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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.

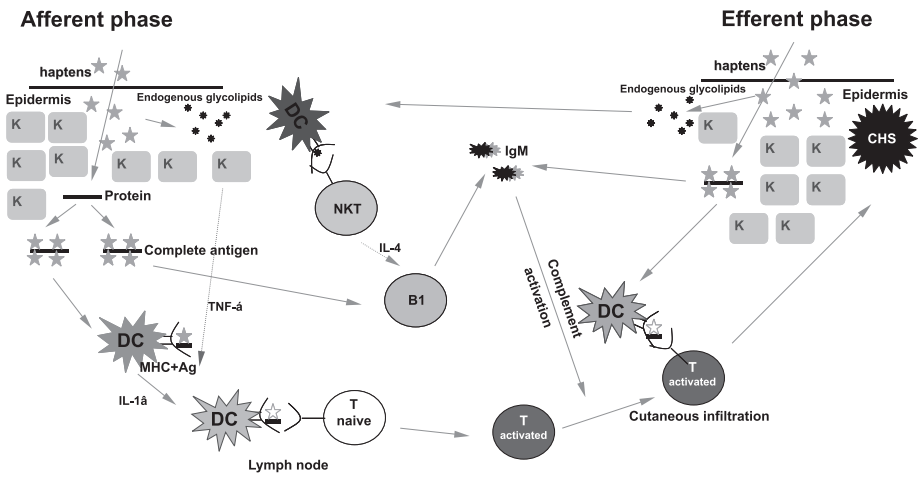

Fig. 1. The mechanism of the contact hypersensitivity reaction. Antidepressants can modulate particular stages of the hypersensitivity reaction, as described in the text. Ag – antigen, B1 – B1 B cell, DC – dendritic cell, K – keratinocyte, NKT – NKT lymphocyte, T – T lymphocyte

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