Effect and mechanism of action of histamine on rat uterine contractility in relation to sex steroid hormones.

Thesis

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The uterus belongs to that group of smooth muscles that are spontaneously active. This means that, without any nervous or hormonal stimulation, a trip of isolated, pregnant or non- pregnant uterus will produce spontaneous contractions.

Many factors affect uterine muscle excitability and contractility, like mechanical and hormonal factors. The hormonal factors include ovarian hormones and other hormones and factors, such as oxytocin, prostaglandins, serotonin, nitric oxide, relaxin, adrenomedullin and histamine.

Histamine plays an important role in the regulation of uterine motility. The mechanical responses induced by histamine on the uterine smooth muscle vary according to species. Moreover, the H_1 and H_2 receptors have been demonstrated to be present on smooth muscle cells and to be involved in the effect of histamine on the uterus.

The aim of this work was therefore to investigate in adult non-pregnant rat the effect of histamine on uterine contractility and to determine through which type of receptors it acts. The aim was also to examine

whether this action of histamine was modulated by sex steroid hormones. Finally it was determined whether Ca^{2+} and K^{+} channels were involved in the mechanism of action of histamine in rat uteri.

The experiments were classified into four groups:

1. Non-pregnant group,
2. Ovariectomized group,
3. Ovariectomized progesterone-replaced group.
4. Ovariectomized oestrogen-replaced group.

Histamine in a dose of 10^{-4}M had a significant inhibitory effects on the contractility of non-pregnant uterine rat. In the Ovariectomized group, however it cause a significantly lower inhibitory effect than in the non-pregnant group, indicating that the strong inhibitory effect of histamine observed in mature rats is influenced by ovarian hormones. In both the oestrogen and progesterone replaced groups histamine caused a significant inhibition of the spontaneous uterine contractions almost stopped. These results suggest that both oestrogen and progesterone augment the effect of histamine on uterine contractions.

In all groups pretreatment of the uterus with H_1 and H_2 receptor blockers were examined. Pretreatment with H_1 receptor blocker in a dose of 9×10^{-6}M did not modify the inhibitory effect of

histamine on uterine contractility, while pretreatment with H_2 receptor blocker in a dose of 10^{-6}M completely abolished the inhibitory effect of histamine in all the experimental groups. These results demonstrated the presence of H_2 receptors in the mature rat uterus and that histamine produces inhibition of the spontaneous uterine contractility in the rat via these receptors.

In the control group the Ca^{2+} channel blocker and K^+ channel blocker were first applied alone then followed by histamine. The Ca^{2+} channel blocker verapamil in a dose of 0.12 µgm alone caused significant inhibition of uterine contractility (25%). When histamine was given after verapamil, it caused further inhibition of uterine contractility (95%). Compared to the effect of histamine alone about (70%), it appears that the effect of both together was equal to the sum of both. These results indicate that Ca^{2+} is required for normal uterine contractility, and that the inhibitory action of histamine does not seem to occur directly via Ca^{2+} channels.

The K^+ channel blocker tetraethyamonium in a dose of 10mM alone caused a significant increase in the height of uterine contractions about (20%). Histamine after tetra ethylamounium significantly reduced these contractions about (45%), but its

relaxant effect was significantly lower than recorded in control group about (70%). This indicated that K^+ channels play a role in the mechanism of action of histamine in uterine contractility.

In conclusion, this study shows that histamine had a relaxant effect on the spontaneous contractility of rat uterine strips obtained from all experimental groups. This inhibitory effect seems to be mediated via H_2 receptors. Both oestrogen and progesterone augmented the observed effect of histamine.

Finally, Ca^{2+} channels do not seem to be involved in the mechanism of action of histamine in the inhibition of uterine contractility, but histamine seems to act partially via K^+ channels, although other inhibitory mechanisms are probably also involved