Organ-specificity of placebo effects on blood pressure

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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, electrodemanal activity, and the electrogastragram 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.

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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 (Finnis 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 sugges-

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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 sphygmomanometer (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, Connem, Ulica, NY, USA) which were positioned in an Einthoven Lead I configuration and connected to the BIOPAC amplifier module EGG100C. Skin conductance was measured using two disposable Ag/AgCl electrodes (Cleartrace, Connem, Ulica, NY, USA) which were attached to the thenar and hypothenar of the right hand and connected to the BIOPAC amplifier module CSR100C. The electrodermal activity (EDA) was measured using two Ag/AgCl electrodes (Cleartrace, Connem, Ulica, 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 Perigos 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. Post-change 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
control (n = 15). Characteristics of the study sample and mean values of physiological outcome parameters are presented in Table 1. Treatment groups were comparable at baseline.

3.2. Systolic blood pressure

Fig. 1 shows the time course of the 7 systolic blood pressure measurements in the homeopathy, placebo and control groups after the intervention. The ANCOVA for the mean systolic blood pressure levels revealed a main effect of “condition” (F(2,41) = 5.178, p = 0.010; Table 2). Bonferroni-adjusted post-hoc comparisons showed a significant difference between mean systolic blood pressure levels in the placebo and the control group (p = 0.009). The difference between the placebo and the homeopathy group was not significant (p = 1.000), nor was the difference between the homeopathy and the control group (p = 0.101).

In a next step, we investigated whether the changes in blood pressure from before to after the intervention differed significantly between the groups. The mixed model ANOVA for systolic blood pressure levels revealed a significant interaction effect between “time” and “condition” (F(2,42) = 6.365, p = 0.004). Bonferroni-corrected post hoc analyses showed that systolic blood pressure levels decreased significantly in the placebo group (−2.3 ± 4.4 SD) and in the homeopathy group (−1.4 ± 2.9 SD) compared to the changes in the control group (2.1 ± 3.0 SD; p = 0.005 vs. placebo group; p = 0.029 vs. homeopathy group). Pre-post changes did not differ between the placebo and the homeopathy groups (p = 1.000).

3.3. Diastolic blood pressure

The ANCOVA for the mean diastolic blood pressure levels did not show significant differences between groups (F = 1.892, p = 0.164; Table 2). In addition, the mixed model ANOVA for diastolic blood pressure levels did not reveal an interaction between “time” and “condition” (F(2,42) = 0.890, p = 0.420).

3.4. Heart rate, RMSSD, gastric frequency, skin conductance level, and state anxiety

The ANCOVAs for mean heart rate, RMSSD, gastric frequency, and skin conductance levels as well as state anxiety after the intervention did not show a significant main effect of “condition” (Table 2). Furthermore, mixed model ANOVAs for heart rate, RMSSD, gastric frequency, skin conductance levels and state anxiety did not show significant interaction effects between “time” and “condition” (all p’s > 0.2).

Table 1
Baseline characteristics of the study sample and means of outcome variables during the 30-minute baseline period.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 15)</th>
<th>Homeopathy (n = 15)</th>
<th>Control (n = 15)</th>
<th>p-value 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD, years</td>
<td>71.2 ± 15.4</td>
<td>69.8 ± 7.1</td>
<td>70.2 ± 16.9</td>
<td>26.2 ± 5.3</td>
</tr>
<tr>
<td>Women/men, n</td>
<td>11/4</td>
<td>9/6</td>
<td>12/3</td>
<td>31.7 ± 4.1</td>
</tr>
<tr>
<td>Mean heart rate ± SD, min 1</td>
<td>71.2 ± 15.4</td>
<td>69.8 ± 7.1</td>
<td>70.2 ± 16.9</td>
<td>30.7 ± 4.0</td>
</tr>
<tr>
<td>Mean MAP ± SD, mmHg</td>
<td>113.3 ± 7.3</td>
<td>116.2 ± 13.7</td>
<td>109.7 ± 9.0</td>
<td>9/6</td>
</tr>
<tr>
<td>Mean diastolic BP ± SD, mmHg</td>
<td>68.7 ± 6.4</td>
<td>70.5 ± 9.2</td>
<td>68.4 ± 6.1</td>
<td>26.2 ± 5.3</td>
</tr>
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</tr>
<tr>
<td>Mean diastolic BP ± SD, mmHg</td>
<td>68.7 ± 6.4</td>
<td>70.5 ± 9.2</td>
<td>68.4 ± 6.1</td>
<td>26.2 ± 5.3</td>
</tr>
<tr>
<td>Mean EGG frequency ± SD, cpm</td>
<td>3 ± 0.2</td>
<td>3 ± 0.2</td>
<td>3 ± 0.2</td>
<td>0.005</td>
</tr>
<tr>
<td>Mean SCL ± SD, log µg</td>
<td>2.0 ± 1.2</td>
<td>1.4 ± 0.9</td>
<td>1.7 ± 0.7</td>
<td>0.180</td>
</tr>
</tbody>
</table>

Abbreviations: SD: standard deviation; BP: blood pressure; EGG: electrocardiogram; RMSSD: root mean square of successive differences; SCL: skin conductance levels.

1 Chi-square test.

4. Discussion

The participants in the placebo group showed a reduction in systolic blood pressure compared to the control group. Changes in diastolic blood pressure and heart rate did not differ between groups. These findings are in agreement with previous studies to lower blood pressure by verbal suggestions, which have also only found reductions in systolic blood pressure (Agras et al., 1982; Amigo et al., 1993; Hunyor et al., 1997). In addition, the absence of concomitant changes in heart rate variability (RMSSD), skin conductance levels, and EGG frequency suggests that the intervention specifically affected systolic blood pressure, thereby confirming and extending previous findings of organ-specific placebo effects within the pulmonary and the gastrointestinal system (Butler and Steptoe, 1986; Meissner, 2009).

Blood pressure is regulated primarily by the sympathetic nervous system (Green and Paterson, 2008). The systolic blood pressure is largely determined by cardiac output, while the diastolic blood pressure is mainly influenced by peripheral vascular resistance (Guyenet, 2006). The reduction in systolic blood pressure by placebo could therefore be due to reduced cardiac sympathetic activation, thereby lowering cardiac output and thus systolic blood pressure.

It is important to ensure that the reduction in systolic blood pressure was caused by the placebo intervention itself and not by placebo-independent factors, such as regression to the mean or unspecified effects of the experimental setting. Regression to the mean usually happens when repeated measurements are made on the same subject, because values are observed with random error, i.e., a non-systematic variation in the observed values around a true mean (Barnett et al., 2005). One widely accepted approach to correct observed measurements for regression to the mean is to use analysis of covariance, which adjusts each subject’s follow-up measurement according to the baseline measurement (Barnett et al., 2005). The primary analysis in this study was performed according to this principle, and regression to the mean can therefore not explain the observed fall of systolic blood pressure in the placebo group. Furthermore, the inclusion of a no treatment group it was possible to control for nonspecific effects of the experimental setting, such as immobility or ennui. Finally, through the use of a homeopathic ‘active’ treatment the fear of possible side effects, and thus the risk of nonspecific increases in blood pressure could be minimized. It should be mentioned that the perceived harmlessness and lack of side effects of homeopathic remedies is a major reason for the popularity and high acceptance of homeopathy in Germany (Allensbach, 2009). The drawback of using a homeopathic drug is clearly the lack of a specific treatment effect (Shang et al., 2005). This may have reduced the
<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo (n = 15)</th>
<th>Homeopathy (n = 15)</th>
<th>Control (n = 15)</th>
<th>ANCOVA F-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean systolic BP±SE, mmHg</td>
<td>110.6±0.9</td>
<td>112.0±0.9</td>
<td>114.8±0.9</td>
<td>5.178</td>
<td>0.010</td>
</tr>
<tr>
<td>Mean diastolic BP±SE, mmHg</td>
<td>68.8±0.8</td>
<td>70.4±0.6</td>
<td>70.1±0.6</td>
<td>1.892</td>
<td>0.164</td>
</tr>
<tr>
<td>Mean heart rate±SE, min⁻¹</td>
<td>70.0±0.9</td>
<td>69.4±0.9</td>
<td>70.0±0.9</td>
<td>0.121</td>
<td>0.887</td>
</tr>
<tr>
<td>Mean RMSSD±SE, ms</td>
<td>37.7±1.9</td>
<td>40.0±1.9</td>
<td>40.9±1.9</td>
<td>1.028</td>
<td>0.367</td>
</tr>
<tr>
<td>Mean SCL±SE, log μS</td>
<td>2.0±1.2</td>
<td>1.6±0.9</td>
<td>1.6±1.4</td>
<td>1.05</td>
<td>0.358</td>
</tr>
<tr>
<td>Mean EGG frequency±SE, cpm</td>
<td>3.1±0.0</td>
<td>3.0±0.0</td>
<td>3.0±0.0</td>
<td>0.537</td>
<td>0.588</td>
</tr>
<tr>
<td>Mean state anxiety±SE, score</td>
<td>28.3±0.8</td>
<td>27.6±0.8</td>
<td>28.5±0.8</td>
<td>0.370</td>
<td>0.693</td>
</tr>
</tbody>
</table>

Abbreviations: SE: standard error; EGG: electrocardiogram; RMSSD: root mean square of successive differences; SCL: skin conductance levels.

In conclusion, results confirm previous findings that placebo interventions along with verbal suggestion of blood-pressure lowering reduce systolic but not diastolic blood pressure, and provided the first evidence for an organ-specific patterned placebo effect in the cardiovascular system. However, this is achieved, that is, how cortical processing of verbal suggestions modulates the activity of preganglionic neurons involved in blood pressure control so specifically remains to be investigated.

Conflict of interest
Conflict of interest: none declared.

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References