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Effect of hyperprolactinaemia as induced by pituitary homografts under kidney capsule on gastric and duodenal ulcers in rats

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Abstract

The effect of hyperprolactinaemia, induced by two or four pituitary homografts under the kidney capsule, on gastric and duodenal ulcers has been studied. The acute gastric ulcer models used were pylorus ligation, indometacin-induced and ethanol-induced gastric ulcers. Chronic gastric ulcers were induced using acetic acid and duodenal ulcers by mercaptamine hydrochloride. After pylorus ligation, there was an approximate 30–40 % increase in gastric secretion, a significant increase in total acidity ($P < 0.01$) and in the ulcer index ($P < 0.01$) in rats bearing pituitary homografts under the kidney capsule when compared with the sham-operated control. Hyperprolactinaemia did not affect the formation of ethanol-induced gastric ulcers but showed a 40 % reduction in the development of indometacin-induced gastric ulcers. It also produced a 20 % increase in the ulcer index in acetic acid-induced chronic gastric ulcers and a 30 % increase in ulcer area in mercaptamine-induced duodenal ulcers. Our results showed that hyperprolactinaemia induced gastric acid secretion and thereby aggravated gastric and duodenal ulcers in rats. Hyperprolactinaemia did not affect gastric cytoprotection.

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Introduction

Prolactin, a mammotrophic hormone, is reported to have a wide range of effects including maternal behaviour, grooming behaviour, sexual behaviour, feeding behaviour, reproductive functions, sleep–awake cycles and stress responses in addition to its endocrine function (Dutt et al 1994). Previously, we had reported that prolactin exhibited antinociceptive action (Ramaswamy et al 1983) and prolactin modulated small intestine function (Pillai et al 1981; Gopalkrishnan et al 1981). Besides, it is documented that prolactin reduced stress-induced gastric ulcers in rats (Drago et al 1990; Fujikawa et al 2000). In contrast, other dopamine receptor antagonists like domperidone, metoclopramide and haloperidol, which raise serum as well as cerebrospinal fluid (CSF) levels of prolactin, have been shown to induce gastric lesions in rats (Simpkins 1992). Prolactin binding sites have been identified in different regions of the gastrointestinal tract (Lobie et al 1993), and it is reported that prolactin receptors are present in the oxyntic cells of the fundic glands in the stomach (Nagano et al 1995; Garcia-Caballero et al 1996). The possibility of prolactin influencing gastric secretion by acting at these receptors has been excluded (Nagano et al 1995).

Prolactin has been shown to gain access to the brain and has been quantitated in the hypothalamus as well as the CSF (Login & Macleod 1977). Most of the actions

of prolactin are mediated through the activation of tuberoinfundibular dopamine (TIDA) neurons, which are outside the blood–brain barrier (Gudelsky & Porter 1980). A variety of other dopaminergic and non-dopaminergic neuronal systems which are located inside the blood–brain barrier participate in prolactin action as well. Prolactin alters neuronal activity in different regions of the hypothalamus also (Hnasko & Buntin 1993; Roky et al 1994; Bridges et al 1997).

There is a marked gastric acid hypersecretion during pregnancy and lactation in rats. The possible role of sex hormones contributing to this effect has been ruled out since when they were administered exogenously a decrease in gastric acid secretion was evident in rats (Takeguchi & Okabe 1984).

In this study, we have investigated the effect of hyperprolactinaemia induced by implantation of adenopituitaries under the kidney capsule on gastric acid secretion and on experimentally-induced gastric and duodenal ulcers in rats.

Materials and Methods

Animals

The experimental protocol was approved by the doctoral committee and the guidelines for animal care were strictly adhered to during experimentation as recommended by the Indian National Science Academy, New Delhi in 1992.

Male Wistar rats (130–150 g) from the Central Animal House of Jawaharlal Institute of Post-Graduate Medical Education & Research, Pondicherry, were used. During fasting, rats were kept in cages with wire grid bottoms to prevent coprophagy. Rats were divided into groups of six to seven animals and were maintained on a 12-h light–dark cycle.

Induction of hyperprolactinaemia (Mena et al 1968)

Hyperprolactinaemia was induced by implanting either two or four adenopituitaries under the kidney capsule. The pituitary transplantation was carried out as follows. Under ketamine anaesthesia (100 mg kg^{-1}, i.p), the kidney was exposed through a flank incision and a 2-mm slit was made in the midportion of the capsule. Through this slit a small pocket was made with a flattened metal rod on the ventral surface of the kidney between the capsule and the parenchyma. The pituitaries were inserted into the pocket and the kidney capsule was closed by interrupted sutures using 6-0 absorbable surgical catgut. The kidney was then replaced carefully into the abdominal cavity, and the wound was closed. Both the kidneys were used for implantation and each of them received half of the implants. The control group rats were sham operated. The animals were allowed 10 days of recovery before being subjected to ulcerogenic procedure. The acceptance of the homograft was confirmed by histological examination and serum prolactin estimation.

Prolactin radioimmunoassay

Serum prolactin estimation was carried out on the eleventh day as per the procedure described in the brochure supplied by the National Pituitary Agency (National Institutes of Health, Bethesda, MD), with modification as reported by Balasinor et al (1993). The minimum detection limit for prolactin (NIDDK-Rat-prolactin-RP-3) was 50 pg mL^{-1}. Inter-assay and intra-assay variations were 13 % and 6 %, respectively.

Acute gastric ulcer

Pylorus-ligated (Shay) rat (Shay et al 1945)

Rats were fasted for 48 h and pylorus ligation was performed under light ether anaesthesia. Nineteen hours after pylorus ligation animals were killed, the stomach was isolated from the body and its contents were collected, measured and centrifuged. The contents were subjected to free and total acidity estimation. The stomach was cut open and the surface was examined for ulceration. The ulcer index was calculated by using the equation:

$$\text{ulcer index} = 10/X$$

where X = total mucosal area/total ulcerated area.

Indometacin-induced gastric ulcers (Dijoseph et al 1987)

Rats were fasted for 36 h and then indometacin (suspended in 1 % carmellose) was given orally at a dose of 20 mg kg^{-1} body weight. Four hours later, animals were killed and their stomachs were examined for lesions and the ulcer index was determined as described above.

Ethanol-induced gastric ulcers (Brzozowski et al 1998)

Rats fasted for 36 h were given 80 % ethanol at a dose of 1 mL/rat orally. One hour later, animals were killed and the ulcer index was determined.

Chronic gastric ulcers

Acetic acid-induced gastric ulcers (*Goswami et al 1998*)
Rats were starved for 24 h before the experiment. Under light ether anaesthesia, a midline epigastric incision was made and the stomach was exposed. Glacial acetic acid (0.05 mL) was applied topically using a cylindrical mould (6.0-mm i.d.) which was allowed to remain there for 60 s. The acid solution was then removed by rinsing the mould with 0.9 % saline to prevent possible damage to the surrounding tissues close to the point of application. The abdomen was closed and rats were then fed normally for nine days. On the tenth day the rats were killed. After removal, the stomach was cut open and the ulcer index and the score for intensity of gastric lesions were measured. The scores were assigned based on the following index; 0 = no ulcer, 1 = superficial mucosal erosion, 2 = deep ulcer or transmural necrosis, and 3 = perforated or penetrated ulcer.

Duodenal ulcers

Mercaptamine-induced duodenal ulcers (*Szabo 1978*)
Duodenal ulcers were induced by administration of mercaptamine hydrochloride (400 mg kg^{-1}, p.o.) twice at an interval of 4 h. All animals were killed 24 h after the first dose of mercaptamine and the duodena were excised carefully and opened along the antimesenteric side. The duodenal ulcer area was determined using a grid (mm^2). The duodenal ulcers were scored for intensity on a scale of 0 to 3: 0 = no ulcer, 1 = superficial mucosal lesion, 2 = deep ulcer or transmural necrosis, 3 = perforated or penetrated ulcer (into the pancreas or liver). The ulcer index was calculated from the following equation:

ulcer index = (arithmetic mean of the intensity in a group) + (number of ulcer positive animals/total number of animals) × 2

Statistical analysis

Values were expressed as mean ± standard deviations. Statistical significance was determined by Student's unpaired *t*-test for all parameters and for the ulcer score a non-parametric Mann–Whitney test was used. The comparisons were made between sham-operated control rats and rats bearing either two or four adenopituitaries and between rats bearing two and four adenopituitaries. Statistical analysis was by computer software (Graphpad Instat DATASET 1, ISD, software version 3.0 for Windows). Values of $P < 0.05$ were considered to indicate statistical significance.

Results

Serum prolactin levels after pituitary homografts

Implantation of either two or four adenopituitaries under the kidney capsule significantly increased the serum prolactin levels in all animals (Table 1). The acceptance of the graft was further confirmed by histological studies after the experiment (Figure 1). There was no sign of rejection of pituitary implants in sections of the tissue stained with haematoxylin and eosin.

Pylorus-ligated rats

There were significant increases in the ulcer index, the volume of gastric secretion and the total acidity after

Table 1 Serum prolactin levels after implantation of adenopituitaries under the kidney capsule.

Group	Serum prolactin level (ng mL^{-1})
Sham-operated control	94.72 ± 101.00
Two adenopituitary transplants	381.46 ± 189.65***
Four adenopituitary transplants	764.04 ± 1072.65***

Values are means ± s.d., n = 25. ***$P < 0.001$ compared with sham-operated control.

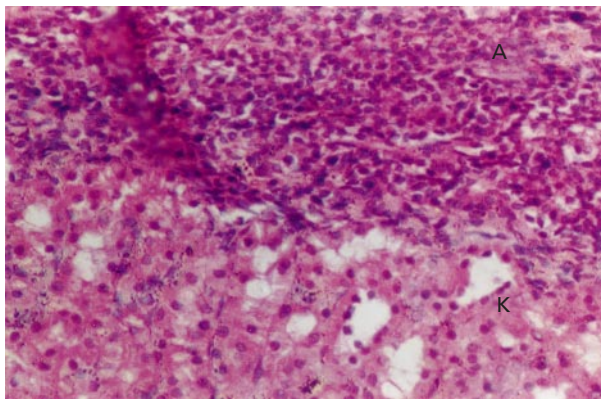

Figure 1 Photomicrograph showing the acceptance of an adenopituitary graft. Seen are the cells of the adenopituitary (A) and kidney cells (K) (H&E × 250).

Table 2 Effect of hyperprolactinaemia on gastric secretion, free acidity, total acidity and ulcer index in pylorus ligated rats.

Group	Volume of gastric contents (mL)	Free acidity (mEq L^{-1})	Total acidity (mEq L^{-1})	Ulcer index
Sham-operated control	7.89 ± 0.83	48.6 ± 9.20	115.3 ± 5.78	0.56 ± 0.02
Two adenopituitary transplants	10.23 ± 1.78**	56.8 ± 5.09	123.0 ± 4.48*	0.76 ± 0.07**
Four adenopituitary transplants	10.98 ± 0.81**	55.1 ± 7.73	130.8 ± 3.77**	0.80 ± 0.12**

Values are means ± s.d., n = 6. *$P < 0.05$, **$P < 0.01$ compared with sham-operated control.

pylorus ligation in rats bearing pituitary homografts when compared with sham-operated control. No significant difference in any parameter was observed between groups of rats bearing two or four adenopituitaries (Table 2).

Indometacin-induced and ethanol-induced gastric ulcers

Animals treated with either indometacin or ethanol orally developed lesions in the glandular portion of the stomach. The gastric lesions induced by alcohol were not affected by hyperprolactinaemia. However, the lesions induced by indometacin were significantly reduced by the hyperprolactinaemia produced after implantation of four adenopituitaries (Table 3).

Chronic gastric ulcers induced by acetic acid

Topical application of acetic acid produced penetrating ulcers at a low perforation rate. Hyperprolactinaemia induced by implantation of either two or four adenopituitaries aggravated the acetic acid-induced gastric ulcers as was evident by the significant increase in the ulcer index. Mortality was not altered by hyperprolactinaemia (Table 4).

Table 4 Effect of hyperprolactinaemia on chronic gastric ulcers induced by acetic acid.

Group	Ulcer index	Ulcer score	Mortality
Sham-operated control	0.36 ± 0.053	2.14 ± 0.63	1/8
Two adenopituitary transplants	0.45 ± 0.060*	2.28 ± 0.68	1/8
Four adenopituitary transplants	0.44 ± 0.047*	2.57 ± 0.47	1/8

Values are means ± s.d., n = 7. *$P < 0.05$ compared with sham-operated control.

Mercaptamine-induced duodenal ulcers

Hyperprolactinaemia produced more than a 30% increase in the mean ulcer area in the groups of the rats bearing either two or four adenopituitaries when compared with sham-operated control (Table 5). Mortality was almost the same in all the groups. The rats that did die had perforated ulcers.

Discussion

This study showed that rats bearing pituitary homografts under the kidney capsule exhibited significant gastric hypersecretory and pro-ulcerogenic effect. As

Table 3 Effect of hyperprolactinaemia on ulcer index in indometacin-induced and ethanol-induced gastric ulcers.

Method	Sham-operated control	Two adenopituitary transplants	Four adenopituitary transplants
Indometacin-induced gastric ulcers	0.28 ± 0.07	0.16 ± 0.09	0.13 ± 0.05**
Ethanol-induced gastric ulcers	1.72 ± 0.66	1.55 ± 1.42	1.24 ± 1.05

Values are means ± s.d., n = 6. **$P < 0.01$ compared with sham-operated control.

Table 5 Effect of hyperprolactinaemia on mercaptamine HCl-induced duodenal ulcers.

Treatment	Ulcer area (mm^2)	Ulcer score	Ulcer index	Mortality
Sham-operated control	7.66 ± 1.81	1.83 ± 1.05	3.49	2/6
Two adenopituitary transplants	10.16 ± 1.54*	2.16 ± 0.88	4.16	1/6
Four adenopituitary transplants	11.00 ± 1.37*	2.16 ± 0.88	4.16	2/6

Values are means ± s.d., n = 6. *$P < 0.05$ compared with sham-operated control.

these homografts are known to secrete very high amounts of prolactin and little, if any, of the other pituitary hormones (Drago & Bohus 1981), it was likely that the changes found in the homografted animals with respect to gastric and duodenal ulcers depended on the high levels of plasma prolactin. Hyperprolactinaemia induced by implantation of adenopituitaries under the kidney capsule caused release of prolactin in pulses at every 8–10 min interval, which was similar to that found in patients with prolactinomas (Vance & Thorner 1995).

The basal serum prolactin level in rats varies from 8–360 ng mL^{-1} (Muller & Dowling 1981). Simpkins (1992) reported that the mean basal serum prolactin levels were approximately 80 ng mL^{-1} in Sprague-Dawley rats and approximately 75 ng mL^{-1} in Wistar rats. However, other reports indicated that serum prolactin levels ranged from 10–115 ng mL^{-1} (Login & MacLeod 1977; Balasinor et al 1993). We obtained basal serum prolactin levels of 94 ng mL^{-1}.

This study was carried out using different experimental models of gastric ulcer that operate by distinct mechanisms of ulcerogenesis. The gastric hypersecretory effect due to hyperprolactinaemia was studied in pylorus-ligated rats. The formation of ulcers in pylorus-ligated rats depends on gastric secretion and gastric cytoprotection. Ethanol-induced gastric ulcers are used to study the effect on acid independent gastric cytoprotection and indometacin-induced gastric ulcers for effect on prostaglandin synthesis. In this study, hyperprolactinaemia induced gastric hypersecretion and pro-ulcerogenic effect. The pro-ulcerogenic effect seemed due mainly to gastric hypersecretion. There was no effect on gastric cytoprotection in ethanol-induced gastric ulcers but the cytoprotective effect was observed in indometacin-induced gastric ulcers after implantation of four adenopituitaries. This difference in the cytoprotective action cannot be explained with the present data. Prolactin is known to increase prostaglandin synthesis (Manku et al 1979). Hence, it can be suggested that reduction in the indometacin-induced gastric ulcers might be due to increased prostaglandin synthesis induced by high circulating levels of prolactin. Prostaglandins are known to reduce the development of gastric ulcers by increasing the gastric mucosal defense (D'Souza & Dhume 1991). We speculated that the increased prostaglandin synthesis induced by hyperprolactinaemia might not be enough to completely protect the gastric mucosa from the effect of increased gastric acid secretion. The pro-ulcerogenic effect due to hyperprolactinaemia was confirmed further by aggravation of acetic acid-induced chronic gastric ulcers and mercaptamine-induced duodenal ulcers. Hyperprolactinaemia did not produce any gastric lesion or ulcer in normal animals up to 40 days after pituitary homografts.

The mechanism of the hyperprolactinaemia-induced gastric hypersecretion and pro-ulcerogenic effect cannot be explained with the present data. This effect presumably could result from the action of prolactin in the brain, as earlier reports suggested that prolactin did not influence gastric acid secretion by acting at its receptors present in the stomach (Nagano et al 1995). Further, we demonstrated that prolactin, when given by the intracerebroventricular route, produced gastric hypersecretory and pro-ulcerogenic effect without affecting gastric cytoprotection (Asad et al 2001).

Prolactin immunoreactivity is found in numerous hypothalamic areas (Siaud et al 1989; Griffond et al 1993). Several approaches have been taken to prove that prolactin found in the hypothalamus is synthesized locally, independent of the prolactin synthesis in the pituitary (Devito 1988). Moreover, prolactin is known to cross the blood–brain barrier as mentioned earlier and prolactin may also enter the brain due to retrograde blood flow from the anterior pituitary to the hypothalamus (Freeman et al 2000). It has been reported that agents which are known to increase the release of pituitary prolactin also caused the release of prolactin from the hypothalamic areas (Bowers et al 1982). However, it is unlikely that implantation of adenopituitaries under the kidney capsule would have caused increase in the synthesis of prolactin in the brain. On the contrary, it may be suggested that the implantation of adeno-

pituitaries might have caused a decrease in the synthesis of brain prolactin, as it is well established that implantation of adenopituitaries under the kidney capsule reduces the prolactin levels in the anterior pituitary gland (Mena et al 1968). In this study, the effect on gastric and duodenal ulcers observed in animals bearing pituitary homografts might have been due to a small amount of the prolactin that had crossed the blood–brain barrier. This hypothesis is supported by the fact that a dose-dependent effect was not obtained after implantation of two or four adenopituitaries (this study), which may be due to limited transfer of prolactin from plasma to the CSF (Walsh et al 1987). Implantation of one adenopituitary did not produce a significant increase in the serum prolactin levels, hence experiments with one adenopituitary graft were not carried out.

Hyperprolactinaemia is the most common hypothalamic pituitary disorder encountered in clinical endocrinology. The causes of hyperprolactinaemia are diverse and many drugs are known to induce hyperprolactinaemia (Vance & Thorner 1995). The results of this study suggested that induction of hyperprolactinaemia might have aggravated the gastric ulcers, and drugs which are known to induce hyperprolactinaemia with no gastric antisecretory activity of their own must be used with caution in patients with gastric and duodenal ulcers.

To conclude, hyperprolactinaemia induced gastric hypersecretion and aggravated experimentally-induced gastric and duodenal ulcers in rats. It reduced the development of indometacin-induced gastric ulcers.

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