

The Effects of Acute Consumption of Heroin on Basal and Vagal-Stimulated Gastric Acid and Pepsin Secretion in Rat

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Abstract

Background: Opioid peptides and their receptors are present in the majority of body tissues including gastrointestinal tract. Heroin is one of the opioid derivatives that abuse increasingly today. So far, there is no study on the effect of acute heroin administration on gastric acid and pepsin secretion.

Objective: To define the effect of the acute heroin consumption on basal and vagal-stimulated gastric acid and pepsin secretion in rat.

Methods: Pure heroin (0.5 mg/kg, ip) was injected to 24 rats. After confirming the signs of heroin effect, animals were anesthetized with sodium thiopental (60 mg/kg, ip). Then, tracheostomy and laparotomy were done, gastric contents were collected by wash out technique over 15 min. The total titrable acid was measured by acid titrator. The pepsin content was measured by Anson method. Vagal electrical stimulation was used to stimulate the secretion of acid and pepsin.

Results: A significant increase in both basal and vagotomized state of gastric acid secretion in that group that received heroin, as compared to the control group was shown. Also, in comparison to the control group, electrical stimulation of vagus nerve increased the gastric acid secretion in animals that received heroin. This change, however, was not significant. The basal and vagally stimulated secretion of pepsin was increased, though not significantly, in heroin group in comparison to control group.

Conclusion: Basal and stimulated gastric acid and pepsin secretions increase after acute heroin administration in rat.

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Keywords • Heroin • acid secretion, gastric • Pepsin secretion • Rat

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Introduction

Heroin is a legally-prohibited opioid with high addictive ability and the highest rate of consumption among other narcotic drugs.¹ Heroin effects appear very quickly. It is consumed in various forms, mostly in form of injection. Yet, pure heroin may

The effects of heroin on gastric acid and pepsin secretion

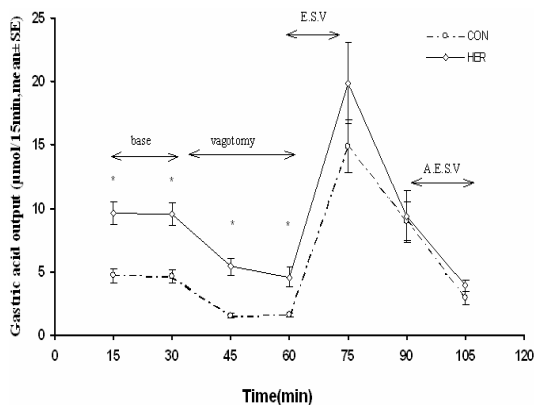


Fig1: Comparison of the acid secretion between the control and case groups (n=12 in each group)
*P<0.001 E.S.V= Electrical stimulation of vagus nerve
A.E.S.V= After Electrical stimulation of vagus nerve

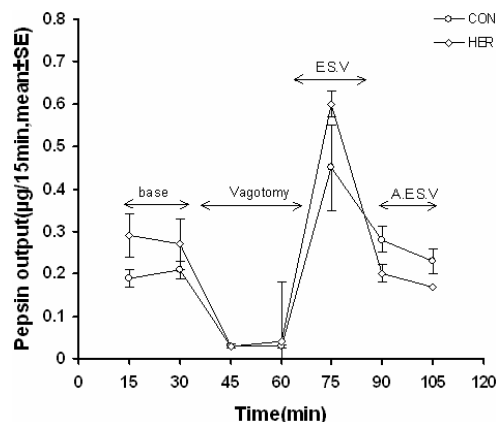


Fig2: Comparison of the pepsin secretion between the control and case groups (n=12 in each group)
E.S.V= Electrical stimulation of vagus nerve
A.E.S.V= After Electrical stimulation of vagus nerve

be smoked.¹ Previous studies have shown that 80% of heroin consumers are under 26 years of age.¹ Heroin exerts its effects as an agonist on mu, kappa and delta receptors in the central nervous system. mu₂ receptors are responsible for respiratory depression, hypomotility in digestive system and myosis.² The distribution of opioids and their receptors in most body organs, such as digestive system and the central nervous system, can affect the motility and secretory activities of the gastrointestinal tract. It has been observed that opioids can affect gastric acid secretion via three mechanisms³:

1. Their central effects on the brain,
2. their indirect peripheral effects, and
3. their direct effects on parietal cells.

It has been shown that morphine increases basal and histamine-stimulated acid secretion, but it decreases pentagastrin-stimulated acid secretion.⁴

Acid and pepsin secretions are affected by vagal stimulation. In vagal stimulation, acetylcholine is released which can increase acid and pepsin secretion directly or indirectly via histamine release, increase of the gastrin level or through the inhibition of somatostatin suppressive effect.⁵⁻⁷

Since heroin is a strong opioid with a lot of harmful effects on body and since the effects of heroin on acid and pepsin secretion have not yet been investigated, we decided to study the effects of acute consumption of pure heroin on both basal and vagally-stimulated acid and pepsin secretion.

Materials and Methods

In this study, 24 N-Mari rats of both sexes with a mean weight of 200-250 gr were used. Animals were kept in the animal room of the Kerman Uni-

versity of Medical Sciences at a temperature of 25±2 °C with a 12 h/12 h dark/light cycle. They were fed with standard food and were divided into two groups of case and control (n=12/group). Animals in the case group received 0.5 mg/kg b.w pure heroin intraperitoneally.⁸ Ten min after the injection, the symptoms of acute heroin consumption in rat, *i.e.*, respiratory depression, hilarity and tail erection were observed.⁹⁻¹² The control group had access to normal food and water. Animals were deprived of food since 24 hours before the start of the experiment. However, they had access to water *ad libitum*.¹³ In the control group, after weighing animals, they were anesthetized by intraperitoneal injection of sodium thiopental (nesdonal 50 mg/kg b.w).¹⁴ In the case group, to prevent death due to respiratory depression, half of the doze prescribed for the control group, *i.e.*, 25 mg/kg b.w of thiopental, was administered. After conduction of anesthesia, tracheotomy was done and esophagus was tied in neck region.¹³ Then, the vagus nerve in both sides was carefully separated from carotid artery for about 1 cm and tied loosely by a string and finally covered with a cotton soaked in normal saline.¹⁵ Following this stage, laparotomy was done by a midline incision about 2 cm. Then, a silicon tube with an external diameter of 2.5 mm was entered into the stomach via duodenum. For emptying the probable remaining gastric contents, it was washed several times with 1-1.5 ml of 37 °C normal saline (pH=7).¹⁶ Thereafter, the vagus nerve's tie was fastened tightly and the nerve was cut in its central part. For measuring the basal acid secretion, 1 ml ringer solution was instilled into the stomach. After 15 min, another 1 ml of ringer solution was added. The stomach content was then

Table 1: Comparison of gastric acid and pepsin secretion (Mean \pm SE) in right and left vagal electrical stimulation in the two groups			
Groups		Right vagal stimulation	Left vagal stimulation
Control	Acid secretion* (n=12)	14.9 \pm 2.13	14.56 \pm 2.06
	Pepsin secretion** (n=12)	0.48 \pm 0.1	0.5 \pm 0.09
Case	Acid secretion* (n=12)	19.83 \pm 3.17	19.51 \pm 3.87
	Pepsin secretion** (n=12)	0.64 \pm 0.14	0.6 \pm 0.14

* $\mu\text{mol}/\text{min}$ ** $\mu\text{g}/15\text{min}$

emptied of which, 1 ml was titrated. This procedure repeated twice. Acid measurement was done by a titrator instrument (W. Germany, DIN) with an accuracy of 0.02 ml, using 0.01 N sodium hydroxide. To measure the vagal-stimulated acid secretion, 1 mm of the peripheral part of the right vagus nerve was stimulated by a stimulator (15 V, 4 Hz) for 15 min. Thereafter, the acid secretion was measured every 15 min until it returned to the basal state. The voltage and frequency of stimulation were chosen in a way that no cardio-vascular problem would arise.¹⁶ The cardio-vascular activity was monitored by EKG.

Pepsin secretion in all stages of basal, vagotomy, vagal-stimulation and its returning back to the basal state was measured by Anson method,¹⁷ using hemoglobin as the pepsin enzyme substrate.¹⁸ Acid and pepsin secretion were recorded as mean \pm SEM. Data analyses were done by paired and unpaired Student's t-tests. A p value <0.05 was considered statistically significant.

Results

Results showed that the mean \pm SEM acid secretion in control group at 15, and 30 min was 4.68 \pm 0.55 and 4.63 \pm 0.57 $\mu\text{mol}/15$ min, respectively (Fig 1). These values were significantly ($p < 0.001$) different from those of case group that were 9.58 \pm 0.88 and 9.51 \pm 0.91 $\mu\text{mol}/15$ min, respectively (Fig 1). There was also a significant ($p < 0.001$) increase in acid secretion at 45 and 60 min of vagotomy in case group as compared to the control group (Fig 1).

Fifteen minutes after vagus stimulation, acid secretion was 19.83 \pm 3.17 $\mu\text{mol}/15$ min in case and 14.9 \pm 2.13 $\mu\text{mol}/15$ min in the control group (Fig 1) ($p = \text{NS}$).

Acid secretion at 90 and 105 min of returning to the vagotomy state was not significantly different between two groups (Fig 1).

The basal pepsin secretion in control group was 0.19 \pm 0.02 $\mu\text{g}/15$ min at 15 min, and 0.21 \pm 0.02 at 30 min. Meanwhile, it was 0.2 \pm 0.05, and 0.27 \pm 0.06 $\mu\text{g}/15$ min, respectively, in the case

group (Fig 2). Although there was an increase in the basal pepsin secretion in case group as compared to the control group, it was not statistically significant. There was an increase in pepsin secretion in case group on 45 and 65 min of vagotomy ($p = \text{NS}$). No significant difference was also observed in pepsin secretion level between case and control groups during 15 min of vagal stimulation and over the whole stages of returning of the secretion level to the vagotomy state (Fig 2).

We found no significant difference in acid and pepsin secretion between control and case groups in the presence of right and left vagal stimulation (Table 1).

We also found that neither the basal acid secretion nor the basal pepsin secretion depended on gender in both groups (Table 2).

Discussion

In this study, we found that heroin can cause a significant increase in basal acid secretion (Fig 1). We also observed an increase—though, not statistically significant—in pepsin secretion level in case group as compared to the control group (Fig 2). The mechanism of basal acid secretion has not been well-known yet. However, it seems that vagus tonic stimulation, gastrin and histamine have some roles, since basal acid secretion decreases after vagotomy, antrectomy or administration of cimetidine.^{19,20,21}

It is known that opioids increase bombazine release,^{22,23} elevate acid secretion due to histamine release²² and increase the basal acid secretion via vagus stimulation and altered acetylcholine or histamine release.^{22,24} Therefore, it is reasonable to assume that heroin might also increase the basal acid secretion via the above-mentioned mechanisms.

Opioids also increase the gastric mucosal blood flow in dog and human which leads to increased acid secretion.^{4,25,26} Consequently, heroin as an opioid, might also increase the basal acid secretion through augmentation of the gastric mucosal blood

Table2: Comparison of gastric basal acid and pepsin secretion (Mean ± SE) in two groups of male and female rats			
	Groups	Basal acid secretion (µmol / 15min)	Basal pepsin secretion (µg/15min)
Control	Male (n=6)	4.79 ± 1	0.19 ± 0.05
	Female (n=6)	4.63 ± 0.59	0.19 ± 0.03
Case	Male (n=6)	9.5 ± 0.88	0.29 ± 0.11
	Female (n=6)	9.6 ± 1.62	0.2 ± 0.04

flow. It is also probable that heroin inserts its effect on basal acid secretion directly via opioid receptors present on the parietal cells. In one study in rat, morphine could increase the basal acid secretion, an effect that could be reverted by using an antagonist, N-methyl nalorphine.²⁷

Considering the results of the present study, acid secretion in vagotomy state is significantly more in heroin group than the control group. In spite of this fact, there was a significant decrease in acid secretion in both groups after vagotomy as compared to the basal acid secretion (Fig 1). By vagotomy, acetylcholine which stimulates acid secretion is eliminated. It seems that besides acetylcholine, some other factors such as histamine, gastrin or opioid receptors existing on parietal cells, might be involved in acid secretion. Moreover, involvement of other modulators derived from enteric nervous system could not be ruled out.

In the current study, acid and pepsin secretion was stimulated by electrical stimulation of the vagus nerve. This led to a significant increase in acid and pepsin secretion in both groups as compared to the basal and vagotomy state (Figs 1 and 2). It has been reported that electrical stimulation of the vagus nerve increases acid and pepsin secretion by release of acetylcholine and other mechanisms.^{7,14,28}

In this study, increased acid and pepsin secretion continued after the stopping of vagus stimulation. It can be due to the presence of gastrin in blood²⁸ or histamine.²⁹ Returning to the basal state was different in the two groups that can be attributed to the heroin effect.

Results of this study showed that acid and pepsin secretory response to vagus stimulation is the same for stimulation of both the right and left vagus nerve (Table 1). Berthoud, *et al*, showed that acid secretion shows no difference in left and right vagus stimulation (1 mA, 1-16 Hz, 0.0001s for 10 minutes) and that the highest secretory response is observed at a frequency of 2-4 Hz.³⁰ Shankly, *et al*, showed that left vagus stimulation (12-15 V, 4-32 Hz, 0.001s for 1 min) increases acid secretion with the highest secretory response observed at a frequency of 16 Hz. It seems that the characteristics of the electrical stimulation used determines the

degree of gastric secretory response and this fact may be the main reason for the observed difference between the results of our study and other reports.

Some previous studies on rat have shown that there is no difference between two sexes in basal acid secretion.³¹ These are in agreement with our findings (Table 2). Moreover, some have reported that the entero-chromafin cells density is more in female than in male rats,³² while parietal cell mass in female rats is lesser.³³ In our study, the similarity of two sexes in basal acid and pepsin secretion may be attributed to an increase in entero-chromafin cells and histamine and a concomitant decrease in parietal cells mass in females than in males.

In short, acute consumption of heroin causes an increase in acid secretion both in basal and vagotomy states. During electrical stimulation there was no significant change.

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