Acid gastric secretion induced with gastrin and histamine in pregnant rats

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Earlier workers have shown that pregnancy affects the gastrin acid secretory response in different species. Diminished secretions of pepsin and hydrochloric acid occur during pregnancy in women (Artz, 1930; Strauss & Castle, 1932; Labate, 1939; Way, 1945; Murray, Erskine & Fielding, 1957; Hunt & Murray, 1958) in the rat (Lozzio, Gagliardi & others, 1961), although in the dog no consistent change in acid gastric secretion was found (McCarthy, Evans & Dragstedt, 1954; Clark, 1957). These have led many workers to seek a relation between female sex hormones, chorionic gonadotrophins and acid gastric secretion. Most of the previous work has been restricted to the study of basal acid secretion and we now report on the parietal cell response to gastrin and histamine.

Pregnant rats, mated in our laboratory, and non-pregnant rats, 180–220 g were used. Vaginal smears were taken daily and the first appearance of sperm was taken as day 1 of pregnancy. The rats were studied in either early, mid or late pregnancy—days 1–7, 8–14 and 15–22 respectively. Most rats were used between days 2–3, 12–14 and 18–20 respectively. They were allowed access to food and water. Anaesthesia was induced with urethane (6 ml of a 25% w/v solution kg^{-1} body wt) intramuscularly; this maintained a uniform anaesthesia for up to 10 h. Stomachs for perfusion were prepared according to Ghosh & Schild (1958) with some modifications. The perfusion fluid was 0·15 M NaCl and 5 ml of effluent (10 ± 2 ml) collected every 10 min was titrated against M/400 NaOH using phenolphthalein as indicator. All injections were given intraventricularly, slowly through a cannulated femoral vein (volumes of 0·05 to 0·3 ml depending on body wt). Gastrin or histamine in specified doses were given to all the rats in a randomized order.

Histamine dihydrochloride was from L. Light & Co. and synthetic human gastrin I from ICI Ltd.

Except in late pregnancy the basal acid secretion was low. The highest acid secretion was obtained during the second 10 min collection with either secretagogue and it took about 6–8 collections before the secretion returned to pre-injection level. Only then were other injections given. Responses to the same dose of secretagogue are shown in Table 1.

Gastric acid secretory responses to histamine in all the animals were typical and agreed with the pattern shown by Ghosh & Schild (1958) and Amure & Ginsburg (1964). In all the experiments the greatest amount of acidity was recorded during the second 10 min collection. Both mid and late pregnant rats appeared to respond more to histamine than did the non-pregnant rats ($P < 0·01$).

Table 1. *Responses to gastrin (0·5 or 1·0 μg kg^{-1} body wt) or histamine (0·5 or 1·0 mg kg^{-1} body wt in pregnant and non-pregnant rats.*

Stage of Pregnancy (n)	m equiv HCl				
		Histamine		Gastrin	
	Basal Sec.	0·5 mg kg^{-1}	1·0 mg kg^{-1}	0·5 μg kg^{-1}	1·0 μg kg^{-1}
Early (10)	0·16 ±0·02	0·30 ±0·02	0·58 ±0·01	0·62 ±0·01	1·14 ±0·01
Mid (11)	0·16 ±0·05	0·34 ±0·04	0·74 ±0·01	0·80 ±0·02	1·54 ±0·03
Late (13)	0·25 ±0·02	0·56 ±0·06	1·18 ±0·02	1·60 ±0·02	3·94 ±0·06
Non-preg. (Proestrus) (10)	0·20 ±0·02	0·46 ±0·02	0·66 ±0·02	0·71 ±0·04	1·50 ±0·03

The acid secretory responses were greater to gastrin than to histamine in all animals ($P < 0·02$). The pattern of response was similar to that of histamine, but took a longer time to reach back to pre-injection levels. The pregnant rats appeared to respond more to gastrin than did the non-pregnant rats. Mid pregnant > non-pregnant ($P > 0·02$) late pregnant > non-pregnant ($P > 0·001$).

The low basal acid secretion in both the early and mid pregnant rats is in agreement with earlier reports that there was a significant reduction in acid secretion during pregnancy in rats (Lozzio & others, 1961). The higher acid secretion during late pregnancy might be due to high concentrations of progesterone fairly well sustained throughout the second half of gestation (Greenwald & Best, unpublished observation in rats and mice as reported by Baranczuk & Greenwald, 1974). While there is no evidence to show that progesterone itself increases acid secretion, it might influence the action of oestrogen.

The varying responses of the animals at different stages of pregnancy are consistent with the increase in the population of the parietal cells at this period (Crean & Rumsey, 1971; Bolarinwa, 1975). They might also be due to the influence of oestrogen on acid secretion, and perhaps the high response in late pregnancy is due to a decline in the circulating oestrogen at this stage. There are conflicting reports about human acid secretion and amelioration of ulcer symptoms during pregnancy. Ulcer symptoms in some pregnant women do not seem to improve during pregnancy but this might be due to other factors such as the presence of a great deal of histaminase in the plasma which could well affect response to secretory stimuli.

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On the relation between the analgesic activity of meptazinol and its plasma concentrations in rats, mice and monkeys

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Meptazinol, [m-3-ethyl-1-methylhexahydro-1H azepin-3-yl)phenol hydrochloride] has been shown to possess analgesic properties in animals (Goode & White, 1971) and to be capable of relieving severe pain in man (Oosterlinck & De Sy, 1975). This communication describes studies carried out to determine whether a relation exists between the intensity of the drug's effects and its plasma concentrations.

Preliminary indications that such a relation might exist were seen from the higher plasma concentrations and the greater potency associated with an intravenous compared with an oral dose of the drug. More extensive studies have now been carried out in which the intensity of the analgesia has been compared with the plasma concentrations of the drug in rats, mice and monkeys.

Analgesic activity in rats was measured by the tail flick test described by D'Amour & Smith (1941). Thus a group of eight female rats received the drug orally at 25 mg kg^{-1} while another group was dosed intravenously at 8 mg kg^{-1}. The intensity of the analgesia was measured at various times up to 8 h after dosing. Plasma concentrations of meptazinol were determined by the method described by Franklin, Aldridge & White (1976) using additional groups of animals dosed with N-$^{14}CH_3$-labelled material. Drug concentrations in a plasma at the precise time of measurement of analgesia were derived from a graph of $\log_{10}$ observed plasma concentrations against time.

Analgesic activity in mice was measured by the acetylcholine-induced writhing test described by Collier, Hammond & others (1964). Thus groups of ten male mice were dosed orally with meptazinol at 25 mg kg^{-1} and the analgesic activity determined at various times up to 2 h after dosing. Plasma concentrations of the drug were determined on pooled samples obtained from groups of five mice which were killed at various times after receiving the ^{14}C-labelled drug at 25 mg kg^{-1}. Again drug concentrations at the precise times of measurement of analgesia were derived from regression analysis of the observed data points.

The results presented in Fig. 1 show that there was a good correlation of analgesic activity and plasma concentrations of the drug. After oral administration of the compound to rats a correlation coefficient of 0·80 (n = 7) was found between $\log_{10}$ plasma concentration and intensity of analgesia. A somewhat better correlation coefficient of 0·90 (n = 7) was observed after intravenous dosage of the compound.

In mice an excellent correlation of analgesic response and plasma concentration was observed, the correlation coefficient being 0·96 (n = 11).

Although no similar studies were conducted in monkeys, no analgesic activity could be demonstrated in the Rhesus monkey after oral administration of the compound up to 80 mg kg^{-1} (Malis, unpublished results) and plasma concentrations in the Patas

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