Review article

Martin Hadamitzky*, Laura Lückemann, Manfred Schedlowski and Harald Engler

# How learning shapes immunity

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**Abstract:** Experimental studies in rodents and humans have convincingly demonstrated that immune functions can be modulated by associative learning processes. We have established a conditioned taste avoidance (CTA) paradigm in rats by pairing a novel taste (conditioned stimulus, CS) with an injection of the immunosuppressive drug cyclosporine A (CsA; unconditioned stimulus, US). Re-exposure to the CS results in a pronounced CTA and, more importantly, in a selective suppression of specific T-cell functions, mimicking the drugs' effects. To provide a basis for using learned immunosuppressive strategies in clinical situations, we are currently investigating the neurobiological mechanisms underlying the extinction of conditioned immunosuppressive responses and the generalizability of our findings to other immunomodulatory drugs.

**Keywords:** classical conditioning; extinction; immunosuppression; reconsolidation; taste-associative learning.

**Zusammenfassung:** Experimentelle Studien bei Mensch und Tier zeigen eindrucksvoll, dass Immunfunktionen durch assoziative Lernprozesse beeinflusst werden können. In einem von unserer Arbeitsgruppe etablierten Konditionierungsparadigma bei Ratten wird die Darbietung eines neuartigen Geschmacks als konditionierter Stimulus (CS) unmittelbar mit der Injektion des immunmodulierenden Medikaments Cyclosporin A (CsA; unkonditionierter Stimulus, US) gekoppelt. Bei erneuter Präsentation des CS zu einem späteren Zeitpunkt vermeiden konditionierte Tiere, die Saccharinlösung zu trinken (konditionierte Geschmacksaversion, CTA). Zudem lassen sich Veränderungen im Immunsystem beobachten, die den pharmakologischen Effekten des als US eingesetzten Medikaments entsprechen. Um einen möglichen Einsatz von Lernprotokollen im Rahmen pharmakologischer Interventionen in der Klinik zu ermöglichen, untersuchen wir gegenwärtig die neurobiologischen Mechanismen, welche der Extinktion konditionierter immunsuppressiver Antworten zugrunde liegen. Darüber hinaus überprüfen wir die Generalisierbarkeit unserer Ergebnisse im Hinblick auf andere immunmodulierende Medikamente.

**Schlüsselwörter:** Klassische Konditionierung; Extinktion; Immunsuppression; Rekonsolidierung; Geschmacksassoziatives Lernen.

## Background

The central nervous system (CNS) and the immune system have been classically considered as independent and autonomously acting systems (Tracey, 2009). During the last three decades, clinical observations and experimental findings in animals and humans have provided compelling evidence that the brain and the immune system are intimately linked, sharing a common chemical language and continuously exchanging information (Dantzer et al., 2008; Tracey, 2010). In this context, the immune system acts as a sensory organ with immune cells as mobile sentinels that inform the brain about the immune status in the periphery (Blalock and Smith, 2007). Interestingly, immunological responses can be learned and memorized by associative learning or Pavlovian conditioning. From an evolutionary perspective, the ability to associate a certain immune response or threat (e.g., allergen, toxin, antigen) with environmental cues (e.g., context or flavor) has evolved as an adaptive mechanism to protect the organism from potentially harmful consequences by avoiding ingestion or contact with contagious or poisonous agents (Ader, 2003; Hadamitzky et al., 2020). However, this phenomenon can be also used therapeutically by combining

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the administration of an immunomodulatory drug with a gustatory or olfactory stimulus.

By applying a conditioned taste avoidance (CTA) paradigm in rats with a saccharin drinking solution as conditioned stimulus (CS) and the injection of the immunosuppressive calcineurin inhibitor cyclosporine A (CsA) as unconditioned stimulus (US), we established a clinically relevant model of behaviorally conditioned immunosuppression (Figure 1). In this model, re-exposure to the CS (i.e., sweet taste) results in conditioned suppression of interleukin (IL)-2 and interferon (IFN)-γ cytokine production as well as reduced splenic T-cell proliferation (Pacheco-Lopez et al., 2009). These conditioned effects on T-cell functions are mediated centrally via the insular cortex (IC) and the amygdala. On the efferent arm, the conditioned response is mediated via sympathetic noradrenergic nerve fibers and adrenoceptor-dependent inhibition of calcineurin activity in splenic T lymphocytes (Pacheco-Lopez et al., 2005). Importantly, the clinical relevance of conditioned immunosuppression has been proven by markedly prolong heart allograft survival (Exton et al., 1998; Hadamitzky et al., 2016a). Moreover, experimental studies in rodents and humans have convincingly demonstrated that suppression of immune functions can be elicited by behavioral conditioning paradigms aiming at a controlled dose reduction of drugs while maintaining efficacy of treatment (Albring et al., 2014; Enck et al., 2013; Hadamitzky et al., 2020; Wirth et al., 2011). However, the mechanisms of this learned immunosuppression are still incompletely understood.

## Abrogating extinction of learned immune responses

To provide a basis for using learned immunosuppressive strategies in clinical situations as supportive therapy together with a standard pharmacological regimen, it is important to elucidate neural processes mediating extinction of the conditioned response at the behavioral level (CTA) and, in particular, at the level of the immune system. We performed a series of experiments to elucidate the mechanism underlying the extinction of conditioned immunosuppression. First, we could show that animals that

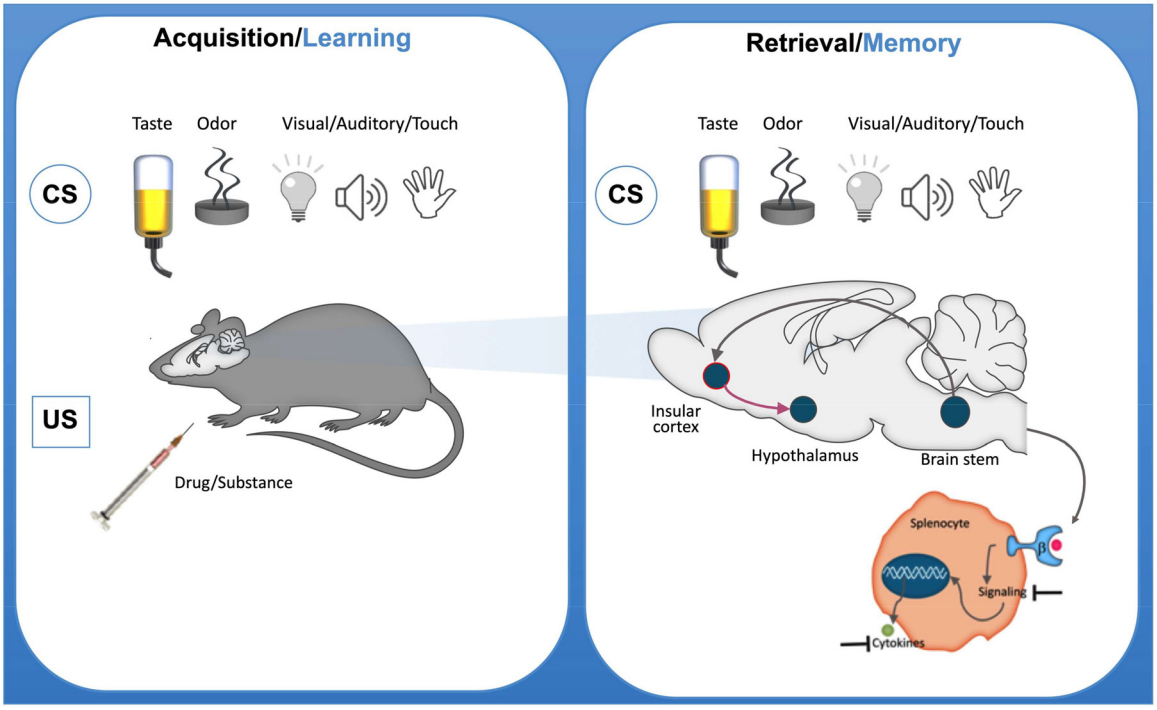


**Figure 1:** Principles of taste-immune conditioning. In rodents the presentation of a conditioned stimulus (**CS**; olfactory, gustatory, visual, auditory, touch, respectively) is paired with the administration of a drug or substance with immunological properties (unconditioned stimulus/**US**). During central perception of the **CS** via neural afferences, the neuro-molecular and/or immunological alterations induced by the **US** are detected by the CNS via neural or humoral afferent pathways (*Acquisition* – Learning). By re-exposing the organism to the **CS** only, the initially conditioned information is processed via the insular cortex, hypothalamus, and sympathetically transferred to secondary lymphatic organs such as the spleen. Subsequently, the changes in immune responses (diminished cytokine production/ T cell proliferation) originally induced by the drug or substance administered as the **US** become apparent (*Retrieval* – Memory).

displayed a strong CS-US association during acquisition phase also showed a strong CTA during unreinforced CS re-exposures (i.e., extinction learning). Moreover, extinction of the conditioned response was accompanied by increased neuronal activity in the IC, measured as enhanced mRNA expression of the unspecific neuronal activity marker c-fos (Hadamitzky et al., 2015). In another study, extinction of the CTA was efficiently prevented by administering the protein synthesis inhibitor anisomycin into the IC immediately after retrieval of the conditioned response (presentation of the CS in the absence of the US), indicating that *de novo* protein synthesis is required for extinction of the CsA-induced CTA (Hadamitzky et al., 2016b). Importantly, taste-avoidance studies with other drugs used as US (e.g., lithium chloride) indicate that extinction learning is affected by context change (Bouton et al., 2006). However, divergent from these findings, extinction of a learned CS-US association with CsA was not sensitive to contextual changes but rather seems to depend on the physiological and neuropharmacological effects of the US (Tuerkmen et al., 2016).

Conditioned responses gradually weaken over time and eventually disappear when animals are repeatedly exposed to the CS in the absence of the US (Berman and Dudai, 2001; Pavlov, 1927). However, experimental data suggest that extinction involves the consolidation of a new trace but may also comprise destabilization of the initially acquired memory. By applying a sub effective dose of the US (LiCl), which was ineffective in inducing CTA in naive rats during extinction, conditioned animals regained a CTA score as if they had never been subjected to the extinction procedure before (Berman et al., 2003). These findings indicate that memories enter a transient labile phase in which they can be impaired or enhanced by a new stabilization process termed reconsolidation (Myers and Carlezon, 2010). This process of reconsolidation seems to be dependent on a narrow time frame, the so-called reconsolidation window (Nader et al., 2000) (Figure 2). However, even though the empirical picture is not clear, data suggest that during retrieval of a memory trace, this reconsolidation window opens up, where the memory trace can be erased when certain proteins cannot be synthesized, or when extinction training is performed (de Carvalho Myskiw et al., 2014; Tronson and Taylor, 2007). Using our standard taste-immune conditioning protocol with CsA as US, we could demonstrate that extinction of CTA and, more importantly, extinction of learned immunosuppressive effects (reduced IL-2 and IFN-γ cytokine production) can be abrogated by subtherapeutic doses of the US, given as reminder cue together with the CS during retrieval. In contrast, such subtherapeutic CsA injections were completely ineffective when administered 8 h after CS re-exposure. These findings suggest that the timing of the reminder cue during the labile phase of the memory trace after retrieval (i.e., inside vs. outside the reconsolidation window) is crucial for initiating a reconsolidation-like process, involving *de novo* protein synthesis. Importantly, this updated learned immunosuppressive response and its maintenance is of clinical relevance because it significantly prolonged the survival time of heterotopically transplanted hearts (Hadamitzky et al., 2016a).

## Generalization and clinical relevance of learned immune responses

The majority of studies on learned immunopharmacological responses in animals and humans were so far focusing on calcineurin inhibitors such as CsA. However, for a more general application of taste-immune associative learning protocols, it is important to investigate whether this phenomenon also applies to other clinically relevant drugs with different immunomodulatory properties. Against this background, we recently started using rapamycin (sirolimus), a small-molecule drug used as antitumor medication and to prevent graft rejection, in behavioral immunoconditioning. For this purpose, presentation of a novel taste (saccharin, CS) was paired with injections of rapamycin (US). Subsequent re-exposure to the CS alone revealed that taste-immune learning with rapamycin induced a moderate CTA but pronounced conditioned immunopharmacological effects, reflected by reduced levels of IL-10 cytokine production and diminished proliferation of splenic T cells (Lückemann et al., 2019). These results provide further evidence that the phenomenon of learned immune responses also applies to other small-molecule drugs with different immunosuppressive properties, thereby providing the basis for using immunepharmacological learning paradigms in clinical contexts, e.g., as supportive therapy (Hadamitzky et al., 2020).

In a model of murine allergic contact dermatitis (contact hypersensitivity), it has been shown that T cell–dependent immune responses can be suppressed by behavioral conditioning, reflected by a conditioned reduction in swelling and leukocyte infiltration into the inflamed tissue (Exton et al., 2000). To extend these observations and to analyze the potential clinical relevance of a reconsolidation-like process, we applied this taste-immune associative learning protocol in rats with collagen type II–induced arthritis (CIA) as a model for T cell–dependent chronic inflammatory autoimmune disease. We could show that this learning protocol together

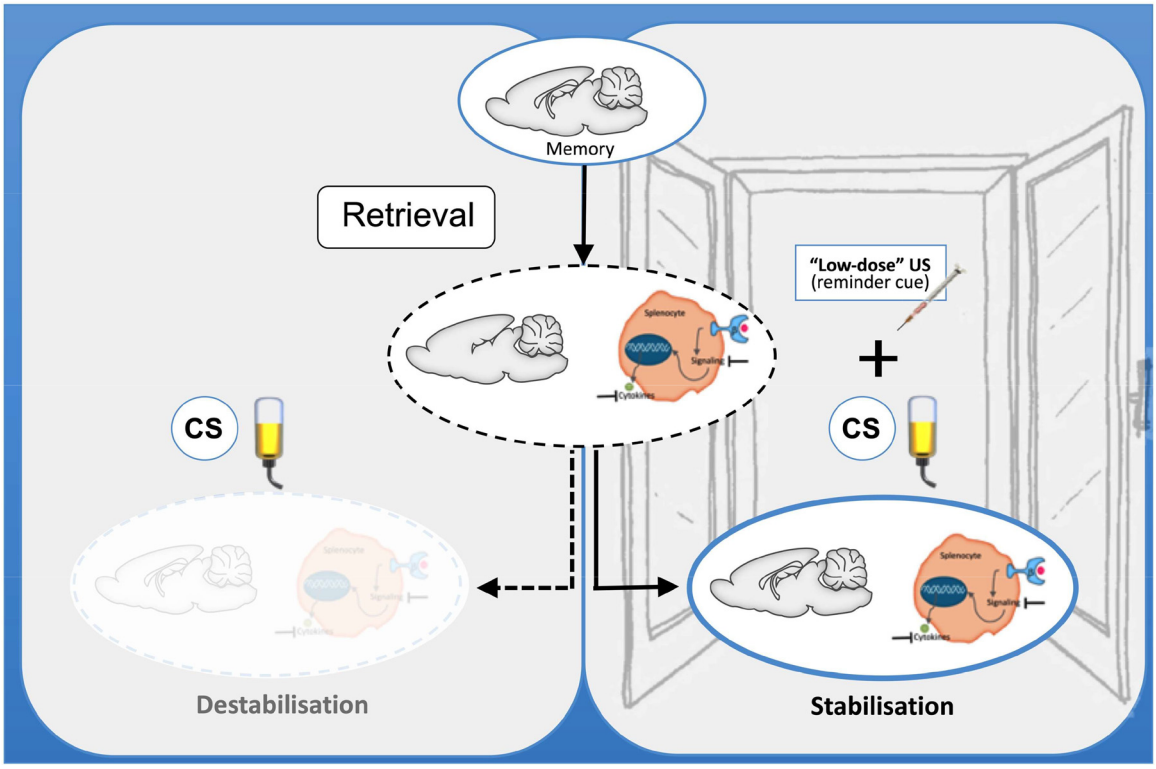


**Figure 2:** Abrogating extinction in conditioned immunosuppression. During recall or retrieval, the taste-immune memory enters a transient labile phase in which it can be modulated. This transient labile phase, which lasts for approx. 4 h (reconsolidation window) is characterized by protein synthesis in the insular cortex and amygdala. Following withdrawal of reinforcement (only the conditioned stimulus is presented), the memory destabilizes and the learned immunosuppressive response ultimately extinguishes (left hand panel). Stabilization or reconsolidation of memory is achieved by simultaneous presentation of sub-therapeutic drug doses of the unconditioned stimulus (CsA) as a reminder cue together with the CS (saccharin) (within the reconsolidation window), thereby abrogating extinction of the conditioned response (right hand panel). When receiving the reminder cues 8 h following CS re-exposure (outside the reconsolidation window) reconsolidation-like processing fails to appear and the conditioned response extinguishes.

with the application of only 25% amount of the drug used as CS lead to an almost identical clinical outcome as seen after full dose (100%) CsA treatment. Conditioned animals showed less signs of inflammation, such as swollen joints and paws, as well as less bone destruction and infiltration in surrounding tissue. In addition, performance in a functional grip strength test was improved. Furthermore, we observed that attenuating effects on inflammatory progression in CIA triggered by conditioning were blocked by continuous application of the $\beta$-adrenoceptor antagonist nadolol (Luckemann et al., 2019). Together, these findings suggest that learned immunosuppression, mediated via $\beta$-adrenoceptors, might be beneficial as a supportive tool in the treatment of chronic inflammatory autoimmune diseases by diminishing disease exacerbation. Importantly, in a distinct approach, a taste-immune associative learning paradigm was recently added to the standard immunosuppressive therapy with CsA or tacrolimus in patients who underwent renal transplantation. At retrieval, when patients were re-exposed to the CS (a novel taste), capacity of T-cell proliferation was significantly reduced compared with baseline kinetics of T-cell functions during pharmacotherapy (Kirchhof et al., 2018). This proof-of-concept study provides evidence for the possible effectiveness of learned immune-pharmacological strategies in clinical situations as supportive therapy together with the standard pharmacological regimen in conditions where continuous immunosuppressive drug treatment is required.

## Future perspectives

Together, experimental data in rodents and first observations in healthy humans and patients demonstrate that taste-immune associative learning and reconsolidation-like processes can interfere with extinction of learned immunosuppression (Hadamitzky et al., 2020). However, a major challenge is to gain deeper insights into the neurobiological underpinnings of learned immunosuppressive responses. Using chemogenetic techniques such as

designer receptors exclusively activated by designer drugs (DREADDs) for interfering with neuronal activity during conditioning, we aim to identify relevant brain structures and to characterize neural mechanisms mediating learning conditioned immunopharmacological effects. Moreover, to exploit these mechanisms for clinical practice, it is necessary to analyze the effectiveness and clinical relevance of reconsolidation-like processes of behaviorally conditioned immunomodulation in different translational disease models, as well as the generalization across distinct immunopharmacological mechanisms. Thorough knowledge of the basic mechanisms of extinction learning is essential to achieve the long-term goal of the learned immune response: to use these learning paradigms in clinical situations as supportive therapy together with the standard immunopharmacological regimen with the aim to maximize the therapeutic outcome for the patient's benefit (Enck et al., 2013; Schedlowski et al., 2015).

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