Identification of the molecule required for transmission of IL-31–induced itch sensation in the spinal cord

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Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by recurrent eczematous legions and intense itch. Itch can be induced by various chemical mediators. Among them, much attention has been paid to interleukin 31 (IL-31) as an AD-associated itch mediator since the discovery of the pruritogenic action of IL-31 in mice. IL-31 is mainly produced by $CD4^+$ T cells and transmits the signals via a heterodimeric receptor composed of IL-31 receptor A (IL-31RA) and oncostatin M receptor (OSMR), both of which are expressed in dorsal root ganglion (DRG) neurons. However, the neuronal mechanism underlying IL-31–induced itch sensation is poorly understood. By analyzing a mouse model for atopic dermatitis, we found that the expression of *Tac2*, which encodes neurokinin B (NKB), markedly increased in the DRG neurons in response to IL-31. While NKB-deficient mice lost IL-31–induced itch response, scratching behaviors induced by other pruritogens such as histamine, chloroquine and protease-activated receptor 2 (PAR2) agonist were unaffected in the absence of NKB. NKB transmits the signal through neurokinin 3 receptor (NK3R), a G protein-coupled tachykinin receptor. When wild-type mice were pre-treated with NK3R antagonists, IL-31–induced scratching was significantly attenuated, without affecting itch responses induced by other pruritogens. These results indicate that NKB-NK3R axis could be a novel therapeutic target controlling IL-31–induced itch in AD patients.