

## **Neurosteroid-induced nociception through a histamine release is regulated by endocrine disrupting chemicals.**

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Most recently, we reported that dehydroepiandrosterone sulfate (DHEAS), a representative neurosteroid, induced nociceptive flexor responses when given intraplantarly in mice. In this study, the intraplantar application of DHEAS showed hyperalgesia in thermal or mechanical nociception test. The DHEAS-induced hyperalgesia was abolished by diphenhydramine (DPH), a H<sub>1</sub> histamine receptor antagonist. It was also blocked by progesterone (PROG), a putative antagonistic neurosteroid. Besides the nociceptive actions, DHEAS increased vascular permeability as measured with Evans blue plasma extravasation. Consistent with behavioral studies, it was blocked by DPH and PROG. On the other hand, endocrine disrupting chemicals (EDCs) are known to disrupt reproductive system in wildlives and humans through the disturbance of the endocrine homeostasis. One of the best known examples is the pesticide, DDT, and its metabolite, p,p'-DDE, is also thought to possess strong steroid modulatory actions. In this study, the nociception and vasodilatation induced by DHEAS were blocked by p,p'-DDE as well as PROG. In addition, bisphenol A, alkylphenols (4-nonylphenol and 4-octylphenol) and phthalates (di-n-butyl phthalate and di-2-ethylhexyl phthalate) showed similar results with p,p'-DDE. These results suggest that neurosteroid has significant nociceptive and vasodilatory actions through a histamine release, and EDCs regulate them.