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Review

Crosstalk between contact hypersensitivity reaction and antidepressant drugs

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Abstract:
Allergic contact dermatitis is a delayed-type hypersensitivity reaction mediated by hapten-specific T cells. Many cell types, inflammatory mediators and cytokines are involved in this reaction. Contact hypersensitivity is a self-limited reaction and can be regulated at different levels. Because it is known that disturbances in the immune system underpin the onset of depression and that antidepressant drugs have immunomodulatory effects, it can be hypothesized that antidepressants may have some efficacy in the treatment of contact hypersensitivity. There are some reports on the effectiveness of antidepressants in the inhibition of cutaneous sensitization in mice, and the aim of this narrative review is to assess the evidence for the effectiveness of antidepressant drugs in reducing the recurrence of contact hypersensitivity reactions.

Key words:
antidepressant drugs, contact hypersensitivity, cytokines, depression, desipramine, fluoxetine

Allergic contact dermatitis and depression – epidemiology

Contact hypersensitivity (CHS) to haptens is an example of a cell-mediated immune response. Allergic contact dermatitis (ACD) is the most frequent type of CHS occurring in humans. It is a delayed hypersensitivity reaction (DTH), mediated by hapten-specific T cells [4]. Contact dermatitis (CD) affects approximately 20% of the general population, whereas occupational CD constitutes up to 30% of all occupational diseases [9]. The number of etiologic CD factors is very high and is still growing. Currently, over 3,700 haptens, which are potential contact allergens, have been identified [31]. The ever-growing number of patients suffering from this disease poses more and more serious social and economic problems, adversely affecting the patients' quality of life and productivity.

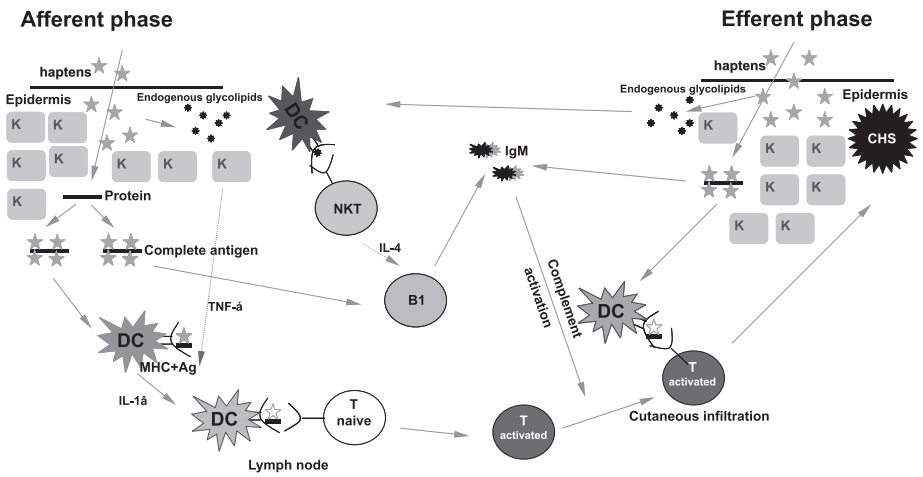

Fig. 1. The mechanism of the contact hypersensitivity reaction. Antidepressants can modulate particular stages of the hypersensitivity reaction, as described in the text. Ag – antigen, B1 – B1 B cell, DC – dendritic cell, K – keratinocyte, NKT – NKT lymphocyte, T – T lymphocyte

Depression is one of the most common mental disorders and is an increasing burden in western countries. According to the WHO, more than 350 million people of all ages suffer from depression (2012). Taking into account the high frequency of both ACD and depression, comorbidity is very likely.

More than one out of every 10 Americans over the age of 12 takes an antidepressant. According to an analysis by the U.S. National Center for Health Statistics (a division of the Centers for Disease Control and Prevention), between 2005 and 2008, antidepressants were the third most commonly used drugs by Americans of all ages and were the most common drugs among people aged 18 to 44. It was found that antidepressant usage in the United States rose by almost 400% in the 2005–2008 survey period compared to the 1988–1994 period. A similar tendency has been observed in Europe.

Because the activation of immune-inflammatory pathways may play a role in the etiology of depression, it may be hypothesized that antidepressants have an immunomodulatory effect on the CHS response.

Mechanism of contact hypersensitivity

CHS is a T cell-mediated immune response that is induced by topical skin immunization with small molecules, i.e., haptens. In this immune response, two phases can be distinguished: an induction phase after the priming contact with a hapten, and an elicitation phase that develops after re-exposure to the hapten [22]. During both stages, a wide variety of cells are involved including antigen presenting cells (APC), endothelial cells, mastocytes, keratinocytes, melanocytes, antigen specific T lymphocytes, natural killer T lymphocytes (NKT), two different subtypes of T effector lymphocytes (Th1 $CD4^+$ or Tc1 $CD8^+$) and peripheral blood leukocytes (monocytes and neutrophils) [29].

After application of the hapten, it penetrates the skin and binds to self-proteins. The hapten-protein complex is taken up by dendritic cells (DC), mostly by epidermal Langerhans cells (LC), and is consequently transported to the local lymph nodes for presentation to antigen-specific T cells. Finally, the T effector lymphocytes are distributed back to the blood and skin and are ready to function as effectors within 4–5 days post-sensitization [2] (Fig. 1).

CHS responses can be mediated either by $CD4^+$ Th1 (MHC class II-restricted lymphocytes locally producing IFN-γ to recruit a typical inflammatory infiltrate [40]) or by $CD8^+$ MHC class I-restricted Tc1 cells that can similarly release interferon (IFN)-γ but predominantly mediate cytotoxic damage to local skin cells, such as keratinocytes and interleukin (IL)-17-producing Th17 cells [34]. Finally, the discovery by von Adrian et al. that natural killer (NK) cells may act as effector cells in CHS in mice was a breakthrough in research on the mechanisms involved in

the CHS response [36]. Further, our studies demonstrated that NK cells that are able to adoptively transfer the CHS response belong to the CXCR6-expressing subset [37].

It was previously shown that an early 2-h initiating response is required for the local recruitment of sensitized T cells. This initiating response is due to the binding of an antigen to specific IgM antibodies produced rapidly post-immunization by B-1 B cells [41]. Local Ag-IgM complexes are generated, leading to complement activation, which initiates the elicitation of CHS by locally generating C5a to activate receptors on mast cells and platelets and results in the release of vasoactive tumor necrosis factor (TNF)-α and serotonin [2]. This stimulates the endothelial expression of the adhesion molecules (ICAM-1 and VCAM-1) needed to recruit circulating CHS Teff cells. These early events of elicitation are called "CHS initiation" because they are required to recruit CHS Teff cells to mediate the 24-h component of CHS [20].

Our further work showed that Vα14i NKT cells are important in the CHS initiation process because they stimulate B-1 cells to quickly produce IgM antibodies after immunization, which eventually leads to local T cell recruitment to elicit CHS. Hepatic NKT cells are preferentially activated to release IL-4, which together with an immunizing Ag, coactivates the B-1 cells [7]. It is noteworthy that Vα14i NKT cells, like B-1 cells, are subpopulations of innate cells [innate like lymphocytes (ILL)]. The rapid response in CHS of B-1 cells and hepatic Vα14i NKT cells, both innate cells, illustrates their cooperative interaction, which bridges the innate and adaptive immune responses [2]. In contrast to Th1- and Tc1-mediated CHS, NK cell-mediated CHS occurs independently of B-1 or NKT lymphocytes but is IFN-γ-, IL-12- and IFN-α-dependent [30]. Additionally, we found that Tγδ cells, which also belong to the ILL population, play an important role in the CHS response by protecting CHS Teff cells from the negative signals produced by natural regulatory cells [3].

Antidepressant drugs

Antidepressant drugs are divided into several classes, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), heterocyclic antidepressants (HCAs), serotonin-noradrenaline reuptake inhibitors (SNRIs), and reversible inhibitors of MAO-A (RIMA). The mechanism of action of most antidepressants is related to their ability to prevent the reuptake of neurotransmitters (i.e., serotonin, noradrenaline) and increase the synaptic concentration of neurotransmitters. Basically, antidepressants are used to treat major depression and other related neurological disorders because they act as neurotransmitter modulating factors in the brain, but they possess a host of beneficial side effects represented by peripheral anti-inflammatory and immunomodulatory properties. It was reported that co-incubation of immunocytes with antidepressants, particularly with SSRIs (e.g., fluoxetine), suppresses the production of IFN-γ and enhances the synthesis of IL-10, which leads to a decrease in the IFN-γ/IL-10 ratio [28]. Moreover, it was reported that the serotonergic receptors (e.g., 5-HT_{1A} and 5-HT_{2A}) are expressed on human keratinocytes, melanocytes and dermal fibroblasts, lymphocytes, dendritic cells and macrophages [10].

Inhibition of the CHS reaction by antidepressant drugs – experimental studies

To the best of our knowledge, we are the only researchers to have examined the effects of antidepressants on contact hypersensitivity. In experimental studies, it has been shown that the CHS reaction is T helper (Th)1-dominant (in CBA/J mice with an H-2^k haplotype, immunized with picryl chloride). In contrast, topical application of 2,4-dinitrofluorobenzene (DNFB), dinitrochlorobenzene (DNCB) and oxazolone (OX) on C57BL/6 mice with the H-2^b haplotype and Balb/c mice with the haplotype H-2^d induced a T cytotoxic (Tc)1 CD8 T cell-dependent reaction [32].

In our studies, we have shown that the repeated administration of antidepressant drugs was effective in inhibiting CHS reactions to picryl chloride (PCL) in CBA/J mice and to DNFB in Balb/c mice. In CBA/J mice, the antidepressants significantly suppressed the CHS reaction mediated by Th1 cells: desipramine by 47% and fluoxetine by 53%. Similar effectiveness of antidepressant drugs was observed for Balb/c mice immunized with DNFB; desipramine inhibited the

Tc1-mediated reaction by 55%, and fluoxetine inhibited it by 54% compared to the positive control [6, 23].

Mechanistic explanations of the inhibitory effects of antidepressants on CHS reactions

In this section of our review, by examining the contact hypersensitivity mechanism and the immunological character of the CHS response, we will try to explain how antidepressant drugs are able to regulate this inflammatory disorder. There are many studies showing a direct effect of antidepressants on inflammatory markers.

Antidepressants first target DC, which are involved in the CHS response and have diverse functions, including the presentation of antigens, the activation of effector cells (T cells and NK cells) and cytokine secretion [17]. The epidermal application of haptens is a factor evoking the mobilization and migration of DC from the skin to the lymph nodes. The application of haptens to the skin triggers IL-1β synthesis [43]. The released IL-1β stimulates keratinocytes to synthesize TNF-α. Both IL-1β and TNF-α diminish the expression of E-cadherin and adhesion molecules in the LC membrane *via* their specific receptors present on LC, causing LC migration from the epidermis to the skin draining lymph node [16]. The neutralization of IL-1β with anti-IL-1β antibodies prevents the induction of CHS [43]. Many studies have demonstrated that antidepressants can inhibit the production and release of pro-inflammatory cytokines and stimulate the production of anti-inflammatory cytokines [24, 26, 28]. In contrast, DC are able to synthesize anti-inflammatory factors, such as IL-10, IL-13 and TGF-β. Previously, it was shown that antidepressants could have negative immunoregulatory actions due to their ability to significantly decrease the IFN- γ/IL-10 ratio [28]. Furthermore, the administration of antidepressant drugs in animal models of depression and *ex vivo* incubation of human blood with antidepressants increased the levels of IL-10 [24, 25]. Finally, the administration of both fluoxetine and despiramine before sensitization increased IL-10 production by Con A-stimulated splenocytes in a PCL model of CHS [23] and increased IL-10 production by Con A lymph node cells in a DNFB model of sensitization [6].

Apart from DC, which may be a potential site of action of antidepressant drugs, the skin also contains keratinocytes and fibroblasts. These cells release a number of substances that may be involved in the CHS reaction and that may be regulated by antidepressants. As previously mentioned, keratinocytes are a source of TNF-α, which indicates a pivotal role in the initial inflammatory response in the skin. In addition, TNF-α KO mice have a compromised CHS reaction [11]. Curzytek et al. [6] have shown that fluoxetine administered to control animals before DNFB sensitization inhibits TNF-α production by Con A-stimulated splenocytes. Both keratinocytes and fibroblasts are able to produce matrix metalloproteinases (MMPs), which cause the degradation of the extracellular matrix and contribute to cutaneous inflammation. An inhibitory effect of antidepressant drugs on MMP synthesis can, however, not be excluded, particularly because of the data showing the suppression of CHS after administration of MMP inhibitors (e.g., GM 6001) [18]. Moreover, our published and unpublished data indicate such an action of antidepressant drugs on MMP concentration in the blood of experimental animals [25]. In contrast, fibroblasts can also produce IL-15, which is involved in the regulation of CHS *via* T regulatory cells naturally occurring in the skin [5]. Wu et al. [42] have shown that depressive-like symptoms are partially reversed by fluoxetine acting through IL-15.

DC infiltration from skin to the local lymph nodes requires both MMP secretion (mainly MMP 9) and chemokines, e.g., MIP3-β and 6Ckine [21]. To date, there have been no extensive studies of the effect of antidepressant drugs on these chemokines. Nevertheless, it has been shown that fluoxetine is able to inhibit the mRNA expression of other chemokines, such as Groα, MIP1α and 1β, after spinal cord injury [27].

After infiltration into the lymph nodes, activated LC present the antigen to circulating naive lymphocytes in the context of MHC class II (i.e., PCL) or MHC class I (i.e., DNFB).

Depending on the specific antigen that has caused the CHS response, there may be two subtypes of T effector cells involved in the induction of DTH reactions, i.e., $CD4^+$ and $CD8^+$ [6, 23]. Numerous studies have indicated that the activity of T lymphocyte subpopulations is impaired by antidepressant drugs. While both Th1 $CD4^+$ and Tc1 $CD8^+$ are able to in-

crease INF-γ synthesis, antidepressants have negative immunomodulatory effects suppressing the production/synthesis of INF-γ [24, 28].

Diamond et al. reported a suppressive activity of serotonin (fluoxetine) or noradrenaline (desipramine) reuptake inhibitors on INF-γ production by human blood lymphocytes [8]. Animal studies also have shown the inhibition of IFN-γ production by Con A stimulated T cells following antidepressant administration [25].

On the contrary, a stimulatory effect of antidepressant drugs on T cell proliferative activity has been shown in *in vitro* and *ex vivo* investigations. The administration of imipramine, amitriptyline, fluoxetine and citalopram for 1 or 2 weeks enhanced the proliferative activity of splenocytes, although after four-weeks these effects were reversed [24]. Experiments with long-term fluoxetine and desipramine administration to control or contact-sensitized animals (PCL, DNFB) revealed the increased spontaneous proliferative activity of splenocytes and lymphocytes from the lymph nodes after drug administration and sensitization treatment. However, when contact sensitization and drug administration were performed simultaneously, the lymphocyte proliferative activity was inhibited. Increased proliferation occurs after both the application of antidepressants and sensitization and is an expected effect, while the inhibition of this process during simultaneous drug application and sensitization is difficult to explain, although desirable from the therapeutic point of view [6, 23].

Similarly, it was reported that the lymph nodes from contact-sensitized animals were two times heavier than those of control animals, while both desipramine and fluoxetine caused a statistically significant weight decrease. The increase in the cellularity of the lymph nodes after hapten challenge is caused by the increased total number of T and B lymphocytes. Drug efficacy in reducing the weight of the lymph nodes and the inhibitory effect of the drugs on lymphocyte proliferation during the DTH reaction are most likely the results of the suppressive action of antidepressant drugs at different stages of the immune response.

Liver NKT cells are activated very soon after immunization, and within 7 min, these cells release IL-4, which stimulates peritoneal antigen-specific B1 lymphocytes with the unique phenotype $Thy1^+CD5^+CD3^-CD4^-CD8^-$ to migrate to the spleen and local lymph nodes and to synthesize IgM specific to the hapten [2]. An inhibitory effect of the drugs on the activity of these subpopulations of lymphocytes could not be excluded. In DNFB-treated mice, desipramine and fluoxetine pretreatment inhibited the IL-4 production evoked by Con A-stimulated splenocytes and lymph node cells, suggesting an inhibitory action of these drugs on the synthesis of IL-4 by liver NKT cells [6].

On the other hand, IL-4 is considered to be a critical cytokine in the development of Th2 cells, which are able to directly inhibit Th1 or Tc1 cell proliferation, thus negatively regulating CHS responses [14]. The important inhibitory role of the NKT cells on CHS reactions has been shown in unpublished studies using sensitized CD1d knockout mice (CD1d expression is required for the development of NKT cells) with antidepressant co-treatment, although long-term drug administration did not affect the CHS response.

Several observations suggest that CHS is a highly regulated process. Despite the long-term persistence of the hapten in the skin, the reaction is complete by itself, suggesting that the regulatory mechanisms are actively involved in the completion of CHS. Contact hypersensitivity can be negatively regulated in the induction and effector phases of the immune response. Gorbachev et al. [15] have indicated that regulatory $CD4^+CD25^+$ T cells may have different inhibitory activities on CHS responses. This subset of lymphocytes is able to eliminate the Tc1-mediated CHS reaction (effector phase), and $CD4^+CD25^+$ cells may interfere with hapten-presenting DC cells (induction phase). This elimination is mediated by apoptosis through Fas-FasL interactions. The effectiveness of antidepressants in inhibiting the Tc1-mediated CHS response was shown in an experimental model of CHS with DNFB-treated mice [6]. In a Th1-mediated model of CHS, antidepressant drugs also effectively blocked the immune response, suggesting that antidepressants may act by decreasing DC activities. Another important player in the DTH inhibition is the type 1 regulatory T cell (Tr1), due to its ability to modulate IL-10 production [13].

It is worth noting that fluoxetine and desipramine administration stimulates IL-10 synthesis in the lymph nodes of DNFB-treated mice and IL-10 synthesis by splenocytes of PCL-treated mice [6, 23]. Moreover, Fei et al. [12] showed an inhibitory effect of astilbin, a flavanone isolated from *Rhizoma smilacis,* on the PLC-evoked CHS reaction and showed that this effect occurred *via* increased IL-10 produc-

tion. As mentioned before, IL-10 is a pleiotropic cytokine with inhibitory potential towards the pro-inflammatory cytokines responsible for CHS development. In several studies, it was observed that not only SSRIs (fluoxetine) and tricyclic antidepressants (desipramine) but also venlafaxine reduce the blood levels of IL-12, TNF-α, and IFN-γ and increase the levels of IL-10 and TGF-β [33].

Antidepressant drugs may affect the CHS reaction by modulating the level of neurotransmitters in the skin, where interaction takes place between the nervous and immune systems *via* neuromediators released by sensory nerves, autonomic nerves and immune cells. These neurotransmitters can modulate the function of the skin immune system *via* specific receptors on target cells. The skin of humans and rodents expresses the components of intrinsic serotonin biosynthetic pathways [39]. Serotonin and noradrenaline act *via* several receptor subtypes [19], and the duration of the serotonergic or adrenergic responses is determined by the activity of serotonin and adrenergic transporter proteins. The expression of serotonin and adrenergic receptors and transporters on human and murine lymphocytes, macrophages and dendritic cells [38] has been established. Moreover, neurotransmitters, mainly serotonin, have been suggested to mediate the signaling between lymphocytes and dendritic cells, the latter being key players in the induction of the CHS reaction [35]. Additionally, selective serotonin or noradrenaline reuptake inhibitors have been shown to modulate the activity of the cells of the immune system [13]. El-Nour et al. [10] showed that 5-HT_{1A} receptors were localized on mast cells and melanocyte-like cells, while 5-HT_{2A} receptors were detected on lymphocytes only and the serotonin transporter on lymphocytes, NK cells and LC cells.

In human contact eczematous skin, a decrease in the number of 5-HT_{1A} receptor-positive mononuclear cells and an increase in 5-HT_{2A} receptor-positive and SERT-positive cells was observed compared to control skin [10]. In contrast, it has been established that the 5-HT_{1A} receptor agonist buspirone, and the 5-HT_{2A} receptor antagonist ketanserin [1] decrease contact allergic reactions in mice. It is speculated that fluoxetine inhibits the contact sensitivity reaction *via* an increase in the serotonin level in mouse skin by stimulating 5-HT_{1A} receptors on mast cells and melanocyte-like cells and by attenuating the expression of 5-HT_{2A} receptors on T lymphocytes (e.g., Tc1 lymphocytes).

In summary, the available studies show that antidepressants may be useful in the treatment of ACD. Taking into account the mechanism of the CHS responses and the immunomodulatory properties of antidepressant drugs, there are several possible targets of antidepressants inhibiting inflammatory processes. Previous experimental investigations have demonstrated the effectiveness of antidepressants in the inhibition of the CHS responses when administered before, during or after cutaneous hapten application. However, it is unclear which stage(s) of the contact hypersensitivity reaction(s) are targeted by antidepressant drugs; thus, the mechanism underlying their therapeutic effects remains unknown. Nevertheless, these findings suggest that antidepressant drugs are useful in treating allergic patients with depression and depressive patients with allergy.

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