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The placebo and its effects: A psychoneuroendocrinological perspective

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ABSTRACT

Placebos are usually employed deceptively in clinical trials in order to control for non-specific effects. However, since placebos themselves have been found to cause clinically relevant changes and in some cases are indistinguishable from the verum they are tested against, this theoretically inert, but practically effective intervention has become a scientific discipline in its own right. In this review, it is argued that placebos are generic and genuine biopsychosocial interventions and as such are highly interesting candidates for a psychoneuroendocrinological perspective. Yet, despite a considerable conceptual proximity between explanatory models of placebos and their effects with psychoneuroendocrine models and findings, placebos have thus far not been subject to systematic psychoneuroendocrine examination. Consequently, it would be highly interesting and informative to make placebos the target of psychoneuroendocrine scrutiny.

1. Introduction

Placebos have a longstanding history, in which their effects to the most part have either been utilized to separate the therapeutic wheat from the interventional chaff or to comfort patients considered untreatable or incurable (Kaptchuk, 1998). But although its use in randomized placebo-controlled trials can be traced back to Henry K. Beecher (1955) notorious claim that the placebo having powerful clinical effects in a third of patients some 60 years ago, the underlying principle – to control incidental and to manipulate characteristic treatment constituents – was employed much earlier and also in non-medical settings. As early as in the 16th century assumingly possessed demoniacs were exposed to either "real" holy or ordinary water or were read excerpts from the Holy Bible or Virgil's Aeneid in so-called "trick trials". Subsequent behavioral responses were then taken as proof or disproof for the devils' possession of those under inquisition as the devil would of course only oppose hallowed objects (Kaptchuk et al., 2009). Thus, their responses to these placebos could be considered as first *bona fide* evidence of its profound – or in these cases even life-saving - effects. It is only relatively recent that placebos have been examined in their own right, with an observable surge in publications on this topic since 2000 (Weimer et al., 2015). Here, their potential and usefulness to elucidate the underlying mechanisms of treatment effects is increasingly recognized and attempts to utilize them clinically have been proposed (Enck et al., 2013). However, despite its various manifestations, connotations and denominations, it needs to be noted that although placebos usually are perceived as inert – at least from the perspective of the given treatment theory – their effects and mechanisms can be quite substantial, i.e. encompass clinically relevant and biologically measurable qualities. As such, placebos and their effects are to be considered a genuine biopsychosocial treatment, in which psychosocial factors and processes are influenced by biological responses as well as triggers thereof, resulting in clinically relevant consequences.

2. What is a placebo?

The concept of placebo is ripe with misconceptions, which either lead to an over- or underestimation of its effects and potency. First, placebos should be understood as a principle rather than a distinct and singular procedure as placebos come in various forms and shapes. Thus, placebos not only encompass placebo pills, substances, creams, but they also include acupuncture needles (Kaptchuk et al., 2008), surgical procedures (Jonas et al., 2016), active substances, such as in the case of so-called "impure placebos" (Fässler et al., 2010), non-medical objects, such as wine (Plassmann et al., 2008) or violins (Fritz et al., 2017) or even behaviors, e.g. being supportive (Cuijpers et al., 2012) or being physically active while cleaning (Crum and Langer, 2007). Furthermore, not everything following the administration of a placebo. i.e. the placebo *response*, is to be considered as a consequence of the genuine placebo, since clinical responses to the administration of placebos could also contain changes in the natural course of the given disorder or disease as well as regression to the mean and the like (Benedetti et al., 2010). Thus, placebo *effects* are understood as the placebo response minus the changes seen with no treatment. Therefore, estimates of the placebo effect are only possible in studies with a no-treatment control condition, keeping in mind that so-called waitlist control conditions

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may be considered as nocebo conditions, at least in psychotherapy trials (Furukawa et al., 2014).

The generic principle (Grünbaum, 1981; Howick, 2016) includes the relativity to a given treatment theory, which in turn is relative to a given disorder. On the basis of a treatment theory, treatments for a given disorder consist of characteristic constituents, i.e. the verum, as a well as incidental constituents, such as the mode of administration, the clinical context and the doctor-patient relationship. A treatment then qualifies as intentional placebo if the treatment is administered to a patient even though the care-provider knows or assumes that this treatment lacks any characteristic constituents for the disorder at hand, but instead is believed to benefit the patients due to its incidental constituents. Interestingly, this operational definition is not based on evident clinical effects, but rather on an ethical stance as the administration of a placebo involves the deception of the patient about the true nature of the treatment received. In this perspective, the different operationalization's of placebo involve different mechanisms, which in itself are of course not "placebo", such as expectancy, conditioning, meaning, somatic attention or the patient-care provider communication and relationship. But although the placebo – with important exceptions, *vide infra* – necessitates deception, this does not make it less applicable, as the placebo allows us to investigate the potential of the treatment context, which then again can be harnessed to increase treatment effects and/or to reduce negative effects (Evers et al., 2018).

It needs to be noted that this generic definition of placebos does not imply a uniform and singular phenomenon, but that several subtypes need to be distinguished. Depending on the type and route of operationalization and administration, placebo effects can be verbally induced, classically conditioned, elicited by comparison of open and hidden administration or through classic randomized placebo-controlled trials, augmented by the practitioner-patient relationship and modulated by contextual factors, such as price, color and size. Accordingly, the psychobiological mechanisms of these placebo subtypes possibly differ as much as they possibly differ with respect to the targeted disorder and condition.

3. The placebo as a biopsychosocial treatment

Whereas placebos are thought to control for anything incidental and subjective in clinical trials, their effects and their underlying mechanisms are anything but just that. Rather, the involved psychological and biological processes and outcomes depend on the specific disorder or symptom as much as on the employed stimuli and strategy to evoke the placebo effect (Kong et al., 2013). Interestingly, placebos astoundingly mimic the intended biological process and their symptomatic outcome. For example, placebos are effective in patients with Parkinson's disease, inducing significant improvements in both hypokinetic symptoms, such as bradykinesia (de la Fuente-Fernández et al., 2001) and rigidity (Rätsep and Asser, 2016), as well as resting tremor (Barbagallo et al., 2018), with at least the former being mediated by endogenous dopamine release in the striatum (Lidstone et al., 2010), which is also a prime target for pharmacotherapeutic as well as brain-stimulation approaches (Oertel and Schulz, 2016). Likewise, placebo-induced analgesia has been shown to be – at least partly (Gracely et al., 1983; Grevert et al., 1983) – mediated through the release of endogenous opioids as the administration of the opioid antagonist naloxone reverses the placebo effect, as shown in the hallmark study by Levine et al. (1978). These early findings paved the way to the current understanding of the neural underpinnings of expectancy-induced analgesia, which now encompasses the complex interplay of opioidergic and dopaminergic influences on cortical and subcortical projections descending the nociceptive system (Büchel et al., 2014), with evidence of placebo-induced modulation of nociceptive spinal cord activity down to the level of the sixth cervical vertebrae (Eippert et al., 2009). Likewise, the administration of either placebo or selective serotonin reuptake inhibitor in patients with Major Depressive Disorder led to a similar pattern of an increase in cortical glucose metabolism as well as a decrease in limbic-paralimbic regions (Mayberg et al., 2002), whereas the deceptive administration of placebo increased μ-opioid neurotransmission in the subgenual anterior cingulate cortex, nucleus accumbens, midline thalamus, and amygdala, which are all known to be of relevance in the pathophysiology of this disorder (Peciña et al., 2015). Noteworthy, the observed placebo-induced release of endogenous opioids in this study predicted 43% of the variance of the outcome of the subsequent open treatment with selective serotonin reuptake inhibitors.

Besides these direct influences on neural activity and brain circuitries, placebos may also induce behavioral effects, which are then likely to positively feedback on biological parameters in turn. In their seminal meta-analysis of 21 studies including over 46′000 participants, Simpson et al. (2006) observed that not only good adherence to medication is associated with better health outcomes, but also that good adherence to placebos reduced the risk of mortality to nearly 50% of those with poor adherence. This so-called healthy adherer effect, which constitutes that adherence to therapy as well as placebo can be considered as a surrogate marker for overall healthy behavior and life style, has since then put forward to question the specificity of statin in the prevention of fractures (Donzelli et al., 2017) or coronary artery disease (Bitton et al., 2013).

Considering these often impressive clinical effects as well as their biological mechanisms, one needs to keep in mind that these are evoked by nothing more than otherwise inert agents in a special context. Thus, placebos and their effects qualify as true instances of a psychobiological treatment. Its potential is further amplified when considering that placebos are an integral and immanent component of virtually all interventions as its effects add to or even interact with the proposedly active treatment components (Kirsch, 2000; Lund et al., 2014).

4. Explanatory models of placebo effects

Placebos are – similar to basically any treatment – administered within the communicative process of the clinical encounter, resulting in the generation of a therapeutic meaning and a subsequent meaning response (Moerman and Jonas, 2002). Also, patients usually have acquired general and/or specific experiences within previous treatments as treatments are often enduring. Therefore, explanatory models need to take into account the tangible aspects of the given clinical encounter, the previous learning history as much as the continuous process of treatment maintenance:

- Verbally-induced treatment response expectations usually encompass the ambiguous or deceptive information of receiving an effective treatment, i.e. "You are randomized to either placebo or drug" or "This is a powerful painkiller", respectively. The effects are functional to the certainty of the expected outcome, thus being 100%, 50% or 0% sure to be administered a potent painkiller led to significant differences in requested dosage of buprenorphine (11.55 mg, 9.15 mg and 7.65 mg) in thoracotomized patients (Pollo et al., 2001). Also, patients receiving a selective serotonin reuptake inhibitor openly had a better clinical response to patients receiving the same medication in the context of a placebo-controlled design (Rutherford et al., 2017). Interestingly, response expectancies can also be enhanced by side effects. Being told to receive either a combined analgesic that might produce dry mouth or inert placebos increased the analgesic effects a nonsteroidal anti-inflammatory drug more than 3-fold when administered with atropine, which caused dry mouth symptoms (Berna et al., 2017). Similarly, standardized differences of clinical responses between antidepressants and placebos are drastically reduced when the latter were "active", i.e. have side effects mimicking those of antidepressants (Moncrieff et al., 2004).
- Previous experiences of having received an effective treatment is a

strong predictor of placebo effects. In placebo research this mechanism is utilized through classical conditioning, e.g. in learned immune functions (for review: Schedlowski et al., 2015) and classical conditioning of analgesic placebo effects, during which participants learn that a placebo effectively reduces heat pain, whereas heat pain is surreptitiously lowered following the application of a placebo cream during conditioning trials (e.g. Martin and Katz, 2010). The classical conditioning of placebo effects has clinical potential. For example, an antihistamine was coupled with a strawberry milk aromatized with lavender oil in patients with allergic rhinitis, whereby exposure to the drink in absence of the antihistamine latter decreased basophil activation, the skin prick test result and the subjective symptom score (Goebel et al., 2008). Also in a clinical trial in children with attention deficit hyperactivity disorder, the effects of a previously determined optimal dose of mixed amphetamine salts were maintained after a 50% dose reduction when paired with a visually distinctive placebo capsule administered open label, i.e. with full disclosure of placebo use to subjects and parents (Sandler et al., 2010).

- Another, rather neglected, but nevertheless important mechanism is the so-called somatic attention and feedback (Allen and Siegel, 2002). Here, bodily perceptions are perceived and interpreted on the basis of current assumptions and previous experiences, influencing the perception itself, channeling attentional processes and adapting behaviors. In the case of receiving an allegedly effective treatment, naturally occurring fluctuations of symptoms in either direction could then be perceived as proof of the treatments effectiveness, e.g. “it has to get worse to get better” and “I think it is working!”, setting off a positive feedback process finally resulting in improved mood, reduced behavioral avoidance and resumption of daily life. For example, the focus on negative side effects of an otherwise inert placebo pill led to increases in anxiety and nausea (Geers et al., 2006) and the taking an otherwise inert placebo led to a reduced mortality risk in adherent patients, which was explained accompanying life style changes (Simpson et al., 2006).
- Furthermore, it needs to be highlighted that placebos are administered and effective in a given social context. The origins of this social embedment have been traced back to the early evolution of man as a social being (Steinkopf, 2015) or related to basic human propensities (Wampold, 2012) and has attracted considerable scientific interest. For example, a patient-practitioner relationship marked by warmth, attention, and confidence doubled the already impressive clinical effects of placebo-acupuncture in patients with irritable bowel disease (Kaptchuk et al., 2008). This finding is supported by the results of recent meta-analysis on the association between health care outcome and patient-clinician relationship (Kelley et al., 2014) as well as trust (Birkhäuer et al., 2017). Furthermore, placing placebos in a social context puts the emphasis on the provider of – in this case: an otherwise inert– treatment. Here, early reports acknowledged the importance of clinician expectations on treatment outcome (Gracely et al., 1985), which has its more recent revenant in the profound impact of researcher allegiance on psychotherapy outcome (Munder et al., 2013). Also, the person of clinician itself is an important moderator of subsequent placebo responses as the treatment provider has been shown to have a 3-fold influence on outcome in comparison to the treatment provided, irrespective of whether the treatment itself is a placebo (Kelley et al., 2009) or verum (McKay et al., 2006).

Importantly, it needs to be noted that these different mechanisms possibly interact (e.g. Kaptchuk et al., 2008), but also represent different subtypes of placebos and different routes of administration of placebos. Furthermore, next to drug and placebo responses being additive (Kirsch, 2000) or less than additive (Lund et al., 2014), it could be possible that placebos also interact with the natural course of the target clinical condition. Clearly, more research is needed to address the interplay of these and possible other mechanisms of placebo effects.

5. A psychoneuroendocrine perspective on placebos

Given that placebos can be considered generic and genuine biopsychosocial treatments and considering its proposed mechanisms, the role of and relatedness to psychoneuroendocrine processes and paradigms to the placebo phenomenon are of potential interest. In this regard, different perspectives should be considered for both placebo and psychoneuroendocrine research.

First, the aforementioned underlying explanatory models of placebos and its effects have conceptual proximity to psychoneuroendocrine models and findings. This refers as much to for example the well-documented importance of the psychosocial context (Dickerson and Kemeny, 2004), social support (Ditzen et al., 2007) and expectancies (Gaab et al., 2005; Schlotz et al., 2011) on cortisol stress responses as to the profound and reciprocal effects between cognitions, affect, behavior and neuroendocrine functioning (e.g. Gaab et al., 2003a, 2003b; Gaab et al., 2004). In this regard, the placebo can be perceived as capitalizing the aforementioned reciprocal interplay between psychological, emotional, behavioral and biological processes and systems for therapeutic benefits in the clinical encounter. Given the conceptual as well as empirical relatedness of psychosocial interventions and placebos (Gaab et al., 2016, 2018), it is thus not unexpected for these psychosocial interventions to have significant effects on acute stress responses in healthy subjects (Gaab et al., 2003a, 2003b; Gaab et al., 2006; Hammerfald et al., 2006; Storch et al., 2007). Likewise, one could consider psychosocial stress as related to the concept of nocebo (Benedetti et al., 2007).

Second, albeit surprisingly, placebos have seldom been the subject of systematic psychoneuroendocrine examination and the results so far point to differential effects depending on the employed approach and rational. For example, while placebo alcohol was found to have profound dampening effects on cortisol as well as anxiety responses to the Trier Social Stress Test (Balodis et al., 2011) – equivalent to those seen after the intoxicating consumption of alcohol above a blood-alcohol level of 0.08% – the administration of placebos over three consecutive days had no effects on cortisol and anxiety responses in the TSST in the context of a randomized controlled phytomedical trial (Meier et al., 2018). Also, using a placebo version of social-evaluative stress, i.e. omitting this characteristic constituent of stress, resulted in the expected lack of the cortisol stress response in healthy subjects (Het et al., 2009). Matters become considerably more complicated when addressing the concundrum of specific actions of antidepressants on central glucocorticoid receptor-mediated processes (Pariante et al., 2012) in face of large to very large placebo effects in depressive disorders across all age groups (Khan and Brown, 2015; Locher et al., 2015, 2017a, 2017b; Rutherford et al., 2017), which are most likely mediated through opioidergic action (Peciña et al., 2015). Likewise, it would be of interest to scrutinize why and how placebos are clinically effective in disorders known to be marked by a hypofunctional hypothalamic pituitary adrenal (HPA) axis, such as irritable bowel syndrome (Kaptchuk et al., 2008, 2010; Videlock et al., 2016), chronic low back pain (Carvalho et al., 2016; Sudhaus et al., 2009) as well as chronic fatigue syndrome and fibromyalgia (Davidson et al., 2011; Tak et al., 2011) and whether and how these inert, but otherwise effective treatments effect HPA axis functioning in these syndromes. In the same line of reasoning, the systematic study of placebo effects in diseases known to be effectively treated with endocrine therapies, such as auto-immune disorders, allergies and asthma, would be informative. For example, although neither placebo inhaler nor sham acupuncture had any effects on maximum forced expiratory volume in patients with asthma, these two placebo treatments were rated equally effective than albuterol on relative improvement in subjective outcome (Wechsler et al., 2011). Also, but associated with considerable controversy, the psychotherapeutic approach of Eye Movement and Desensitization – which has been

considered a modern equivalent of Franz Anton Mesmers 18th century animal magnetism (McNally, 1999) and not containing any specific effects (Davidson and Parker, 2001; Herbert et al., 2000) – is found to be effective in the treatment of posttraumatic stress disorder, which in turn is marked by a hypofunctional HPA axis (Ehlert et al., 2001).

Third, besides considering conceptual proximities and addressing the impact of placebos on neuroendocrine parameters, it would of scientific interest to make placebos the target of psychoneuroendocrine examination. As a suitable example for this undertaking, a recent study addressed the impact of acute psychological stress on placebo and nocebo effects in experimentally induced visceral pain (Roderigo et al., 2017). Interestingly, previously experienced stress increased observed placebo as well as nocebo effects in visceroception. Given that patients often are distressed by symptoms as well as by the clinical encounter, this finding is of great clinical relevance, stressing the need to further examine how stress and emotional states in general affect placebo effects. Also, previous experiences as well as classical conditioning are major routes to establish placebo effects and as such are of psychoneuroendocrine interest for two reasons. On the one hand, the classical conditioning of neuroendocrine parameters could be of clinical potential, perhaps similar to the clinical potential of conditioned immune responses (Albring et al., 2014). As noted by others, there are a few, but clearly not enough studies on this matter (Schedlowski et al., 2015). On the other hand, learning processes themselves are subject to neuroendocrine modulation. Relevant to the matter at hand, retrieval of previously learned material is interrupted as well as learning of new associations is facilitated by glucocorticoids, making this a prime candidate for clinical application (Bentz et al., 2010; de Quervain et al., 2011; Walter et al., 2015). For example, Lass-Hennemann and Michael (2014) examined the influence of endogenous cortisol levels on the effects of exposure therapy – understood to stimulate inhibitory learning processes – in patients with spider phobia. The study showed that exposure training in the early morning hours, with high endogenous cortisol levels, showed better treatment outcomes compared to exposure sessions in the evening with low cortisol levels (Lass-Hennemann and Michael, 2014). It would be of interest to investigate the role of endogenous glucocorticoid levels or exogenous glucocorticoids administration in the formation of learned placebo association as this would be of relevance in disorders marked by either hypo- or hyperfunctional HPA axis functioning.

Finally, several neuroendocrine parameters are known to have modulatory effects on placebo-related phenomenon. For example, oxytocin has been shown to enhance empathy, trust, and social learning, which in turn are key for placebo effects (Meyer-Lindenberg et al., 2011). Interestingly, the administration of intranasal oxytocin enhanced the analgesic placebo effect in healthy males (Kessner et al., 2013), but not in healthy female subjects (Skvortsova et al., 2018). Also, the social properties of oxytocin have themselves been used to induce effective response expectancies to an 'oxytocin' placebo in stressed, but otherwise healthy subjects (Darragh et al., 2016). Also, a recent study provided first evidence that placebos not only rely on the quality of the interpersonal encounter, but can also induce effects similar to those seen after the intransal administration of oxytocin, i.e. increased trust in others as well as the preference for being physically close to others (Yan et al., 2018).

6. Perspective

Placebos are not only effective tools in scrutinizing the effects of the treatment context per se in clinical trials, they also allow for insights in the powerful works of the clinical context with its interpersonal contact, social persuasion and the formation of meaning with a plausible narrative. It can be reasoned that the application of these processes is fundamentally hindered by the deceptive nature of placebos and its incommensurateness with basic moral obligations (Trachsel and Gaab, 2016). But first, aspects and mechanisms of placebo effects can not only be harnessed in a non-deceptive manner (e.g. Birkhäuer et al., 2017; Kelley et al., 2014; Peerdeman et al., 2016), but have been shown to be effective (Charlesworth et al., 2017) and even as effective as deceptive placebos even when administered open-label (Locher et al., 2017a, 2017b). Thus, given this potential as well as its conceptual proximity, placebos should and needs to be also addressed by psychoneuroendocrinology. This could entail the assessment of the effects of deceptive and open placebos on neuroendocrine parameters in healthy as well as clinical populations as much as the examination of neuroendocrine moderation and mediation of placebo effects.

Conflict of interest

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