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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, 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.

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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 (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 endogenous 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-

tions 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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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

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" ($F_{(2,42)} = 1.390$, p = 0.260).

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 for 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.

Characteristic	Placebo (n = 15)	Homeopathy (n = 15)	Control (n = 15)	p-value[1]
Mean age ± SD, years	23.6 ± 4.3	26.2 ± 5.3	25.9 ± 3.7	0.222
Women/men, n	11/4	9/6	6/9	0.177[2]
Mean state anxiety ± SD, score	30.7 ± 4.0	33.1 ± 4.7	31.3 ± 5.2	0.360
Mean systolic BP ± SD, mmHg	113.3 ± 7.3	116.2 ± 13.7	109.7 ± 9.0	0.239
Mean diastolic BP ± SD, mm Hg	68.7 ± 6.4	70.5 ± 9.2	68.4 ± 6.1	0.707
Mean heart rate ± SD, min⁻¹	71.2 ± 8.5	69.8 ± 7.0	68.2 ± 6.9	0.548
Mean RMSSD ± SD, ms	39.6 ± 15.4	39.9 ± 13.2	37.8 ± 18.4	0.924
Mean EGG frequency ± SD, cpm	3.0 ± 0.2	3.1 ± 0.3	3.1 ± 0.2	0.507
Mean SCL ± SD, log µS	2.0 ± 1.2	1.4 ± 0.9	1.7 ± 0.7	0.180

Abbreviations: SD: standard deviation; BP: blood pressure; EGG: electrogastrogram; RMSSD: root mean square of successive differences; SCL: skin conductance levels.
[1] t-test if not otherwise stated.
[2] Chi-square test.
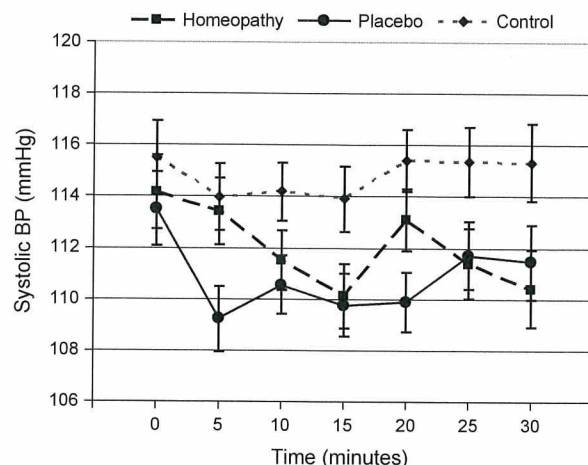
Fig. 1. Time course of the 7 measurements of systolic blood pressure (BP) after placebo, homeopathy or no intervention. Values are means ($\pm$ SE) adjusted for baseline values.

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 unspecific 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, by 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 2
Mean values of outcome variables after the intervention (adjusted for baseline levels).

Measure	Placebo (n = 15)	Homeopathy (n = 15)	Control (n = 15)	ANCOVA	
				F-value	p-value
Mean systolic BP ± SE, mmHg	110.9 ± 0.9	112.0 ± 0.9	114.8 ± 0.9	5.178	0.010
Mean diastolic BP ± SE, mmHg	68.8 ± 0.6	70.4 ± 0.6	70.1 ± 0.6	1.892	0.164
Mean heart rate ± SE, min^{-1}	70.0 ± 0.9	69.4 ± 0.9	70.0 ± 0.9	0.121	0.887
Mean RMSSD ± SE, ms	37.7 ± 1.9	40.0 ± 1.9	40.9 ± 1.9	1.028	0.367
Mean SCL ± SE, log μS	2.0 ± 1.2	1.6 ± 0.9	1.6 ± 1.4	1.05	0.358
Mean EGG frequency ± SE, cpm	3.1 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	0.537	0.588
Mean state anxiety ± SE, score	28.3 ± 0.8	27.6 ± 0.8	28.5 ± 0.8	0.370	0.693

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

expectations of the experimenter on a blood-pressure lowering effect, and hence the size of the placebo effect in the present study. However, it should be mentioned that placebo effects can be achieved also by deceptive placebo administration, and even when a placebo is openly prescribed in a non-deceptive and non-concealed manner (Kaptchuk et al., 2010).

The placebo effect on systolic blood pressure can most probably not be explained by stress reduction, because such a response would also include reductions in heart rate, SCL, and state anxiety. Moreover, the fact that gastric EGG frequency was affected in a previous study investigating placebo effects on the stomach (Meissner, 2009) but not in the present paradigm supports the hypothesis of an organ-specific patterned placebo effect.

From an anatomical point of view, the possible organ-specificity of placebo effects on autonomic organ functions is not astonishing. There is increasing evidence for a somatotopic organization of both afferent and efferent autonomic pathways. Animal studies have shown that the vagal afferent pathways from the periphery to limbic cortices are somatotopically organized (Cechetto, 1987), and neuroimaging studies confirmed equivalent results in humans (Cechetto and Shoemaker, 2009). Moreover, sympathetic and parasympathetic efferents are functionally specific, thereby allowing for a precise organ-specific regulation (Morrison, 2001; Jänig, 2006). ANS specificity is also in agreement with present knowledge about the distributed organization of the central autonomic network, which allows for multiple avenues to a given autonomic response (Berntson et al., 1994).

In addition to evidence from anatomical studies, several psychophysiological studies indicate that the anticipation of specific activities, such as bodily activity or eating, can induce functionally specific changes in the ANS, such as the increase of heart rate and blood pressure during central command (Williamson et al., 2002; 2003; 2006; Williamson, 2010), or the increase of gastrointestinal activity during the cephalic phase response (Power and Schulkin, 2008). The functional specificity of efferent autonomic pathways is likewise illustrated by psychophysiological studies showing that discrete emotions are accompanied by different autonomic patterns (Kreibig, 2010). Hence, it is reasonable to assume that other external stimuli, such as placebo interventions that aim to lower blood pressure, may also induce a specific autonomic response. Possibly, the anticipation of activities generally assumed to be associated with "lower blood pressure", such as reduced bodily and mental activity, activates association areas in the brain that are specifically engaged in systolic blood pressure control.

Given the small sample size of our study the results need to be tested again in a larger sample. Furthermore, the hypothesis that the current placebo intervention lowered systolic blood pressure by decreasing cardiac sympathetic tone needs to be tested directly, for example, by assessing the pre-ejection period. The simultaneous measurement of different organs' autonomic activity, however, seems to be a fruitful approach to further elucidate the specificity of placebo effects on organ functions controlled by the autonomic nervous system.

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, how 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.

Acknowledgments

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