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Role of indomethacin-induced peptic ulceration in gastric acid secretion in pregnant rats

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Summary

The role of indomethacin-induced peptic ulceration in gastric acid secretion was investigated using albino rats of Wistar strain in early, mid and late pregnancy. The weight ranged between 120 and 180 gm. Non-pregnant rats in estrus served as control. Estrus was induced using the method of Dejalon, Bayo and Dejalon[1] while pregnancy was induced using the method of Bolarinwa and Amure[2,3]. Stomach for perfusion was prepared according to Ghosh[4] with some modification and perfusion was done with 0.15M NaCl solution, using the modified Langerdoff's apparatus. Gastric acid secretion was induced with histamine and carbachol.

In general, gastric acid secretion was found to be higher after indomethacin administration than in a control study, and the secretory response was higher to carbachol than to histamine in either case. In rats to which indomethacin had been administered, basal and induced gastric acid secretion was highest in the non-pregnant rats and least in the early-pregnant rats.

Resume

Le role de L'ulceraton peptique induite per L'indomethacine dans le secretion de L'acide gastrique a ete etudie utilisant des rats albinos du type Wister au debut, au milieu et vers la fin de la grocesse. Le poids se situeait entre 120 et 180gms. Les rats non-enceintes dants l'estrus servaient de reference.

L'estrus a ete induit en utilisant la methode de Dejalon, Bayo et Dejalon[1] alors que la grocesse e ete induite par la methode de Bolarinwa et Amure[2,3]. L'estomac pous la perfusion a ete prepare selon Ghosh[4] avec quelques modifications, et la perfusion a ete effectuee avec une solution NaCl de 0.15M avec L'appreil de Langerdoff modifie. La secretion de l'acide gastrique etait induite avec L'histamine et carbachol.

En generale, nous avons observe que la secretion de l'acide gastrique etait plus elevee apres l'administration de L'indomethacin que dans l'etude servant de reference, et la response secretrice etait plus elevee avec Le carbachol qu'avec L'histamine dans les deux cas. Pour les rats qui ont subit une administration de L'indomethacine la secretion basale ef de L'acide gastrique etait 'le plus elevee dans les rats non- enceintes et le plus faible dans celles en debut de grocesse.

Introduction

Previous work by Walsh *et al*[5] showed that ulcer patients maintained abnormally high rates of acid secretion at low intra-gastric pH. This abnormal pattern of secretion became apparent during the second hour after stimulation with a meal. One possible reason why acid secretion failed to decrease normally at low pH in ulcer patients was that gastrin release was not suppressed normally. Indeed, acid suppression of gastrin was significantly less in ulcer patients during the second postprandial hour. It has also been shown that pregnancy effects the gastric acid secretory response in different species of animals. Diminished secretion of pepsin and hydrochloric acid (HCl) occurs during pregnancy in women[6] and in the rats[7].

It is however not known if pregnant rats with ulcer are able to maintain higher rates of acid secretion than non-pregnant rats without ulcer. Previous work has been restricted to the study of gastric acid secretion in non-pregnant ulcer patients[5] normal pregnant women[6] and normal pregnant rats[2]. We now report on the role of indomethacin-induced peptic ulceration in gastric secretion induced by histamine and carbachol in pregnant rats.

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Materials and Method

Pregnant and non-pregnant female albino rats of Wistar strain bred in our laboratory and weighing between 120 and 180gm were used. The rats were mated by putting one male to two female rats in a cage, and the first appearance of sperm in a daily vaginal smear was taken as day 1 of pregnancy. All the non- pregnant rats were in estrus prior to being used. The rats were divided into groups 1 and 2. Rats in group 1 were studied for gastric acid secretion in the absence of induced ulceration, while in group 2 rats, ulceration was induced with indomethacin (40mg/kg body weight), given oro-gastrically by means of an oral dosing needle from a suspension of indomethacin in distilled water (10mg/ml), four hours prior to the gastric acid secretory studies. Preliminary trials showed that a dose of 40mg/kg body weight of indomethacin produced gastric ulceration in all rats in 4 hours, a finding similar to that of Djahanguiri and Zamindast[8]. Each group was divided into four subgroups. Subgroup I was made up of normal non-pregnant rats in estrus, subgroup II was made up of rats in early pregnancy (2-3 days pregnant), subgroup III was made up of rats in mid-pregnancy (12- 14 days pregnant), while subgroup IV was made up of rats in late pregnancy (18-20 days pregnant). They all had free access to food and water prior to the experiment.

Anaesthesia was induced with urethane (0.6ml/100gm body weight of a 25% W/V solution) given intramuscularly; this maintained uniform anaesthesia for up to 10 hours. Stomach for perfusion was prepared according to Ghosh[4] with some modifications, using the modified Langerdoff's apparatus. The perfusion fluid was 0.15M NaCl, and 5ml of effluent (10 ± 2ml) collected every 10 minutes was titrated to end point against N/400 NaOH using phenolphathalein as indicator. Acid secretion was induced with histamine (1.0mg/kg body weight) and carbachol (1.0mg/kg body weight). All injections were given intravenously, slowly through a cannulated femoral vein, at volumes of 0.2-0.3ml depending on body weight.

Results

The results (Tables 1 and 2) of the gastric acid secretory studies showed that in general, gastric acid secretion was higher after indomethacin administration than in a control study, and that the secretory response was higher to carbachol than to histamine in either case. Also, in the absence of indomethacin administration, induced gastric acid secretion was higher in the late pregnant rats than in other groups of rats, and least in the early pregnant rats. However, basal secretion was least in the mid-pregnant rats.

Discussion

In the rats with indomethacin-induced peptic ulcer, the relatively low basal and induced gastric acid secretion in the pregnant rats, as compared to the non-pregnant rats, was in agreement with earlier reports that there was a significant reduction in acid secretion during pregnancy in rats[7]. This may be due to the high blood estrogen level at this time. The higher acid secretion during late pregnancy in relation to other stages of pregnancy might be due to high concentration of progesterone fairly well sustained throughout the second half of gestation[9]. While there is no evidence to show that progesterone itself increases acid secretion, it might inhibit the action of estrogen in decreasing acid secretion.

In conclusion, the present study has confirmed that pregnancy in the rat decreases gastric acid secretion, and except for basal acid secretion in mid-pregnant rats, the presence of indomethacin-induced gastric ulceration stimulates basal and induced gastric acid secretion in pregnant rats.

Tables 1 and 2 show gastric acid secretion in response to histamine (1.0mg/kg body weight) or carbachol (1.0mg/kg body weight) in pregnant rats. Acid values are all expressed in mequiv HCl/hr.

Table 1: Without indomethacin

State of Rat	Basal Secretion	Histamine (1.0mg/kg)	Carbachol (1.0mg/kg)
Non-pregnant in Estrus	0.25 ± 0.01	1.10 ± 0.01	1.21 ± 0.02
Pregnant for 2-3 days (early pregnancy)	0.17 ± 0.02	0.66 ± 0.01	0.73 ± 0.01
Pregnant for 12-14 days (mid-pregnancy)	0.16 ± 0.01	0.65 ± 0.01	0.85 ± 0.02
Pregnant for 18-20 days (late pregnancy)	0.27 ± 0.02	1.16 ± 0.02	1.23 ± 0.01

Table 2: After indomethacin

State of Rat	Basal Secretion	Histamine (1.0mg/kg)	Carbachol (1.0mg/kg)
Non-pregnant in Estrus	0.74 ± 0.01	1.72 ± 0.01	1.98 ± 0.01
Pregnant for 2-3 days (early pregnancy)	0.58 ± 0.03	1.00 ± 0.01	1.21 ± 0.01
Pregnant for 12-14 days (mid-pregnancy)	0.66 ± 0.01	1.05 ± 0.02	1.40 ± 0.01
Pregnant for 18-20 days (late pregnancy)	0.68 ± 0.03	1.54 ± 0.01	1.82 ± 0.01

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