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Review article

# Route of placebo administration: Robust placebo effects in laboratory and clinical settings

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ABSTRACT

Recent advances in laboratory and clinical research have greatly enhanced our understanding of placebo effects. However, little progress has been made in translational research that can well integrate these findings. This article examines pivotal role of placebo administration in subsequent placebo responses, providing a unified framework that accounts for robust placebo effects in both laboratory and clinical settings.

## 1. Introduction

Sensory experience of pain is heavily shaped by the cognitive and emotional context in which pain presents itself (Price, 2000). Nowhere can this be better demonstrated than in analgesic effects induced by a placebo treatment (an inert substance or a sham procedure) (Colloca and Benedetti, 2005; Finniss et al., 2010; Geuter et al., 2017; Hoffman et al., 2005; Price et al., 2008; Tracey, 2010). Although many mechanisms might be involved in psychological construction of therapeutic effects following a placebo treatment, a sound body of evidence supports the view that a placebo treatment acts by means of inducing an expectation of beneficial responses (Kirsch, 1985; Kirsch et al., 2014; Montgomery and Kirsch, 1997; Pollo et al., 2001; Price et al., 1999; Wager and Atlas, 2015). In attempt to understand mechanisms of placebo effects, a basic fact needs to be carefully considered that a placebo treatment produces therapeutic effects in direct response to its administration, which possibly suggests that placebo administration *itself* should have a potential role in subsequent placebo responses. This article examines how route of placebo administration (i.e., the specific nature of a placebo treatment and the way in which it is delivered) can influence the recipient's expectations regarding placebo and hence placebo responsiveness, providing a unified model for interpreting robust placebo effects in both laboratory and clinical settings.

## 2. Robust placebo analgesic effects in laboratory settings

For better investigating neural and psychological mechanisms underlying effects of a placebo treatment on pain, replicable and robust placebo effects need to be induced. To do this, the vast majority of experimental studies have used a well-established placebo analgesia paradigm which includes include two stages. In the pretest learning stage, verbal suggestions with or without conditioning (i.e., placebo treatment paired with painful stimulation of surreptitiously lowered intensity) are used to convince subjects of the effectiveness of a placebo

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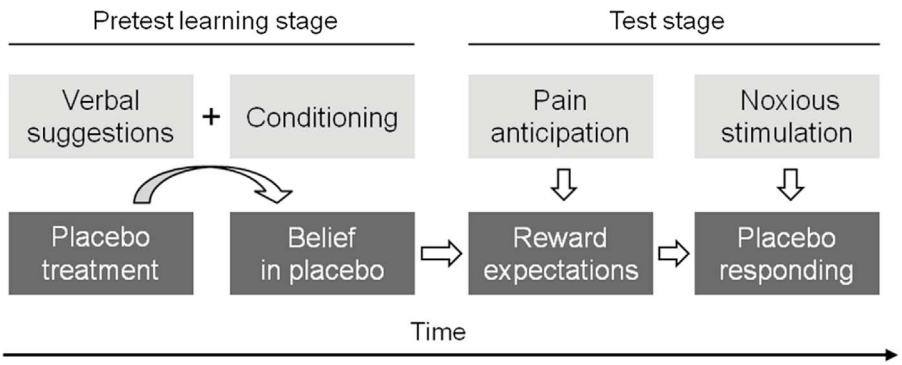


**Fig. 1.** Respective contributions of learning and pain anticipation to, and their relationship in, placebo responses following the application of a placebo treatment in the context of an unavoidable pain.

treatment. In the following test stage, this placebo treatment is applied in the context of an unavoidable pain—that is, the placebo treatment is administered by method of imposing an unavoidable pain challenge on the subject—whereby learning-based placebo analgesic effects are induced and evaluated immediately after a prestimulus anticipation period during which subjects anticipate an upcoming painful stimulation with the treatment in place. To date, much research attention has been given to the contribution of learning to expectation-mediated placebo analgesic effects (Amanzio and Benedetti, 1999; Benedetti et al., 2011; Colloca and Benedetti, 2006, 2009; Colloca and Miller, 2011; Colloca et al., 2010; Meissner et al., 2011; Schafer et al., 2015; Voudouris et al., 1989, 1990; Williams-Stewart and Podd, 2004); however, the critical importance of pain anticipation itself, which characterizes the route of administration of a placebo treatment applied in the context of unavoidable pain, for these effects has been overlooked.

### 2.1. Pivotal role of pain anticipation in subsequent placebo responses

When it is not possible to avoid an impending aversive event such as pain, cognitive strategies need to be used for dealing with the situation (Folkman and Lazarus 1998). There is evidence showing that anticipatory coping itself can change subsequent perception of pain (Petrovic and Ingvar, 2002; Thompson, 1981; Weisenberg et al., 1996). A placebo treatment, when it is applied in the context of an unavoidable pain, might affect pain perception during actual noxious stimulation by altering the subject's coping strategy during the anticipation period prior to stimulation. In support of this view, neuroimaging studies (Eippert et al., 2009a; Lui et al., 2010; Wager et al., 2004, 2011; Watson et al., 2009) showed that analgesic effects following pain anticipation in the presence of a placebo treatment were positively associated with placebo-increased anticipatory activity in the prefrontal cortex (PFC), which is thought to be an area centrally involved in maintaining and updating internal representations of goals and expectations (Miller and Cohen, 2001), indicating that these effects are attributable to placebo-related therapeutic expectations which are formed and maintained during the anticipation period preceding noxious stimulation. The determinant role of placebo-induced cognitive and emotional processes during pain anticipation in subsequent placebo responses is further corroborated by the finding that when the normal function of the dorsolateral PFC was transiently disrupted by repetitive transcranial magnetic stimulation (rTMS) during anticipation of pain, placebo analgesic effects were significantly suppressed (Krummenacher et al., 2010).

The subject has a unique experience when being exposed to a placebo treatment in anticipation of an upcoming pain. On the one hand, a painful stimulus is fast-approaching; on the other hand, however, the stimulation might be reduced or avoided, given the placebo treatment which the pretest learning has conceivably established to have an analgesic property. Since pain reduction is "rewarding", thus the placebo treatment has appetitive motivational power while an upcoming stimulus is being anticipated. Once pain-signaling warning cue has been given, the subject is immediately motivated to obtain the rewarding therapeutic benefits the placebo treatment is suggested to possess. In a word, when a placebo treatment is applied in the context of an unavoidable pain, it elicits a reward expectation (i.e., a motivation to obtain therapeutic reward or a desire for avoiding painful stimulation) during pain anticipation, which directly leads to subsequent placebo responses.

While stressing the role of pain anticipation as a motivational driver in the generation of reward expectations and hence subsequent placebo responding, what we should bear in mind is that the subject's reward expectations induced by a placebo treatment when anticipating an upcoming pain source from nowhere but his or her belief that the treatment is an effective pain killer. Without the belief in the effectiveness of placebo treatment, the subject has nothing to expect, thus placebo effects does not occur. Obviously, the subject's belief in a placebo treatment is acquired via the pretest learning procedures including verbal suggestions (i.e., instructional learning) which provide the initial information about the effectiveness of a placebo treatment and conditioning which allows subjects to personally experience the therapeutic effect the treatment is suggested to have. Importantly, the learning-based belief in placebo does not automatically and directly evoke reward expectations in the subject; instead, it is the pain-signaling warning cue that triggers the transition from belief in placebo to an expectation of therapeutic reward, and this process lasts throughout the anticipation period between the onset of warning cue and actual noxious stimulation. In short, learning has a fundamental role in expectation-mediated therapeutic effects following a placebo treatment for it makes subjects believe that the placebo treatment is potentially effective (i.e., learning makes the placebo treatment meaningful). However, learning does not directly contribute to these effects; it has to be through pain anticipation, which represents the process of placebo administration, that learning-based belief in placebo can be translated into a reward expectation/anticipation which in turn directly activates placebo responses (Fig. 1). This idea strongly points to the suggestion that pain anticipation should have a shaping role in subsequent placebo responses.

In fact, the mediating role of reward expectation generated during pain anticipation in subsequent placebo responding is directly supported by neuroimaging studies reporting that placebo-related activity in dopaminergic brain reward regions during pain anticipation reliably tracks following placebo analgesia. Geuter et al. (2013) investigated neural underpinnings of placebo analgesia by comparing learning-based analgesic responses to a strong and a weak placebo. Both placebos induced significant pain reduction, and the strong placebo was associated with larger analgesic effects. Importantly, activation in the ventral striatum, which is part of the mesolimbic reward system, was identified during anticipation of pain when comparing placebo to control condition, and the striatum response was higher with the strong placebo than the weak one. More compelling findings come from a study by Scott et al. (2007) which examined the correlation between