Brain allopregnanolone is involved in itch-associated scratching in atopic dermatitis mice

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[Background] Itch (or pruritus) is an unpleasant sensation that evokes a desire or reflex to scratch. Although over the last decade remarkable progress has been made in understanding neuronal molecular mechanisms of itch in the periphery and spinal cord, there are few studies on itch in the supraspinal central nervous system. Allopregnanolone (ALLO) is one of neurosteroids produced in the brain, but little is known about the relationship between ALLO and itch. We previously reported a unique, diet-induced mouse model for atopic dermatitis, the most common pruritic chronic skin disease (Fujii et al., Exp. Dermatol., 14, 460-468, 2005). In this model, administration of ethanol markedly aggravated itch-associated scratching, as in human atopic dermatitis (Fujii et al., Eur. J. Pharmacol., 611, 92-99, 2009). Therefore, we hypothesized that ALLO, which has similar actions to ethanol, is involved in itch-associated scratching in atopic mice.

[Methods] HR-1 hairless mice were fed the special diet (called HR-AD) to induce atopic dermatitis symptoms. Hindlimb scratching behavior was videotaped and then the cumulative duration of scratching bouts was determined by playing back the videotape. ALLO was extracted from whole brain samples and subsequently measured by enzyme immunoassay.

[Results] Intraperitoneal administration of ALLO dose-dependently and significantly increased scratching in atopic mice, but not in normal ones. ALLO increased scratching when administered intracisternally, but neither intrathecally nor intradermally, suggesting that ALLO-induced scratching was mediated mainly through a supraspinal mechanism. ALLO-induced scratching was significantly inhibited by a GABA₆ receptor antagonist picrotoxin, but neither the L-type voltage dependent calcium channel agonist Bay K 8644 nor the glutamate receptor agonist N-methyl-D-aspartate. Next, we examined whether endogenously produced ALLO is involved in ethanol-induced scratching in atopic mice, because it has been reported that ethanol increases ALLO in the brain. Oral administration of ethanol increased brain ALLO levels, which coincided with the increase in scratching. Pretreatment with finasteride, a synthetic inhibitor of ALLO, significantly suppressed ethanol-induced scratching and ALLO production in the brain.

[Conclusions] We first demonstrate that ALLO enhances itch-associated scratching in atopic mice, partly through brain GABA₆ receptors. Furthermore, ethanol-induced scratching may be mediated through endogenously produced ALLO.