THE EFFECT OF INTRALUMINALLY ADMINISTERED DRUGS ON IMPLANTATION IN NORMAL PREGNANT RATS

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It has been suggested that histamine released by an oestrogen surge at the time of implantation plays an important part in nidation of the fertilized ovum in the rat. These observations were based on findings by Shelesnyak and his co-workers that (a) administration of intraluminal histamine caused an induction of deciduomata, (b) intraluminal administration of histamine antagonists could inhibit deciduomata, (c) intraluminal administration of histamine antagonists could inhibit ovum implantation, and (d) systemic administration of histamine and histamine-releasing agents induced deciduomata (Shelesnyak 1952a, b, c, 1954; Kraicer & Shelesnyak, 1958). These workers also observed a fall in the level of the histamine content of the uterus at the time of implantation. The results of other investigators have, however, not confirmed this hypothesis (Finn & Keen, 1962; Wrenn, Bitman, Cecil & Gilliam, 1964). Tachi, Tachi & Lindner (1970) have also shown that intraluminal administration of pyrrathiazine, promethazine and benadryl into the uterus of pseudopregnant rats at dose levels reported to suppress the decidual reaction caused extensive necrosis of the endometrium. The suppression of the decidual reaction could not, therefore, be attributed to the antihistaminic action of these drugs.

In this study, the possible rôle of histamine in implantation has been investigated by studying the effect of intraluminally administered drugs which release histamine, such as Compound 48/80 and polymixin β sulphate, antihistaminic drugs such as dimethindene maleate and pheniramine maleate, another pharmacologically active agent found in the uterus, 5 hydroxytryptamine, and the 5 hydroxytryptamine antagonistic drug, 1-methyl-d-lysergic acid butanolamide (ULM-491), on implantation in normal pregnant rats. These drugs were administered at different doses on Days 3 and 4 of pregnancy.

Adult female rats of proven fertility were left overnight with males and the presence of thick clumps of spermatozoa in the early morning vaginal smear was taken to indicate Day 1 of pregnancy. These females were then left in separate cages and on Day 3 or 4 of pregnancy, the rat was anaesthetized with ether and the uteri exposed. Intraluminal administration of the test drug was made into the uterine horn as described by Wrenn *et al.* (1964) with the modification that,

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whereas these investigators did not administer anything in the control horn, the same volume of normal saline, 0.05 ml or 0.1 ml according to the experiment, was administered by means of a No. 30 gauge needle with blunt point into the control horn. The animals were subjected to laparotomy on Day 10 of pregnancy to observe the number of implantation sites.

TABLE 1
THE EFFECT OF INTRALUMINALLY ADMINISTERED DRUGS ON IMPLANTATION IN NORMAL PREGNANT RATS

Substance administered intraluminally	Dose (μ g)	Day of pregnancy of recipient rats	Mean no. of implantation sites on Day 10 of pregnancy. 5 D		Statistical significance (P)
			Right horn (control)	Left horn (treated)	
Compound 48/8	10	3	4.2 $\pm$ 2.8	3.4 $\pm$ 2.0	> 0.05
Polymixin β sulphate	10	3	3.5 $\pm$ 2.5	3.3 $\pm$ 2.49	> 0.05
Polymixin β sulphate	10	4	3.0 $\pm$ 2.2	3.4 $\pm$ 2.1	> 0.05
Dimethindene maleate	10	3	2.8 $\pm$ 2.5	3.6 $\pm$ 2.1	> 0.05
Dimethindene maleate	10	4	5.4 $\pm$ 1.8	4.8 $\pm$ 2.2	> 0.05
Dimethindene maleate	50	3	5.2 $\pm$ 2.6	3.0 $\pm$ 1.5	> 0.05
Pheniramine maleate	10	3	3.1 $\pm$ 3.0	2.5 $\pm$ 2.8	> 0.05
Pheniramine maleate	10	4	2.4 $\pm$ 2.3	1.8 $\pm$ 2.0	> 0.05
Pheniramine maleate	20	3	2.9 $\pm$ 2.4	2.5 $\pm$ 1.8	> 0.05
5-Hydroxytryptamine	50	4	4.4 $\pm$ 1.2	2.4 $\pm$ 2.0	> 0.05
5-Hydroxytryptamine	200	3	5.0 $\pm$ 1.5	2.4 $\pm$ 1.8	> 0.05
5-Hydroxytryptamine	200	4	3.0 $\pm$ 3.0	2.4 $\pm$ 2.5	> 0.05
5-Hydroxytryptamine	200	6	2.8 $\pm$ 3.3	4.2 $\pm$ 2.4	> 0.05
Lysergic acid butanolamide	50	3	4.6 $\pm$ 1.8	4.0 $\pm$ 3.0	> 0.05
Lysergic acid butanolamide	50	4	2.8 $\pm$ 1.9	2.0 $\pm$ 2.0	> 0.05

Table 1 shows the substance and dose administered, and the number of implantation sites in both uterine horns on Day 10 of pregnancy. The results indicated clearly that, at the doses used, histamine-releasing agents, anti-histaminic drugs, 5-hydroxytryptamine and the 5-hydroxytryptamine blocking agent administered intraluminally on Day 3 or 4 of pregnancy had no effect on subsequent implantation. The results do not provide any support for the hypothesis that histamine has any such rôle to play in the implantation of the fertilized ovum.

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