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Review

Applications and limitations of behaviorally conditioned immunopharmacological responses

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ABSTRACT

The importance of placebo responses for the treatment of various medical conditions has increasingly been recognized, whereas knowledge and systematic application in clinical settings are still sparse. One possible application for placebo responses in pharmacotherapy is given by learning paradigms, such as behaviorally conditioned immunosuppression, aiming at drug dose reduction while maintaining therapeutic efficacy of drug treatment. In an established learning paradigm of conditioned taste aversion/avoidance (CTA) in both, rats and humans, respectively, a novel-tasting drinking solution (conditioned stimulus, CS) is paired with an injection of the immunosuppressive drug cyclosporine A (CsA) as unconditioned stimulus (US). The conditioned response, evoked by re-presenting the CS alone at a later time, is reflected by avoidance behavior of consuming the solution (conditioned taste aversion; CTA) and a diminished interleukin (IL)-2 and interferon (IFN)-γ cytokine production as well as mRNA expression of rat splenic T cells or human peripheral T lymphocytes, closely mimicking the immunosuppressive effects of CsA. However, due to unreinforced CS-re-exposure conditioned responses progressively decreases over time (extinction), reflecting a considerable challenge for potential clinical applications of this learned immunosuppression. The present article discusses and critically reviews actual approaches, applications but also limitations of learning paradigms in immune pharmacotherapy.

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1. Introduction

Placebo responses can be defined as positive treatment outcomes that are caused by nonspecific treatment ingredients (Enck, Bingel, Schedlowski, & Rief, 2013). In clinical trials, a drug is compared to an 'inert' placebo under double blind conditions to estimate the extent to which the effects of the drug exceed the nonspecific placebo-treatment effects (Price, Finniss, &

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Benedetti, 2008). To date many approaches have discovered that placebo responses are complex psycho-neurobiological phenomena modulated and regulated centrally by distinct brain areas and peripherally by physiological processes (Benedetti, Carlino, & Pollo, 2011; Klosterhalfen & Enck, 2006; Price et al., 2008). Primarily two aspects drive placebo responses: (1) the formation of expectation by patients towards the benefit of a treatment; (2) associative learning processes. Admittedly, for pharmacological and non-pharmacological placebo effects, the importance of these two aspects differ (Colloca & Miller, 2011; Price et al., 2008; Stewart-Williams & Podd, 2004). For a pharmacological placebo effect it is necessary to gain a direct experience with a pharmacologically active substance during treatment. For non-pharmacological placebo responses it is sufficient to present just inert substances with ascribed pharmacological properties (e.g. by deceptive information). It is assumed that pharmacological placebo effects are attributed to additive effects of non-conscious learning and conscious expectancy. More precisely, pharmacological placebo effects are present when an active drug has been withdrawn and replaced by a placebo. In contrast, non-pharmacological placebo effects are primarily mediated by expectancies alone (Stewart-Williams & Podd, 2004).

However, a systematic application of placebo responses in pharmacotherapy may be seen in behavioral conditioning processes aiming at a controlled drugs-dose reduction while simultaneously maintaining efficacy of treatment. Even though studies have gathered preliminary evidence for the efficacy of placebo-controlled dose reduction in humans by employing associative learning procedures, they also show the difficulties and limitations of these approaches (Doering & Rief, 2012). We here critically review and discuss experimental findings in humans and animals that seem appropriate to investigate, better understand, and utilize behavioral conditioning paradigms as part of the placebo response in immune pharmacotherapy.

2. Behavioral conditioning of drug responses in pharmacotherapy

Even though classical or *Pavlovian* conditioning of drug responses has been shown to be a promising supportive tool to improve treatment outcomes (e.g. in analgesia) and to modulate neuroendocrine and immunological functions, drug intake is rarely analyzed from the perspective of associative learning processes (Doering & Rief, 2012). Reframing long-term treatment as a learning process provides new possibilities for maximizing treatment efficacy that could also decrease drug dosages, thereby reducing unwanted side effects and lowering the costs of treatment (Enck et al., 2013; Schedlowski, Enck, Rief, & Bingel, 2015). One possibility to experimentally achieve this goal is to use full-dose medication for a set period of time (*acquisition* phase) followed by a maintenance or *retrieval* period administering the full pharmacological dosage only every other day with interspersed placebo treatment (Doering & Rief, 2012; Rief, Bingel, Schedlowski, & Enck, 2011). By using this procedure, also known as *partial reinforcement* (Acosta, Thiel, Sanabria, Browning, & Neisewander, 2008), drug efficacy can be maintained while drug dosage is reduced. *Partial reinforcement* has impressively been demonstrated to work in corticosteroid-treated patients with psoriasis (Ader et al., 2010) and in amphetamine salt-treated patients with attention-deficit hyperactivity disorder (Sandler, Glesne, & Bodfish, 2010). However, the potential for reducing the negative consequences of long-term drug applications need to be analyzed in more detail. Thus, it is unavoidable to characterize the physiological systems, which are particularly susceptible for and involved in conditioning processes. Moreover, it needs to be evaluated which reinforcement or conditioning schedules are suitable to gain optimal effects and prevent learned pharmacological responses from habituation or extinction (Ader, 1997).

3. Behavioral conditioning of immune functions

The bi-directional interactions between the central nervous system (CNS) and the peripheral immune system are known for a long time (Metal'Nikov & Chorine, 1926). The CNS is able to affect peripheral immune functioning, however, it also has the capacity to sense and process signals from the peripheral immune system (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Exton, Herklotz, Westermann, & Schedlowski, 2001; Tracey, 2010). Behavioral conditioning of immune functions is one fascinating example for this bi-directional communication between the two (Ader & Cohen, 1975; Schedlowski & Pacheco-Lopez, 2010; Wayner, Flannery, & Singer, 1978). Associative learning processes such as immune conditioning have probably evolved over years as adaptive mechanisms to protect an organism from potentially harmful immune responses by avoiding ingestion or contact with immune-modulating substances (Ader, 2003; Bermudez-Rattoni, 2004; Schedlowski & Pacheco-Lopez, 2010). However, it has also been shown that conditioning of immune functions can be triggered experimentally by using artificial substances or drugs (Ader, 1976).

Conditioned taste aversion/avoidance (CTA) is a classical protocol to behaviorally condition immune functions. Most commonly it pairs a novel taste as a conditioned stimulus (CS) with the injection of an immunosuppressive drug as unconditioned stimulus (US). Following one or several CS/US pairings, re-presentation of the CS alone evokes the conditioned response (CR). The conditioned response is reflected on the behavioral level by avoiding ingestion of the CS (CTA) (Garcia, Kimeldorf, & Koelling, 1955; Garcia, Lasiter, Bermudez-Rattoni, & Deems, 1985). Concomitantly to this response, animals display a conditioned suppression of immune functions, similar to that formerly induced by the immunosuppressive drug administered as US (Ader, 2003). Using a CTA paradigm with the calcineurin (CaN) inhibitor and potent immunosuppressive drug cyclosporine A (CsA) it has been shown that conditioned immunosuppression is mediated on the efferent arm via the splenic nerve through noradrenaline and adrenoceptor-dependent mechanisms (Exton et al., 2002b; Pacheco-Lopez et al., 2005). Sympathetic nerves innervate lymphatic organs like the spleen, facilitating noradrenaline and adrenaline to directly interact with immune cells (Felten & Olschowka, 1987; Panuncio, De La Pena, Gualco, & Reissenweber, 1999; Straub, Westermann, Schölmerich, & Falk, 1998). This interaction takes place among other β2-adrenergic receptor (β2-AR) on the surface of CD4 + T cells. It is already known that there is a link between the β2-AR mediated pathway and the T cell receptor mediated pathway (Kin & Sanders, 2006; Kohm & Sanders, 2001), and that stimulation of β2-AR results in inhibition of CaN (Exton et al., 2002a; Riether et al., 2011). On the afferent arm neurotransmitters, cytokines or prostaglandins can reach the brain as putative messengers via the circumventricular organs (Goehler, Erisir, & Gaykema, 2006) and by crossing the blood-brain barrier (Banks, 2005). Moreover, the vagus nerve with its relays in brain stem nuclei detects and informs the brain about changes in the visceral immune status (Dantzer, Konsman, Bluthe, & Kelley, 2000; Goehler, Lyte, & Gaykema, 2007; Goehler et al., 2000; Maier, Goehler, Fleshner, & Watkins, 1998). Importantly, CsA itself has the capability to signal the brain by activation of neurons in the insular cortex and amygdala (Doenlen et al., 2011; Pacheco-Lopez et al., 2013) and it is also able to change brain neurochemistry (Gottschalk et al., 2011; von Horsten et al., 1998). It is suggested that *conditioned taste avoidance* and *conditioned taste aversion* represent different processes even though they are often used synonymously in the literature. In most animal models the actual amount of saccharin consumed is mea-