

## REVIEW

## DIFFERENT CONTEXTS, DIFFERENT PAINS, DIFFERENT EXPERIENCES

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**Abstract**—Pain is an ambiguous perception: the same pain stimulation can be perceived differently in different contexts, producing different experiences, ranging from mild to unbearable pain. It can be even experienced as a rewarding sensation within the appropriate context. Overall, placebo and nocebo effects appear to be very good models to understand how the psychosocial context modulates the experience of pain. In this review, we examine the effects of different contexts on pain, with a specific focus on the neurobiological mechanisms. Positive and rewarding contexts inform the patients that an effective treatment is being delivered and are capable of producing pain relief through the activation of specific systems such as opioids, cannabinoids and dopamine. Conversely, a negative context can produce pain exacerbation and clinical worsening through the modulation of different systems, such as the activation of cholecystokinin and the deactivation of opioids and dopamine. In addition, when a therapy is delivered unbeknownst to the patient, its effects are reduced. A better understanding of the neurobiological underpinnings of the context–pain interaction is a challenge both for future pain research and for good clinical practice.

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**Key words:** context, placebo, nocebo, reward, analgesia.

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**Abbreviations:** CCK, cholecystokinin; FAAH, fatty acid amide hydrolase; MOR,  $\mu$  opioid receptor; NSAIDs, non-steroid anti-inflammatory drugs.

## INTRODUCTION

Pain is a subjective sensation that cannot be attributed only to the incoming nociceptive information. Indeed, pain is modulated by a variety of cognitive and emotional factors as well as by a number of sensory inputs (Wiech et al., 2008; Bushnell et al., 2013). For example, shifting the attentional focus can reduce the strength of a painful experience, whereas full attention on the incoming painful stimulus can worsen its perception (Villemure and Bushnell, 2002). The role of emotions on pain perception has been widely investigated as well. For example mood, stress, anxiety and more in general positive or negative emotions can exert a potent modulatory influence on pain, causing either a reduction or exacerbation of the global experience of pain (Jennings et al., 2014), along with neural changes in different regions of the brain (Villemure and Bushnell, 2002; Wiech and Tracey, 2009; Yang and Symonds, 2012; Rütgen et al., 2015). In addition, sensory stimuli, such as pleasant and unpleasant odors, may lead to different degrees of pain (Marchand and Arsenault, 2002; Villemure and Bushnell, 2002, 2009). In general, all cognitive, emotional and sensory processes that affect pain arise from the context surrounding the painful experience. For this reason, the study of the context offers additional therapeutic opportunities for pain management (Bushnell et al., 2013) and, more in general, can be fundamental to increase the efficacy of different medical treatments. Indeed, evidence-based medicine has traditionally focused on the effect of pharmacological agents, underestimating those psychological and environmental factors that significantly contribute to therapeutic effectiveness.

According to Balint (1955), the context surrounding the patient and the therapy represents the “atmosphere around the treatment”, including both external and internal elements (Wager and Atlas, 2015). The external elements are the physical properties of the medication, such as color, shape, taste and smell, the physical aspect of the hospital room, the sight of healthcare professionals and medical instruments, and the interaction with the doctor. The internal elements are the patient’s characteristics, such as personal beliefs, hopes and expectations about the therapy outcome, memories about previous medical

treatments, as well as different psychological traits and genetic variables.

In the last decade, the effect of the context on the response to a medical treatment, be it pharmacological or not, has been extensively investigated using placebo and nocebo effects as models (Enck et al., 2008; Tracey, 2010; Carlino et al., 2011, 2012; Arnold et al., 2014; Benedetti, 2014). In the present review we examine how the exposure to different contexts affects pain perception and the therapeutic outcome through the activation of specific neurobiological mechanisms. On the one hand, a positive and rewarding context is capable of producing pain relief and, in general, clinical improvement. On the other hand, a negative context is capable of producing pain exacerbation and clinical worsening (Fig. 1).

### CONTEXTS INDUCING POSITIVE EXPECTATIONS

Over the past few years, several studies have investigated the effect of the positive psychosocial context on the therapeutic outcome, using the placebo effect as a model. In fact, the study of the placebo effect is basically the study of the psychosocial context surrounding the patient and the therapy (Colloca and Benedetti, 2005; Benedetti, 2014). The positive psychosocial context includes several sensory and social stimuli, such as the hospital environment, the medical equipment and the words of the doctor. All these aspects “inform” the patient that a treatment is being delivered. Beside the external factors, also internal variables, such as individual psychological and personality traits, motivation, optimism and anxiety play a key role (Price and Barrell, 2000; Price et al., 2001, 2008; Geers et al., 2005, 2007). The effect of the context has been studied mainly in the field of pain using healthy volunteers exposed to different painful stimulations, such as ischemic pain (Benedetti et al., 2003b), electric stimulation (Colloca et al., 2008a, 2010) and laser stimuli (Colloca et al., 2008b; Carlino et al., 2015), or patients suffering from acute or chronic pain (Petersen et al., 2012).

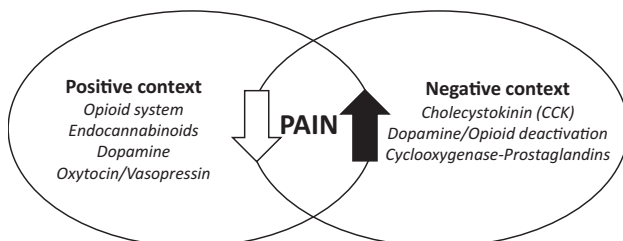
At least two psychological mechanisms have been found to relate a positive context to the therapeutic outcome. The first is a conscious mechanism that involves positive expectations (Kirsch, 1985), whereby

positive contextual elements forecasting benefit may either reduce anxiety or activate reward mechanisms (Benedetti, 2013, 2014). The second is an unconscious mechanism that involves classical conditioning: after a repeated association between external cues, e.g. color, shape and taste of an analgesic pill, and the active principle inside the pill, e.g. morphine, a conditioned placebo response may occur, whereby any pill with the same physical features will produce the same effect as morphine, even without the active principle (Benedetti, 2013, 2014).

Learning mechanisms, ranging from behavioral conditioning to social learning, and conscious mechanisms involving expectations are not necessarily mutually exclusive, since learning can lead to the reinforcement of expectations or can even create de novo expectations. For this reason, an important issue is to understand how these mechanisms interact with each other. On the one hand, different studies have found that expectations alone produce analgesic responses that are less robust compared with those induced by a preconditioning procedure (Colloca and Benedetti, 2006, 2009). On the other hand, expectations induced by verbal suggestions have been found to reverse the effects of a preconditioning procedure (Montgomery and Kirsch, 1997; Benedetti et al., 2003b) and to play a key role in conditioned analgesic responses (Carlino et al., 2015). Therefore, learning and expectations seem to cooperate in a variety of situations.

Both context-induced positive expectations and context-induced conditioning produce a cascade of neurobiological changes, and the investigation of these changes has recently received a great deal of attention. Different studies have so far documented the activation of two different neurochemical systems: the opioid and cannabinoid systems (Benedetti et al., 2011a). The activation of these systems is tightly related to the pharmacological context to which the patient had been previously exposed: if a placebo is administered after a pharmacological pre-exposure to  $\mu$  opioid receptor (MOR) agonists, the placebo response is mediated by the MOR receptors, whereas if the placebo is given after a pharmacological pre-exposure to non-steroid anti-inflammatory drugs (NSAIDs), which are known to activate the CB1 cannabinoid receptors (Escobar et al., 2012), the placebo response is mediated by the CB1 receptors. Thus, a placebo administered within a pharmacological context of repeated MOR activation triggers different mechanisms compared to a context of repeated CB1 activation.

The placebo-activated opioid system has been extensively investigated in the last years using pharmacological and neuroanatomical approaches. From a pharmacological point of view, some types of placebo analgesic responses, e.g. those obtained after a pre-exposure to opioid drugs, are blocked by naloxone (Amanzio and Benedetti, 1999; Guo et al., 2010; Zhang et al., 2013) and cholecystokinin (CCK) has been found to reduce placebo analgesia due to its anti-opioid action (Benedetti et al., 1995, 2011b). Moreover, this analgesic response can be boosted by proglumide, on the basis of its anti-CCK action (Benedetti et al., 1995; Benedetti,



**Fig. 1.** The same pain stimulation can be perceived differently in different contexts. A positive context is capable of producing pain relief, along with the activation of specific systems (e.g. opioid, cannabinoid and dopaminergic systems) and the involvement of prosocial hormones (e.g. oxytocin and vasopressin). Conversely, a negative context can produce pain exacerbation, along with the modulation of different systems, e.g. activation of the CCK system and deactivation of opioid and dopaminergic systems, as well as the enhancement of the cyclooxygenase-prostaglandins pathway.

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