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Research report

Haloperidol blocks dorsal striatum activity but not analgesia in a placebo paradigm

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ABSTRACT

Although placebo analgesia has been associated with an engagement of the endogenous opioid system there is growing evidence from neuropharmacological studies for an involvement of additional neurotransmitter systems. An increased dopaminergic neurotransmission in the ventral basal ganglia that has been found during placebo analgesia suggests a role for the dopaminergic system (Scott et al., 2007). It is, however, unclear whether striatal dopaminergic activity is causally involved in this type of analgesia. This study aimed at exploring the functional role of the dopaminergic system in placebo analgesia. To this end, we investigated the effect of the dopamine D2/D3 receptor antagonist haloperidol on behavioral and neural measures of placebo analgesia using functional magnetic resonance imaging (fMRI) in healthy volunteers. We found that 2 mg haloperidol p.o. significantly reduced the correlation between dorsal striatum activity and the individual placebo response, but had no significant effect on placebo analgesia at the behavioral or neural level, as indexed by activity in sensory or pain-modulatory brain regions.

Our study therefore suggests that dopaminergic neurotransmission might not be causally involved in placebo analgesia but is related to phenomena associated with placebo analgesia such as reward processing and learning.

1. Introduction

Placebo analgesia represents a prime example of endogenous pain modulation and impressively demonstrates our ability to inhibit ascending nociceptive information under certain conditions. Evidence from neuroimaging studies indicates that placebo analgesia involves a top-down activation of endogenous analgesic mechanisms via the descending pain-modulatory system at all levels of the central nervous system, including the spinal cord (Bingel, Lorenz, Schoell, Weiller, & Buchel, 2006; Eippert et al., 2009; Petrovic, 2005; Wager et al.,

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Table 1 – Participants demographics and questionnaire results.

	Haloperidol	Saline		
N	21	17	38	
Age	24.2 ± 1.3	23.5 ± 1.4	23.7 ± 1.0	
Gender (women)	9	7	16	
Center for Epidemiological Studies Depression Scale	11.6 ± 0.59	12.07 ± 1.15	$t(36) = -.386$	n.s.
State–Trait Anxiety Inventory				
State	43.8 ± 1.2	45.95 ± 2.43	$t(36) = -.828$	n.s.
Trait	37.4 ± 1.86	35.2 ± 2.5	$t(36) = .721$	n.s.
Crowne–Marlowe Social Desirability Scale	11.85 ± 0.87	11.87 ± 1.17	$t(36) = -.012$	n.s.

2004). Activity in this pathway is complemented by intracortical mechanisms, predominantly involving limbic and paralimbic regions (Wager, Atlas, Leotti, & Rilling, 2011).

Both Positron emission tomography (PET) studies using μ-opioid sensitive tracers (Scott et al., 2008; Wager, Scott, & Zubieta, 2007; Zubieta et al., 2005) and pharmacological studies using the opioid antagonist naloxone (Amanzio & Benedetti, 1999; Eippert et al., 2009; Grevert, Albert, & Goldstein, 1983; Levine & Gordon, 1984; Levine, Gordon, & Fields, 1978) have shown that the endogenous opioid system is an important mediator of placebo analgesia. However, neuropharmacological studies also suggest an involvement of additional, non-opioidergic components of placebo analgesia (Amanzio & Benedetti, 1999). Functional molecular imaging investigating changes in the binding potential of carbon 11 [^{11}C]-labeled raclopride has shown an increased dopaminergic neurotransmission in the nucleus accumbens (NAc), putamen and caudate that correlated with the individual placebo-analgesic response (Scott et al., 2007). Furthermore, Schweinhardt et al. reported a close positive relationship between gray matter density in the ventral striatum and the magnitude of placebo analgesia as well as dopamine-related personality traits using voxel-based morphometry (Schweinhardt, Seminowicz, Jaeger, Duncan, & Bushnell, 2009). These findings suggest a potentially relevant role of the dopaminergic system and specifically the striatum in placebo analgesia. It is, however, unclear whether striatal dopaminergic activity is causally involved in the generation of this type of analgesia.

To explore the role of the dopaminergic system in placebo analgesia, we performed pharmacological functional magnetic resonance imaging (fMRI) (Honey & Bullmore, 2004; Leslie & James, 2000; Schweinhardt et al., 2009) using a classical placebo heat pain paradigm in healthy volunteers who were randomly assigned to either receive the D2/D3-antagonist haloperidol or an inert substance in a double-blind design. We used an established placebo analgesia paradigm that comprised an initial expectation manipulation (conditioning) phase and a later test phase.

2. Material and methods

2.1. Subjects

50 healthy volunteers (mean age: 26.56 years; range: 22–34; 23 females) participated in this study. All subjects had heat pain thresholds in a normal range at the site of stimulation and had no known history of neurological or psychiatric diseases, including recurrent or chronic pain. The study was approved by the local Ethics committee of the Medical Board in Hamburg, Germany and all experimental procedures conformed to the Declaration of Helsinki. All participants gave written informed consent to the experimental procedures and were free to withdraw from the study at any time. Please note that the participants were partially decepted to the nature of the study (i.e., placebo manipulation).

Participants were randomly assigned to one of two groups. The experimental group received the dopamine antagonist haloperidol (*haloperidol group*) while the control group received saline (*saline group*), see Section 2.4 for details.

Twelve participants did not complete the study or were excluded after scanning due to the following reasons: technical problems with the thermal stimulation ($N = 3$), lack of compliance during or failure of temperature calibration ($N = 3$), excessive movement during the scanning session [$N = 2$; >10 mm initial misalignment (summed across x/y/z dimensions) (Ardekani, Bachman, & Helpern, 2001)] and incidental findings in their anatomical scans (large cysts $N = 4$ that impaired an adequate preprocessing of the images). Data from the remaining 38 participants (21 in the haloperidol group, 17 in the saline group) were included in the final behavioral and neuroimaging analyses.

The groups did not differ significantly with regard to age, gender distribution, weight (mean weight 75 kg), psychological scores (depression, anxiety, social desirability), or pain thresholds. For participants' characteristics see Table 1.

2.2. Experimental paradigm

We used a 2 × 2 mixed-factorial design with the between-subject factor group (*haloperidol vs saline*) and the within-subject factor condition (*control vs placebo*) in a well-established placebo heat pain paradigm involving both expectation and conditioning components (Colloca & Benedetti, 2006; Eippert et al., 2009; Montgomery & Kirsch, 1997; Voudouris, Peck, & Coleman, 1990; Wager et al., 2004). In this paradigm the expectation of pain relief is induced by applying a supposedly analgesic cream which is de facto inert. The expectation manipulation (conditioning) procedure mimics the analgesic effect of the analgesic cream by manipulating the temperature applied to the placebo site and has been shown to strengthen the expectation of pain relief.