

The Effects of Estradiol on Acetic Acid Induced Pain in Writhing Test in Female Mice

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Abstract—Steroid hormones can modulate pain response. The aim of this study was to investigate the effects of estradiol on pain induced by acetic acid injection in writhing test in female mice. In this laboratory experimental study, female mice were randomly divided to control and animals receiving morphine and rats receiving different doses of estradiol. Following intraperitoneally administration of hormone, pain threshold was measured using writhing test and data were analyzed using ANOVA. Our result showed that low, moderate and high dose of estradiol (100, 200 and 500 mg/kg/body weight, respectively) resulted in suppressing of pain induced by acetic acid injection ($P<0.05$). The findings suggest that estradiol plays a pivotal role in pain killing area.

Keywords---Estradiol, Pain threshold, Writhing Test, Female Mice

I. INTRODUCTION

PAIN is an unpleasant sensation that can range from mild, localized discomfort to agony. Pain has both physical and emotional components. The physical part of pain results from nerve stimulation. Pain may be contained to a discrete area, as in an injury, or it can be more diffuse, as in disorders like fibromyalgia. Pain is mediated by specific nerve fibers that carry the pain impulses to the brain where their conscious appreciation may be modified by many factors. Pain is a feeling triggered in the nervous system [1]. Pain is one of the most common and distressing symptoms experienced by many patients. Pain is known to negatively affect all aspects of health-related quality of life, including physical, emotional, social, and role functioning [2]. Evidences of gender-specific differences exist in the receiving pain [3]-[5], indicating that sex steroid hormones play significant role in pain perception. There are many evidences indicating that administration of steroids help relieve pain [6]-[8]. Among steroids, estradiol is most important estrogen acting on many organs [9] and is expected to modulate pain perception. Estradiol, or more precisely, 17 β -estradiol, is the primary female sex hormone. Estradiol is essential for the development and maintenance of female reproductive tissues but it also has important effects in many other tissues including bone. Estradiol is produced especially within the follicles of female ovaries, but also in other endocrine (i.e., hormone-producing) and non-endocrine tissues (e.g., including fat, liver, adrenal, breast, and neural tissues) [10].

The main aim of this study was to investigate the effects of different doses of estradiol on pain induced by acetic acid injection in writhing test in female mice.

II. MATERIAL AND METHODS

A. Animals

Adult mice were purchased and raised in our colony from an original stock of Pasteur institute (Tehran, Iran). The temperature was at 23 ± 2 °C and animals kept under a schedule of 12h light:12h darkness (light on at: 08: 00 a.m.) with free access to water and standard laboratory chow. Care was taken to examine the animals for general pathological symptoms. Food was withheld for 12-14h before death.

B. Protocol of Study

In this laboratory experimental study, female mice were randomly divided to control group (receiving normal saline), and animals receiving morphine and groups receiving low, moderate and high dose of estradiol (100, 200 and 500 mg/kg/body weight, respectively). Pain threshold was measured by acetic acid induced writhing test. In the trend of this test, mice were injected intraperitoneally with 0.6% aqueous acetic acid (10ml/kg) 1hr after injection of morphine (as positive control) or estradiol. The number of writhing movement of each mouse was counted for 10min, starting from 5 min after the injection of acetic acid. All animal experiments were carried out in accordance with the guidelines of Institutional Animals Ethics Committee.

C. Statistical Analysis

Statistical significance was evaluated by one-way analysis of variance (ANOVA) using SPSS 19. Significance was measured using Fisher's least significant for the exact P values and significant differences. Differences with $P<0.05$ were considered significant.

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III. RESULTS

Figure I shows recorded time (latency) before and 30 minutes and one hour after estradiol injection in female mice.

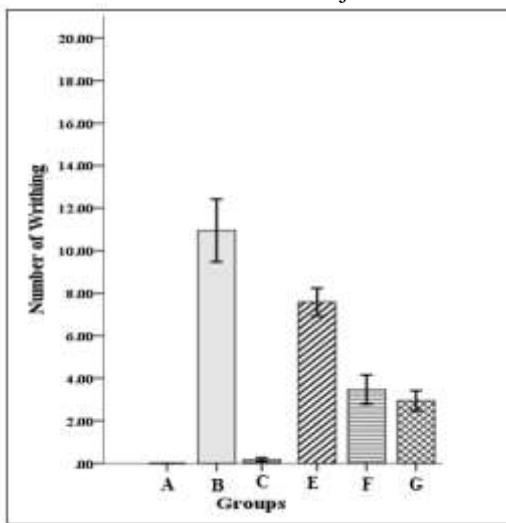


Fig. 1 Number of writhing in female mice. A: control (normal saline receiving), B: acetic acid receiving, C: morphine (10mg/kg) receiving, E: estradiol (100mg/kg) receiving, F: estradiol (200mg/kg) receiving, and G: estradiol (500mg/kg) receiving rats.

The results of the present study show that there was writhing movements in acetic acid receiving groups; however, no writhing was observed following injection of normal saline. Morphine injection also almost completely suppressed writhing induced by acetic acid ($P<0.0001$). low, moderate and high dose of estradiol (100, 200 and 500 mg/kg/body weight, respectively) also resulted in suppressing of pain induced by acetic acid injection ($P<0.05$). Our findings also indicated that with increasing of hormone dose, the suppressing effect increases proportionally.

IV. DISCUSSION

Our study indicated that administration of etsradiol can suppress the pain induced by chemical substances (such as acids) in females. In line with our findings studies show that several hormones, including sex steroid hormones, can influence pain perception [11]. The studies show that administration of the ovarian steroid estradiol in male and female animals h have neuromodulatory and neuroprotective effects in a variety of experimental models [12]. There are also reports indicating that a pharmacological dose of estradiol reduces central pain possibly via suppression of glial activity in VPL region in nervous system [13]. The studies also showed that nomegestrol acetate and 17 β -estradiol was associated with a significant reduction in menstrual pain [14]. However, in contrast to our finding, there are reports suggesting that in humans, contrary to experimental animals, changes in estrogen levels have little influence on pain sensitivity [15]. It has also been shown that estrogen can cause rapid reduction in the mechanical pain threshold leading to enhanced pain sensitivity [16]. In mechanism of action, etradiol can relieve pain by acting on its receptors resulting in enhanced bradykinin signaling in peripheral sensory neurons of female rats [17]. On the other hand, findings suggest that estrogen

regulates peripheral pain by acting on its receptors in primary afferent neurons, which probably involves the intracellular pathway [18].

In general, high estrogen results in an increase in pain-blocking neurochemicals, whereas pain-producing neurochemicals increase when estrogen falls to low levels [19] , [20].

V. CONCLUSION

The findings suggest that estradiol plays a pivotal role in pain killing area. So, pain is partly modulated by estradiol particularly in females.

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