Autonomic Neuroscience: Basic and Clinical 164 (2011) 62–66

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Organ-specificity of placebo effects on blood pressure

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ARTICLE INFO

Article history:
Received 29 December 2010
Received in revised form 24 May 2011
Accepted 20 June 2011

Keywords:
Placebo effect
Blood pressure
Verbal suggestion
Autonomic nervous system
Anxiety

ABSTRACT

There is increasing evidence that verbal suggestions accompanying placebo interventions can alter autonomic functions. The underlying mechanisms of these changes are not well understood. However, previous studies point at the specificity of such effects. The aim of the experiment was to lower blood pressure by a placebo intervention and to investigate the specificity of autonomic changes. Forty-five healthy participants received a single administration of an active drug (a homeopathic remedy), an identically-looking placebo drug, or no drug. Active drugs and placebo drugs were administered in a double-blind design and were accompanied by verbal suggestions of a blood-pressure lowering effect. Systolic and diastolic blood pressure, the electrocardiogram, electrodermal activity, and the electrogastrogram were recorded during 30 min before and after the intervention, and changes in situational anxiety were assessed. Results indicated a decrease of systolic blood pressure in the placebo group, as compared to the control group. Diastolic blood pressure levels, heart rate, respiratory sinus arrhythmia, skin conductance, gastric slow-wave frequency and situational anxiety did not change differentially between groups. In conclusion, the reduction in systolic blood pressure following the placebo intervention could not be attributed to stress relief or anxiety reduction. Rather, results suggest that the placebo intervention specifically reduced systolic blood pressure.

1. Introduction

During the last decade, considerable progress has been made to understand the mechanisms of placebo effects in several neurological and psychiatric conditions, such as pain, Parkinson's disease, depression, and anxiety (Finniss et al., 2010). These studies pointed to the specificity of placebo effects. For example, many forms of placebo analgesia are associated with the release of endogeneous opioids, while placebo-induced motor improvement in patients with Parkinson's disease is related to the release of dopamine in the dorsal striatum (de la Fuente-Fernandez et al., 2004) and reduced activity of single neurons in the subthalamic nucleus (Benedetti et al., 2004). Furthermore, two studies found site-specific placebo effects on pain, that is, analgesia only in the placebo-treated part of the body (Montgomery and Kirsch, 1996; Benedetti et al., 1999). This specificity of placebo effects suggests that different placebo interventions may activate different networks in the brain, which set in motion discrete somatic and symptomatic responses.

Besides good evidence for placebo effects in several neurological and psychiatric diseases, there is increasing evidence that placebo interventions can also affect peripheral organ functions controlled by the autonomic nervous system (ANS). For example, verbal suggestions delivered during placebo interventions can change blood pressure, gastrointestinal motility, and lung function in comparison to adequate control conditions (Meissner, 2011). Only a few studies as yet have looked at the specificity of the effects. Butler and Steptoe (1986) addressed the specificity of a placebo intervention that prevented the bronchoconstriction of airways following a nocebo intervention (i.e., a placebo intervention accompanied by harmful suggestions, such as narrowing of the airways). Interestingly, the placebo intervention reversed the nocebo effect on the airways but not the concomitant effects on heart rate and skin conductance. The authors concluded that the placebo effect was organ specific in nature. In a recent study, Meissner (2009) showed that placebo interventions along with verbal suggestions of gastric stimulation or relaxation modulated the length of gastric contractions independently from changes in skin conductance, heart rate, and heart rate variability, likewise suggesting an organ-specific effect.

Regarding blood pressure, experiments in both healthy and hypertensive volunteers showed either a decrease or an increase of systolic blood pressure following verbal suggestions of a hypotensive or a hypertensive effect, respectively. Interestingly, diastolic blood pressure and heart rate were affected only by suggestions of blood pressure increase (Agras et al., 1982; Amigo et al., 1993; Hunyor et al., 1997). These findings suggest that blood pressure increases may be the result of a sympathetic stress response, while reductions in systolic blood pressure possibly reflect a target-specific effect. In order to further investigate the specificity of blood pressure reduction achieved by verbal suggestion, the present study aimed to decrease

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doi:10.1016/j.autneu.2011.06.006

blood pressure by a placebo intervention and to investigate concomitant autonomic changes not only in the cardiovascular, but also in the electrodermal and gastrointestinal system.

2. Methods

2.1. Participants

Forty-five healthy, medication-free participants (26 women, mean age 24.7 ± 4.5 SD) screened for the absence of acute and chronic diseases were recruited via advertisements placed on university notice boards. All participants provided written informed consent and were paid 30 euros for participation. The study protocol was approved by the University Ethical Review Board.

2.2. Study design

The 45 participants were randomly assigned to one of the following 3 groups according to a computer-generated randomization list: homeopathic treatment (10 pre-manufactured homeopathic pills of "histaminum hydrochloricum" in a D8 dilution, i.e., the pills have been moistened by the manufacturer with a solution of histaminum hydrochloricum diluted by a factor of 10^{-8}), placebo treatment (10 pre-manufactured placebo pills of identical appearance), or control (no treatment). Allocation of treatment was performed after completion of the baseline measurement. Placebo and homeopathic drugs were administered in a double-blind design, and participants were informed about the supposed working mechanisms of the homeopathic drug and received a short introduction about physiological blood pressure regulation. Participants in the control group did not receive any globuli or suggestions, but were informed about the importance of including a no-treatment control group in such a trial. All participants were informed that the goal of the present study was to investigate placebo effects on blood pressure.

2.3. Measurements

Participants were instructed not to eat anything or to take any caloric or caffeinated drink in the 2 h prior to testing. State anxiety as a possible confounder was assessed before and after the experimental session using the state scale of the State-Trait-Anxiety Inventory (Laux et al., 1981). An experimental session consisted of a 30-minute baseline measurement, the intervention, and a 30-minute post-intervention measurement. Systolic and diastolic blood pressure was assessed every five minutes using an electronic sphygmanometer (Medisana MTM, Medisana AG, Meckenheim, Germany). The blood pressure device stored the data automatically and allowed exporting the raw data to a personal computer after the experiment. All other physiological signals were recorded using a BIOPAC MP 150 device (BIOPAC Systems Inc., Goleta, CA, USA) with AcqKnowledge 3.7.2 software for data acquisition. Signals were digitized at a rate of 15.625 samples per second, with the exception of the electrocardiogram signal, which was sampled at 500 Hz.

Participants were instructed to adopt a comfortable position and to avoid moving, speaking, or breathing deeply during the recording session. For blood pressure measurement, the deflated blood-pressure cuff was placed approximately 2.5 cm above the antecubital space of the left arm and at the level of the heart (Shapiro et al., 1996). The electrocardiogram signal was measured using three disposable Ag/AgCl electrodes (Cleartrace, Conmed, Utica, NY, USA) which were positioned in an Einthoven Lead I configuration and connected to the BIOPAC amplifier module ECG100C. Skin conductance was measured using two disposable Ag/AgCl electrodes (Cleartrace, Conmed, Utica, NY, USA) which were attached to the thenar and hypothenar of the right hand and connected to the BIOPAC amplifier module GSR100C. The electrogastrogram (EGG) was measured using two Ag/AgCl electrodes (Cleartrace, Conmed, Utica, NY, USA) attached at standard positions to the skin above the abdomen (Parkman et al., 2003), which was cleaned with sandy skin-prep jelly to reduce skin impedance (Nuprep, Weaver & Co., Aurora, CO, USA). The respiration signal was measured using a strain gage transducer (TSD201, BIOPAC Systems Inc., Goleta, CA, USA) which was attached around the thorax and connected to the BIOPAC amplifier module RSP100C.

2.4. Data reduction

Seven measurements of systolic and diastolic blood pressure levels were obtained from the 30-minute baseline and post-intervention periods.

Cardiac interbeat intervals between successive R peaks were extracted from the electrocardiogram signal using the peak-detection function implemented in AcqKnowledge 3.7.2. Cardiac interbeat intervals were examined and screened for artifacts based on the procedure developed by Porges and Byrne (1992). Intervals were subsequently converted into heart rates, and mean values were computed for baseline and post-intervention measurements.

To estimate parasympathetic neural regulation of the heart, the root mean square of successive differences (RMSSD) was calculated based on the cardiac interbeat interval time series of both baseline and post-intervention measurements (Thayer et al., 2006).

Average skin conductance levels (SCL) were computed for both baseline and post-intervention measurements and log-transformed to obtain normal distributions.

The dominant frequency of the gastric pacemaker was derived from the EGG signal as described in an earlier study investigating placebo effects on gastric motility (Meissner, 2009). In short, a running spectral analysis was performed for both baseline and post-intervention measurements. Peak frequency (dominant frequency) within the normal gastric frequency range (2 to 4 cycles per minute) was determined for each spectrum in order to estimate the frequency of the gastric slow wave associated with normal digestive activity of the stomach (Parkman et al., 2003). For the purpose of statistical analysis, mean dominant frequency values were determined for both baseline and post-intervention measurements.

Respiration frequency was used to control for possible respiratory artifacts in the electrogastrogram signal (Koch and Stern, 2004) and did not constitute a primary dependent variable in the study.

2.5. Statistical analyses

Mean values of outcome variables (i.e., systolic and diastolic blood pressure, heart rate, RMSSD, skin conductance levels, dominant frequency of the gastric slow wave, and state anxiety scores) for the post-intervention period were tested for group differences using univariate analyses of covariance (ANCOVA) with "condition" (placebo, homeopathy, control) as between-subject factor and mean values of the baseline periods as covariates. In case of significant *F*-values, ANCOVAs were followed up by Bonferroni-corrected post hoc comparisons. Pre-post changes of the outcome variables were analyzed by analyses of variance (ANOVA) with "time" (before and after intervention) as a within-subject factor and "condition" (placebo, homeopathy, control) as a between-subjects factor. Significant interaction effects between "time" and "condition" were followed up by Bonferroni-corrected post hoc comparisons of pre-post changes between groups. A *p*-value of $p<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, Illinois).

3. Results

3.1. Participants

Forty-five participants met all inclusion criteria and were randomly allocated to placebo (n = 15), homeopathy (n = 15), or