Journal of Psychosomatic Research 78 (2015) 489–494

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

The placebo effect in inflammatory skin reactions
The influence of verbal suggestion on itch and weal size

Margot Darragh, Joshua W-H. Chang, Roger J. Booth, Nathan S. Consedine *

The University of Auckland, New Zealand

ARTICLE INFO

Article history:
Received 26 August 2014
Received in revised form 19 January 2015
Accepted 21 January 2015

Keywords:
Placebo response
Placebo effect
Inflammatory skin reactions
Suggestion

ABSTRACT

Purpose: To investigate suggestion-induced placebo effects in inflammatory skin reactions.
Methods: A healthy sample of volunteers (N = 48) attended two laboratory sessions. In each, a local short term inflammatory skin reaction was induced with histamine. Participants were told that one session was a control session and the other was a treatment session in which an antihistamine cream would be applied to the arm to reduce the size of the weal and the experience of itch. Inert aqueous cream was applied in both sessions. Participants were randomly allocated to undergo either the control or the treatment session first.
Results: The placebo manipulation successfully reduced self-reported itch from the control to the placebo treatment session, but no placebo effect was demonstrated in weal size. Order effects were observed such that only those who underwent control procedures first had a smaller weal in the placebo treatment session as compared to the control session. The same order effect was seen for reported itch at one minute post histamine administration, but this disappeared at the three and five minute measures.
Conclusion: Findings suggest that explicit verbal suggestion can reduce the experience of itch. In addition to conscious awareness, a concrete representation of the suggested changes gained from prior experience to the stimulus may be an important component of placebo effects on inflammatory skin reactions.

Introduction

The relative importance of psychological factors in skin conditions such as urticaria continues to be debated [1], but there is empirical evidence to suggest that they can influence the experience of itch [2,3] and contribute to idiopathic conditions such as chronic spontaneous urticaria [4]. The way an individual thinks and feels appears to impact the status of the skin; however, whether this 'mind–body' relationship can be harnessed to ameliorate the symptoms of skin conditions is less clear.

The placebo effect is an intriguing phenomenon in which individuals experience benefit from pharmacologically inert treatments [5]. Expectation, an established mechanism of some placebo effects, is when the patient or participant's expectation of improvement generates real psychobiological changes [6]. Explicit suggestion of benefit is often used to induce expectations, such as providing verbal instructions that a treatment cream will reduce the experience of pain [7]. Placebo-induced expectations are thought to modulate internal homeostatic processes by activating top-down, neurobiological pathways [6,8]. Thus, placebo research has been described as investigations into the 'impact of expectations on brain–mind–body interactions' [9 p. 1922].

While psychological factors are known to influence the immune system [10], there is a paucity of evidence demonstrating that placebo expectancy can exert changes on immune parameters [11]. One possible reason for this is that certain placebo protocols may be more appropriate for the manipulation of certain outcomes. For example, those outcomes of which we are consciously aware (such as pain or motor function) can be influenced by suggestion, unlike those that are not consciously detectable, such as hormone release [12]. Therefore, in order for a suggestive placebo protocol to be effective, a conscious awareness of the suggested changes may be needed [13]. Given the nature of the immune system, this type of awareness is often not possible; however, inflammatory skin reactions can be seen and felt [14], and may be an appropriate target for suggestive placebo protocols.

Only a few studies have attempted to influence inflammatory skin reactions by way of suggestive placebo protocols. One study aimed to reduce histamine induced skin reactions with verbal suggestion and the application of topical 'anti-histamine' (placebo) cream [15]. While the manipulation was not successful, the suggestion did not *explicitly* suggest a smaller weal size or a reduction in perceived itch, but instead a 'dampened' response to the histamine. Another study demonstrated a suggestion-induced *increase* in itchiness, but the suggestion of *decreased* itchiness was not successful [16]. A recent study demonstrated that while verbal suggestion alone did not modulate itch, placebo effects

* Corresponding author at: University of Auckland, Department of Psychological Medicine, Faculty of Medical and Health Sciences, Private Bag 92019, Auckland Mail Centre, Auckland 1142, New Zealand. Tel.: +64 9 923 5976.
E-mail addresses: m.darragh@auckland.ac.nz (M. Darragh), wcha657@aucklanduni.ac.nz (J.W.-H. Chang), rj.booth@auckland.ac.nz (R.J. Booth), n.consedine@auckland.ac.nz (N.S. Consedine).

http://dx.doi.org/10.1016/j.jpsychores.2015.01.011
0022-3999/

were demonstrated when suggestion was coupled with a conditioning procedure [17].

While attempts to demonstrate placebo effects in this area have been more successful when conditioning protocols are employed [11], hypnosis (a form of suggestion) can influence immune parameters [18], cognitive-hypnotic protocols have been shown to modulate local inflammatory skin reactions [10,19–21], and emotion and arousal mood states can affect hypersensitivity skin reactions [22,23]. Further, reviews of placebo responses arising from the placebo-control arm of allergy treatment trials found placebo treatments can reduce skin symptoms [24,25]. The possibility that local inflammatory skin reactions may be modifiable by suggestion alone remains worthy of investigation.

The aim of the current study was to investigate whether a histamine-induced inflammatory skin reaction could be modulated by a suggestive placebo protocol. Explicit suggestions of a reduced weal size and less itching were provided conjointly with a topical 'anti-histamine' (placebo) cream. It was hypothesised that when the application of the cream combined with the suggestion of a reduced reaction, participants would experience reduced itchiness and a smaller weal size.

Materials and methods

Design, randomization and blinding

This was a randomized, cross-over, experimental study using a deceptive placebo protocol. Participants were told that the study was investigating the relationship between personality and allergic responses, and each participant attended two laboratory sessions. Local type-I hypersensitivity-like skin reactions were induced on both arms in each session (histamine prick tests). Participants were told that one session was a control session, and the other a treatment session in which an anti-histamine treatment cream would be applied to reduce the skin reaction. In reality, an inert aqueous cream was applied to the arms in *both* sessions. Participants were randomized to undergo either the control session first (Group 1), or the treatment session first (Group 2) (Fig. 1), and were informed of which session they were in ('Session') by receipt of an envelope at the start of each session. The research assistant (RA) performing the experiment was kept blind to Group and Session by providing information to the participants through video and written information in sealed envelopes.

Participants, recruitment and enrolment

Ethical approval was granted by the University of Auckland Human Participant Ethics Committee. A healthy sample of 50 volunteers was recruited, primarily through the distribution of flyers and notices posted on the University intranet (Fig. 2). No course credit was offered for participation. The sample mean age was 22 years (SD = 3.25), predominantly female (79%), with Caucasians as the largest ethnic group (42%), followed by non-Indian Asians (33%), Indian (15%), 'Other' (6%) and Māori and Polynesian (4%). Inclusion criteria were English-speaking adults aged between 18 and 45. Exclusion criteria were recent anti-histamine or anti-inflammatory medication, pregnancy, cardiac, autoimmune, psychological, or dermatological conditions, life threatening allergies, injury to either arm, or chronic illness. Eligibility was determined by a screening questionnaire prior to enrolment.

Procedure

Prior to the first laboratory session, participants completed an online survey consisting of personality, demographic, and health behaviour measures. Participants were then scheduled for two, 30-minute laboratory sessions, which were a minimum of one day and a maximum of three days apart. The two sessions were carried out at the same time of day (±1 h) to avoid circadian fluctuations in physiological processes and mood affecting experimental procedures [23,26]. Participants were asked to avoid food, caffeine, smoking, applying any cream to their forearms, and strenuous exercise, in the two hours prior to their sessions, and to avoid alcohol on the session days.

Both sessions started with a general overview of procedures. Participants were given an envelope explaining whether this was a control or a treatment session; then, to facilitate adaption to the laboratory context and help balance arousal between the sessions, participants listened to a 5-minute relaxation exercise which focused on mindful attention and calm and steady breathing. Participants completed a measure of negative mood (see Measures) before watching a ~2-minute information video, the content of which differed depending on the session. In the control session, participants were told that the purpose of the session was to get an indication of their skin reactivity without treatment, and that an inert aqueous cream would be applied to their arms before the histamine was administered. In the treatment session, the video explained that an anti-histamine treatment cream would be applied to their arms before the histamine was administered and that the cream would work to counteract the effects of the histamine, reduce itchiness, and the size of the weal:

> '*The cream works as anti-histamine and has been shown to be effective in reducing the effects of histamine and alleviating the symptoms. When applied to the skin, it reduces itching, and reduces the size of the weals (which are the red raised lumps).*'

Participants were then provided with a one-page information sheet which re-iterated the information in the video (that the cream was either an inert moisturizer or that it was an anti-histamine cream which would reduce weal size and itchiness). Participants were then seated comfortably on a chair and asked to place their arms palm up and in a natural position on a large pillow sitting on their lap. Aqueous cream was applied to an eight centimetre area in the middle one-third of the anterior surface of the right, then the left forearm with a cotton bud, and left to dry for approximately two minutes. As noted, video and information sheets led participants to believe that the cream had either no effect (control session) or it had antihistamine effects (treatment session).

Approximately 2 min after application of the cream, histamine was administered. Three droplets of histamine (all 10 mg/ml in 5% glycerol, physiological saline) were placed on the same section of arm that the cream had been applied. The drops were placed approximately two centimetres apart, avoiding veins, hair, or other blemishes where possible. The skin was then pricked through each histamine droplet with a

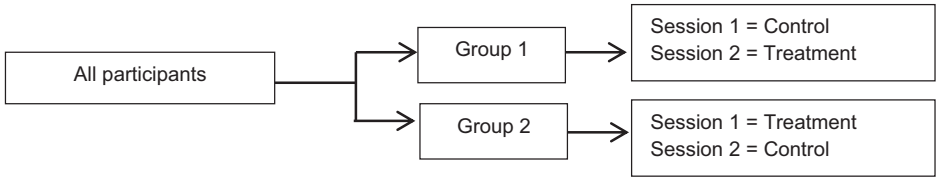

Fig. 1. Overview of study design.