Scott et al., 2008).

As mentioned in a previous chapter, it has been demonstrated that differences in individuals opioids systems seem to be an important factor in the response variability (Aslaksen et al., 2018; Klinger et al., 2017; Vambheim & Flaten, 2017). Aslaksen et al. (2018) made a study with 296 participants investigating in the interaction between the opioid receptor MOR and catechol-O-methyltransferase (COMT). COMT is an enzyme involved in degrading dopamine in placebo analgesia. The results of their study demonstrated that the interaction between the MOR-receptor and COMT was significantly associated with the placebo analgesic response. This points to that genotyping with regard to the MOR-receptor and COMT might predict who responds to placebo analgesic treatment and who does not (Aslaksen et al., 2018).

According to Colloca (2019), the importance of opioid systems for placebo analgesia is not surprising since MOR-receptors are widely distributed in the brain and are critical for the reduction of pain. But, even though many studies have clarified that endogenous opioids have an important role in placebo analgesia, studies suggest that there are other neurotransmitters involved as well (Benedetti et al., 2018; Colagiuri et al., 2015; Colloca, 2019; Gracely et al., 1983). For example, it has been suggested that CCK might have an inhibitory role in placebo analgesic responses (Benedetti, 1996; Colloca et al., 2013).

Neurotransmission and function of cholecystokinin

CCK is a molecule that binds to receptor subtypes; CCK-1 receptors and CCK-2 receptors (Colloca et al., 2013) which are widely distributed in the central nervous system (Wank, 1995). The main biological actions of CCK are among other; regulation of satiation, stimulation of gall bladder contraction, induction of anxiety, and interactions with dopamine in the mesolimbic system (Crawley & Corwin, 1994). CCK is known as an anti-opioid molecule that blocks endogenous opioids. This means that blocking CCK leads to an increase in opioid effects (Price et al., 2008). It has been demonstrated that the biochemical link between the anticipatory anxiety (i.e., negative expectation) and pain increase is represented by the CCK-systems. Anticipatory anxiety is, unlike general anxiety, always connected to thinking about a future event or situation (Colloca et al., 2013). A study by Hebb, Poulin, Roach, Zacharko, and Drolet (2005) demonstrated that there is a close neuroanatomical association between CCK and endogenous opioids. They further propose that it might be a CCK-opioid link in the regulation and the expression of anxiety and other stress-related behaviors (Hebb et al., 2005).

The role of cholecystokinin in placebo analgesia

A study by Benedetti (1996) using experimentally induced ischemic arm pain demonstrated that the CCK antagonist proglumide increased placebo analgesia. The study further demonstrated that the placebo analgesic effect can be elicited in two opposite directions; partially suppressed by naloxone and potentiated by proglumide. Additionally, CCK seems to have an inhibitory role in placebo analgesic responses (Benedetti, 1996; Colloca et al., 2013).

Many studies have demonstrated that nocebo hyperalgesia is mediated by CCK (Benedetti, Amanzio, Casadio, Oliaro, & Maggi, 1997; Büchel et al., 2014; Colloca et al., 2013; Kong et al., 2008; Manchikanti, Giordano, Fellows, & Hirsch, 2011). Nocebo hyperalgesia is a nocebo effect limited to the experience of pain and is defined by IASP as; ” Increased pain from stimuli that normally provokes pain” (International Association for the Study of Pain, 2019). In other words, nocebo hyperalgesia is the opposite of ’placebo analgesia’ (Benedetti, Amanzio, Rosato, & Blanchard, 2011a). This means that an expectation of pain going to be worse can increase the painful experience (Benedetti et al., 2011a; Wager & Atlas, 2015). It has been demonstrated that the subject’s negative expectations about pain increase trigger the activation of CCK which further facilitates pain transmission. Accordingly, CCK antagonists have been found to prevent hyperalgesia (Colloca & Benedetti, 2007).

It has been demonstrated that the placebo analgesic effect elicited by proglumide only occurred in placebo-responders, suggesting that activation of endogenous opioid systems is crucial for the action of proglumide (Benedetti, 1996; Colloca et al., 2013). Benedetti, Amanzio, Vighetti, and Asteggiano (2006) claim that since hyperalgesic nocebo effects and analgesic placebo effects seem to involve the opposite activation of CCK-systems and endogenous opioid-systems, these two probably have a close interaction (Benedetti et al., 2006; Colloca et al., 2013). This suggestion is in line with a study by Benedetti, Amanzio, and Thoen (2011b) proposing both that the balance between CCK-systems and opioid-systems is central in placebo responsiveness and that CCK-2 receptor hyperactivity may be present in placebo non-responders. In other words, a change in the balance between endogenous opioids and CCK might influence placebo analgesia in opposite directions, depending on the activity of these two molecules, so when CCK activity outweighs opioid activity the placebo analgesic response is reduced and vice versa (Benedetti, et al., 2011b).

To sum up, CCK is affecting placebo analgesia by mediating the release of endogenous opioids. Release of CCK results in nocebo hyperalgesia while blockade of CCK results in placebo analgesia. This means that CCK cannot elicit a placebo analgesic effect itself. However, as mentioned earlier, placebo analgesia has been found to be elicited by other mechanisms than

endogenous opioids. Schafer et al. (2018) suggest that while endogenous opioids are underlying expectation-dependent placebo analgesia, expectation-independent placebo analgesia is supported by endogenous cannabinoids.

Neurotransmission and function of endocannabinoids

Endogenous cannabinoids (i.e., endocannabinoids) are molecules that bind to the receptors; CB1 and CB2 (Iversen, 2003; Woodhams, Sagar, Burston, & Chapman, 2015). CB1-receptors are found in high quantities in the frontal regions of the cerebral cortex, in the hippocampus, in the cerebellum, and in the basal ganglia (Peciña et al., 2014), while CB2-receptors are expressed in peripheral tissues, such as in the immune system (Iversen, 2003). As mentioned earlier, basal ganglia have also shown to be involved in placebo analgesic effects (Colagiuri et al., 2015). The endocannabinoids have a crucial role for many biological functions such as the maintenance of homeostasis and the immune regulation (Colloca et al., 2013). It is also known to be one of the key endogenous systems regulating pain sensation (Woodhams et al., 2015).

The role of endocannabinoids in placebo analgesia

Compared to endogenous opioids, little is known about the involvement of endocannabinoids in placebo analgesia (Benedetti, 2013). However, some studies have demonstrated that endocannabinoids play a crucial role in NSAID-induced placebo effects (Benedetti et al., 2011a; Colloca et al., 2013). For example, Benedetti et al. (2011a) made an experiment where they induced either opioid or non-opioid placebo analgesic responses and evaluated the effects of an endocannabinoid antagonist called rimonabant. The results of their study demonstrated that rimonabant had no effect on opioid-induced placebo analgesia, but completely blocked placebo analgesia following non-opioid preconditioning with NSAIDs. These results suggest that a placebo analgesic response elicited by conditioning with an NSAID is mediated by CB1-cannabinoid receptors (Benedetti et al., 2011a; Colloca, 2019; Colloca et al., 2013).

Schafer et al. (2018) suggest that placebo analgesic effects that are conditioned with subliminal cues depend on the release of endocannabinoids rather than on endogenous opioids. And further that the placebo analgesic effects that are totally independent of expectation are also most often elicited by endocannabinoids. In other words, when conditioned analgesia is independent if expectations, the placebo analgesic effect is mediated by endocannabinoids (Schafer et al., 2018). This claim goes in line with a study by Peciña, et al. (2014) showing that the cannabinoid system is

involved in the formation of some conditioned placebo analgesic effect (Benedetti, 2014; Peciña, et al., 2014).

In conclusion, there are not many studies made on the role of endocannabinoids in placebo analgesia, compared to the role of endogenous opioids. Still, the hypothesis that endocannabinoids support conditioned placebo analgesia and are independent of expectations (Schafer et al., 2018) is supported by a few studies. It seems like there are no studies that support a role for endocannabinoids in any placebo analgesic effect when it is elicited by expectations.

Discussion

This thesis aims to introduce the current state of research regarding the neuroscience of placebo analgesia and specifically to present research findings regarding the neurotransmission. When looking at the gathered results from all the studies presented in this thesis, some patterns begin to emerge. In this section, these patterns will be discussed. The discussion will be followed by limitations of placebo analgesic research and future directions regarding gaps in the scientific literature of placebo analgesia. The section will end up with conclusions about what has been said.

Neural correlates of placebo analgesia

Many cortical brain areas have been found to be correlated to placebo analgesia (Peciña & Zubieta, 2018; Petrovic et al., 2002; Wager et al., 2004). First of all, a variety of cortical pain-relevant brain areas including basal ganglia, amygdala, the S1, the S2 (Colagiuri et al., 2015), ACC, thalamus, and insula have shown decreased activation during placebo analgesia (Wager et al., 2004). Besides the cortical pain-relevant brain areas, activation of brain areas in the pain adjusting areas has been found including PAG, hypothalamus, and the RVM (Eippert et al., 2009a). Further, a connection between placebo analgesia and activation of the NAC and the VS has been found (Frisaldi et al., 2018). Studies have also demonstrated a covariation between the rostral ACC and the brainstem (Colagiuri et al., 2015). Additionally, even though it has been suggested that placebo analgesia can occur without higher order cognitions like PFC (Jensen, 2018), it has been found that inactivation of the PFC disturbs the placebo analgesic effect (Benedetti & Frisaldi, 2014).

The role of endogenous opioids in placebo analgesia

It has been clarified that placebo analgesia can be elicited by endogenous opioids (Benedetti, 1996; Colloca, 2019; Eippert et al., 2009a; Zubieta et al., 2005). It has even been proposed that variations in the individual opioid systems can be the reason why people respond so differently to

placebo (Vambheim & Flaten, 2017). For example, it seems as if genotyping with regard to the opioid-receptor MOR and COMT might predict who responds to placebo analgesic treatment (Aslaksen et al., 2018). However, research has also suggested that placebo analgesia can occur without the involvement of endogenous opioids (Benedetti, 1996; Benedetti et al., 2018; Colagiuri et al., 2015; Colloca, 2019; Gracely et al., 1983; Vase et al., 2005).

As Fields and Levine (1984) claim, different situations might affect endogenous opioid systems in different ways. Endogenous opioids have been shown to be released during situations providing an expectation of pain relief (Amanzio & Benedetti, 1999; Benedetti & Amanzio, 1997; Colloca et al., 2013; Schafer et al., 2018; Scott et al., 2008). It has further been demonstrated that endogenous opioid activity is associated with the expected effectiveness of the placebo, where a high expectation of pain relief is associated with greater opioid activity than low expectation (Scott et al., 2008). Placebo analgesia induced by cues was also shown to appear in a ’dose’-dependent way, mediated by the levels of expectancy for pain relief. Further, placebo activated endogenous opioids due to expectation also seem to have a point-for-point correspondence, rather than a general release of opioids (like an increased opioid concentration in the cerebral fluid)(Benedetti et al., 1999; Finniss et al., 2010; Price et al., 2008).

Expectations are not the only way to elicit a placebo analgesic effect. A different way to elicit a placebo analgesic response is through unconscious processes such as conditioning (Amanzio & Benedetti, 1999; Price et al., 2008). If conditioned with an opioid drug a placebo treatment can release opioids without expectation of pain release, leading to a placebo analgesic effect. However, if conditioned with a non-opioid drug, it cannot be blocked by naloxone, leading to the proposal that conditioned placebo effects works via specific biological systems activated by the pharmacological agent (Benedetti & Amanzio, 1997; Amanzio & Benedetti, 1999). This means that other substances than endogenous opioids are involved in the conditioned placebo analgesic effect as well (Amanzio & Benedetti, 1999; Benedetti, 1996; Gracely et al., 1983; Vase et al., 2005).

The role of CCK in placebo analgesia

Studies point to that the balance between CCK-systems and opioid-systems is central in placebo responsiveness so that a change in the balance between endogenous opioids and CCK might influence placebo analgesia in opposite directions (Benedetti, et al., 2011b). CCK-blockers has shown to increase placebo analgesia and to enhance analgesia induced by procedures that activate endogenous opioids. It has therefore been suggested that CCK has an inhibitory effect on placebo analgesia by affecting the modulation of endogenous opioids (Benedetti, 1996; Benedetti et

al., 2006; Colloca et al., 2013). In other words, CCK itself does not seem to elicit placebo analgesia, but it can modulate the placebo analgesic effect by affecting the activation of endogenous opioids. Additionally, it has been suggested that CCK-2 receptor hyperactivity might be present in placebo non-responders (Benedetti, et al., 2011b).

The role of endocannabinoids in placebo analgesia

It has been shown that endocannabinoids are involved in the formation of some placebo analgesic effects (Benedetti, 2014; Peciña, et al., 2014). Peciña, et al. (2014) presented that the major degrading enzyme of endocannabinoids affect the analgesic responses to placebos, which provides evidence that the cannabinoid system is involved in the formation of the placebo analgesic effect (Benedetti, 2014; Peciña, et al., 2014). As demonstrated by Benedetti et al. (2011a) placebo analgesic responses elicited by a conditioning process of NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are mediated by CB1 cannabinoid receptors (Benedetti et al., 2011a; Colloca et al., 2013). Some studies have also suggested that the placebo analgesic effects mediated by endocannabinoids, contrary to endogenous opioids, are independent of expectation (Schafer et al., 2018). According to the studies used in this review, it does not seem like there are any studies supporting the role of endocannabinoids in any placebo analgesic effects if it is elicited by expectation.

Limitations in placebo measurements

Demonstrations of placebo analgesic effects rely generally on self-reports. The reason for that is mainly that self-reports are the only measure for finding out the subjective experience of pain at this moment. Just like most measures, self-reports has its disadvantages. For example, combined information about prior experiences and prior expectations might affect the participant's reports (Wager & Atlas, 2015). Overestimation might happen because of social desirability or interviewer bias. Social desirability bias happens when an individual reports socially desirable behavior when he or she is being asked. Interviewer bias is nearly the same thing, except that the individual tries to please the interviewer with the response he or she thinks the interviewer would like to hear. This bias is often greatest when the interviewer is, for example, a leader in the field or a respected colleague (Adams, Soumerai, Lomas, & Ross-Degnan, 1999). Certainly, these biases are always a risk while measuring subjective experiences (Wager & Atlas, 2015).

Measuring placebo analgesia is further complicated by the fact that placebo and pain involve multiple functions such as affective, cognitive and social factors, meaning that the resultant pain is

not necessarily linearly related to the nociceptive input (Büchel et al., 2014; Tracey & Mantyh, 2007; Wager & Atlas, 2015). Many of the mentioned brain regions generating pain, and later demonstrates the strongest response to the placebo effects, are also involved in numerous other affective and cognitive processes that are independent of pain. Adding all these aspects together makes it clear that it is an extremely difficult task to try to figure out what parts of the brain that truly affects the different types of placebo treatments (Wager & Atlas, 2015).

Ethical limitations

Even if the purpose of a placebo analgesic treatment is to be beneficial, and most of the time leads to pain relief, it has given rise to some ethical complications (Elander, 1991).

To be able to morally discuss placebo treatments it might be good to look at some moral theories like deontology and consequentialism. Deontology is the ethical view that what is morally right are based on whether the action itself is right or wrong which in turn is determined by a series of rules (e.g., the ten commandments in the Bible). In this case, not telling the truth is considered as doing wrong and therefore a clinician would be doing wrong by ’lying’ while giving a placebo treatment to a patient (Elander, 1991). To give a placebo treatment claiming that it is something else violates informed consent and threatens the trust which is fundamental in clinical practices (Finniss et al., 2010).

If we are looking at different ways of making placebo studies in clinical settings like open-hidden experiments, numerous studies have demonstrated that open treatments are significantly more effective in reducing pain than hidden treatments (Amanzio et al., 2001; Colloca et al., 2004; Finniss et al., 2010). But since an open placebo treatment requires suggestions of a beneficial outcome the deontological view would still claim that this is not a very ethical way. Even if it is still not know how it works, there are studies demonstrating that placebos sometimes work even if the patient knows that he or she is receiving placebo (i.e., open-labeled studies; Carvalho et al., 2016; Schaefer et al., 2018). Open-labeled studies would, of course, enable for a more ethical way of using placebos as treatments according to the deontological view. On the other hand, if you are having a consequentialistic perspective on placebo, open treatments would be the most ethical way despite the deception (Elander, 1991).

Consequentialism says that actions are right or wrong depending on their consequences. Looking at the placebo treatment from this point of view, placebo treatments are appropriate as long as no negative consequences arise (Elander, 1991). This view goes in line with the claims of Evers et al. (2018) arguing that open treatments would be more morally correct than hidden treatments

despite the untruthful suggestions since these are known to alleviate larger placebo effects (Evers et al., 2018).

Having these two moral theories in mind, one could also ask if the underlying intention of placebo treatment should be counted into the equation? Is it more ethical if the intention of the clinician is to give a placebo treatment to elicit a beneficial clinical outcome, rather than to make a demanding patient quiet? Further, ignoring the placebo effect could also be considered unethical since we know we could enhance the placebo effect to reduce pain and enhance the clinical outcome. According to Finniss et al. (2010), it is both ethically adequate and clinically relevant to provide a clinical meeting aiming to reduce anxiety and develop positive expectations to try to induce placebo effects and reduce the risk of inducing a nocebo effect (Finniss et al., 2010). Repeated, conscious efforts to try to identify and make use of features of the clinical meeting to improve placebo effects would not require untruthful suggestions. This would, therefore, represent an ethical way of applying the understanding of placebo mechanisms to enhance clinical outcomes (Finniss et al., 2010).

Placebo and nocebo effects are still very under-recognized in the clinical practices today (Chavarria et al., 2017; Finniss et al., 2010) because of both ethical and practical restrictions (Evers et al., 2018). But even though prescriptions of inert pills or saline injections are rare, it is claimed that clinicians quite often prescribe active treatments with the main intention of eliciting a placebo effect or to satisfy the wishes of their patients (Finniss et al., 2010). Since beneficial placebo effects and harmful nocebo effects occur continuously in the clinical context (even if a clinician is not purposely prescribing placebo pills), it is crucial to understand the underlying brain mechanisms to be able to fully understand all kinds of treatments (Chavarria et al., 2017; Kaptchuk et al., 2008; Kelley et al., 2009; Peciña & Zubieta, 2018; Price et al., 2008).

Looking at societal implications, clarifying how to elicit as large placebo response as possible and as little nocebo response as possible could drastically improve the medical outcomes. This can further lead to great economic benefits since fewer drugs would be needed to be prescribed. This money could instead be used to make more pharmaceutical research and to improve medical care in developing countries. In other words, getting a better understanding of placebo and find ways to apply this knowledge in the clinical context would powerfully develop the whole medical society.

Future directions

Even if the placebo analgesic research has grown exponentially during the last few years, there are still many questions needed to be answered. It is stated that endogenous opioids have a role in placebo analgesia while modulated both by expectations and by conditioning with opioid drugs. But are endogenous opioids always involved in placebo analgesia while modulated by expectations, or are there any exceptions? Further, Benedetti, et al. (2011b) point to that the balance between endogenous opioid-systems and CCK-systems is central in placebo responsiveness. If this is true, the question of how to obtain the balance between these two systems remains (Klinger et al., 2017; Vambheim & Flaten, 2017).

In discussing the role of endocannabinoids, it has been demonstrated that this neurotransmitter can elicit placebo analgesic effects if a conditioning process with NSAIDs is made. However, can endocannabinoids only cause placebo analgesia while it is conditioned with NSAIDs or are there any other situations where this neurotransmitter is creating the placebo analgesic effect?

Studies have demonstrated that the longer the conditioning period the larger the placebo analgesic effect (Colagiuri et al., 2015) and further that it is possible to make non-responders become placebo responders (independent of expectation) if preconditioned with analgesic treatment (Benedetti & Frisaldi, 2014; Schafer et al., 2018). Still, it is not clarified to what extent this is possible. Does this mean that you could teach all patients to respond to placebo? Finding out how to maximize placebo effects is truly an important question for future research since it could powerfully improve a variety of medical outcomes.

At last, despite the findings of the prefrontal brain regions seeming to be involved in the eliciting of the placebo effect (Benedetti & Frisaldi, 2014; Wager et al., 2004), there has been suggested that placebo effects can occur even without higher-order cognitions (Jensen, 2018). If this is true, maybe it would be possible to elicit placebo analgesic effects by teaching patients to subconsciously respond to placebos? The role of neurotransmitters and consciousness in placebo analgesia remains to be fully clarified.

Conclusions

To sum up, the brain areas showing to be involved in the placebo analgesic effects are; the brainstem, basal ganglia, amygdala, hypothalamus, thalamus, insula, PAG, ACC, RVM, NAC, VS, and the PFC. While looking at the neurotransmission, endogenous opioids and endocannabinoids have demonstrated to subserve various aspects of placebo analgesia. The research literature suggests that endogenous opioids are involved in the placebo analgesic effect when elicited by

expectation or conditioned by an opioid drug, while endocannabinoids seem to be involved in placebo analgesia while it occurs due conditioning with non-opioid drugs. CCK itself does not elicit placebo analgesia but modulates the activation of endogenous opioids. However, there are still many gaps in the scientific research regarding the neural correlates and the neurotransmission of placebo analgesia. For example, it is not clarified if endogenous opioids always are involved in placebo analgesia while modulated by expectations or if endocannabinoids only cause placebo analgesia while it is conditioned with NSAIDs. Conducting studies aiming to answer these questions would be a great starting point for helping placebo analgesic research to reach the next level. Getting a better understanding of placebo and find ways to apply this knowledge in the clinical context could further develop the whole medical society.

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