Effect of Damage to Medial Amygdaloid Nucleus on Pancreatic Exocrine Secretion Stimulated by Hydrochloric Acid in the Rat*

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ABSTRACT

This study was undertaken to investigate the effect of the medial amygdaloid nucleus on the pancreatic exocrine secretion and plasma secretin concentration in 44 male albino rats. Twenty-three rats in which the medial amygdaloid nucleus was damaged bilaterally by radio frequency a.c. through stereotaxically inserted electrodes (medical amygdaloid group, MA) and twenty-one rats which received the same operation without damage (operated control, OC), were prepared. Under urethan anesthesia, 0.01 N hydrochloric acid (HCl) or physiological saline (0.9% NaCl) was infused at a rate of 0.18 ml/min into the duodenum for 20 minutes. Pancreatic jucie was collected for the 20 min infusion period. After collection of pancreatic juice, blood was sampled from the abdominal aorta for the radioimmunoassay of plasma secretin concentration.

In the MA group, the exocrine pancreatic secretory response to 0.01 N HCl as well as saline infusion was significantly inhibited compared with that in the OC group. The pancreatic protein output of the MA group significantly decreased after the saline infusion and tended to decrease after the 0.01 N HCl infusion, compared with that of the OC group. However, there was no significant difference in plasma secretin concentration between the two groups.

Therefore it is strongly suggested that the rat medial amygdaloid nucleus has a facilitatory influence on both basal and acid-stimulated pancreatic exocrine secretion, but the releasing mechanism of secretin appears not to be involved in the influence.

Key Words: Medial amygdala, Pancreatic exocrine secretion, Secretin, Rat

INTRODUCTION

The pancreatic exocrine secretion has been known to be regulated by hormonal and by neural mechanism partly. Although the cephalic phase of pancreatic exocrine secretion was demonstrated in rats (Alphin & Lin, 1959), dogs(Preshaw et al., 1966), and humans (Sarles et al., 1968; Novis et al., 1971;

Anagnostides et al., 1984), the central mechanism of the cephalic phase has not been well understood.

Recently it has been shown that there are some brain sites which are involved in regulating the pancreatic exocrine secretion (Gilsdorf et al., 1966; Rozé et al., 1980; Rozé et al., 1981; Park et al., 1986). Amygdala, one structure of the limbic system, has been reported to influence the pancreatic exocrine secretion (Mine et al., 1985; Sim & Kim, 1988; Yoon & Kim, 1988) as well as the gastrointestinal function (Zawoiski, 1967; Kim & Choi, 1985; Grijalva et al.,

1986). Already we reported that the electrical stimulation of the medial amygdala increases the volume of the pancreatic juice in response to intraduodenal infusion of 0.01 N HCl (Sim & Kim, 1988).

Moreover, the lesion of the medial amygdala decreased the basal pancreatic exocrine secretion in response to intraduodenal infusion of saline, but the damage had no influence on that in response to infusion of higher concentration of acid, 0.1 N HCl(Yoon & Kim, 1988). It is possible to speculate that the influence of the medial amygdala on the pancreatic exocrine secretion is masked by stimulating with unphysiologically high concentration of acid.

Thus, we investigate the effect of damage to the rat medial amygdaloid nucleus on the pancreatic exocrine secretion stimulated by intraduodenal infusion of lower concentration of hydrochloric acid.

Materials and Methods
Animals

Experiments were performed on forty-four male albino rats with a mean body weight of 245(200–290) g. All rats were divided into two groups; medial amygdaloid (MA, n=23) and operated control (OC, n=21) groups. Each animal was housed in separated animal cage and kept under a 12 hour reversed light-dark cycle (by 30 W small red bulb in the daytime and by 40 W fluorescent lamp in the nighttime) for at least 15 days before experiment.

Brain surgery

All rats were deprived of food but not water overnight. Under intraperitoneal pentobarbital anesthesia(45 mg/kg, body weight), the animals were fixed in a stereotaxic apparatus (Model 1504, David Kopf Instruments, USA). A pair of monopolar stainless steel electrodes(tip diameter 0.2 mm, contact length 0.5 mm) were bilaterally inserted into the medial amygdaloid nucleus. The stereotaxic coordinates of the tips of electrodes (A-P: 5.0 mm, L: 3.3 mm, H: -3.2 mm) were determined according to a

stereotaxic atlas of rat brain(Pellegrino et al., 1979).

In the MA group, bilateral medial nuclei were lesioned by passing a 20 mA radio frequency alternating current for 15 seconds (Radio Frequency Lesion Generator, Model RFG-4, DKI). The OC animals received the same operating procedures without passing radio frequency a.c. through the electrodes. Pancreatic juice was collected at least 2 weeks after brain surgery.

Abdominal surgery

All rats were fasted for 18 hr with free access to water. Under intraperitoneal urethan anesthesia (25 % wt/vol, 0.4 ml/100 g, body weight), a midline abdominal incision was made. After exposing the bile duct, the duct was cannulated with a polyethylene tube (ID 0.28 mm, OD 0.61 mm: PE-10, Clay Adams, USA) through the opening made by incision on the duct at the junction with pancreatic tissue. The other end of the tube was introduced into the proximal jejunum to divert the bile juice.

Another polyethylene tube of the same size was inserted into the pancreatic duct near its entrance to the duodenum for the collection of pancreatic juice. The opposite side of the pancreatic duct was ligated with 3-0 silk. For the measurement of the volume of the pancreatic juice, the tube was connected to a glass capillary tube (Micropet, Clay Adams) with a capacity of 25 μl/9 cm tube length. For infusion of physiological saline and 0.01 N hydrochloric acid into the duodenum, a large polyethylene tube (ID 1. 2 mm, OD 1.8 mm) was inserted into the proximal duodenum through the rumen of stomach. The pyloric ligation was performed to prevent the gastric juice from entering into the duodenum. Another large tube was inserted into the distal duodenum through the jejunum, and the ligation was performed at Treitz's ligament.

Experimental procedures

The infusion of HCl or saline was performed 10

minutes after the abdominal surgery. Before the collection of pancreatic juce, physiological saline (0.9 % NaCl) was infused into the duodenum at a rate of 0.18 ml/min through a large proximal tube for 20 minutes (control period). Immediately after the control period, intraduodenal infusion of 0.01 N HCl (310 mOsm) or physiological . saline was performed through, the same proximal tube for another 20 minutes and the pancreatic juce was collected during the 20 minute infusion period. At the end of infusion, the volume of pancreatic juice was measured and protein concentration of pancreatic juice was also measured by determining optical density at 280 nm of samples (Keller et al., 1958).

Blood samples were obtained from the abdominal aorta in ice-chilled heparin-treated glass tubes after the infusion. The plasma was separated by refrigerated centrifugation (1,500 g) for 15 minutes at 4 ℃, and was stored frozen at a temperature below -20 ℃ until the plasma secretin concentration was determined by radioimmunoassay method(Chang & Chey, 1980).

Brain histology

After the experiments, all rats were perfused transcardially with saline and 10% formalin phosphate buffer. The brains were fixed in the buffer for at least 1 week. They were frozen and sectioned frontally at 70 μm. Around 10 informative sections from each brain showing the lesions were photographed with six times magnification. The extent of brain damage was estimated in terms of its proportion to the total tissue bulk.

Statistical analysis

All values were expressed as the mean±standard deviation. Student's t test was used to evaluate the statistical significance of difference between the groups. A probability value was considered statistically significant less than 0.05.
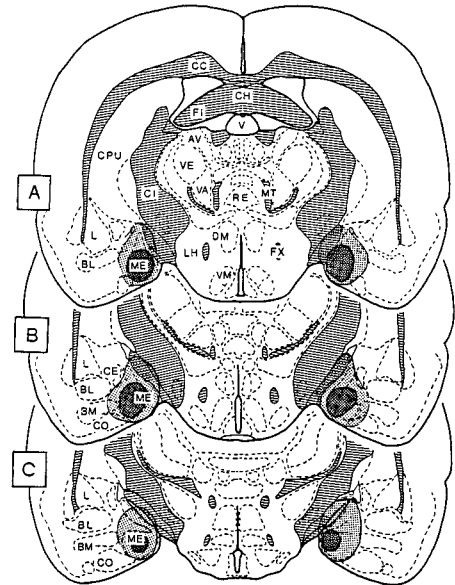

Fig. 1. Reconstruction diagrams of the minimum (crosshatched) and maximum (dotted) extent of damage to the medial amygdaloid nucleus on coronal sections redrawn from the Pellegrino et al. (1979) stereotaxic atlas.
A : hippocampal commissure level, B : anterior thalamic level, C : tuberal region level.

Abbreviations; AV: anteroventral thalamus, BL: basolateral nucl., BM: basomedial nucl., CC: corpus callosum, CE: central nucl., CH: hippocampal commissure, CI: internal capsule, CO: cortical nucl., CPU: caudate & putamen, DM: dorsomedial hypothalamus, FI: hippocampal fimbria, FX: fornix, L: lateral nucl., LH: laterl hypothalamus, ME: medial nucl., MT: mammillothalamic tract, OT: optic tract, RE: nucl. reuniens thalami, V: ventricle, VA: vertroanterior thalamus, VE: ventral thalamus, VM: ventromedial hypothalamus

RESULTS

Histologic findings

The extent of the damage of the medial amygdaloid nucleus in the MA group was shown in Fig. 1. The damaged site was located primarily in the medial amygdaloid nucleus. The damage was found to be ovoid or round shape with maximum diameter of 1. 0-1.9 mm. The extent of the damage was 70(45-80)
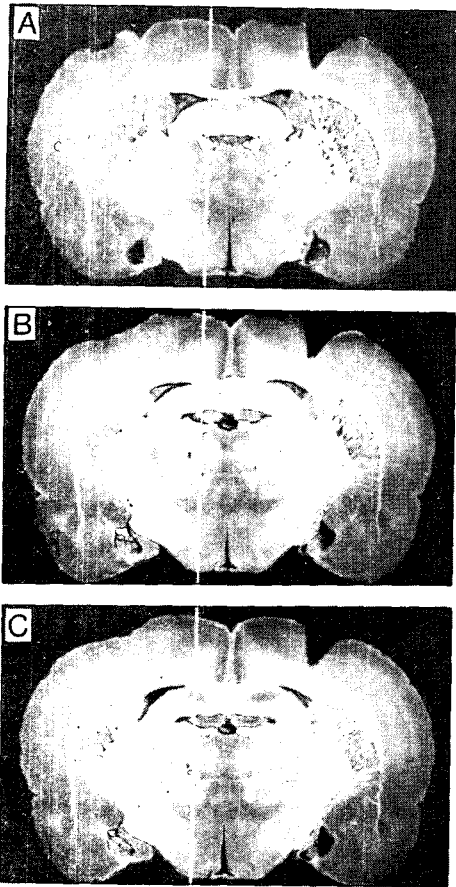
Fig. 2. Coronal sections through the brain of a rat damaged to the amygdala at the levels of hippocampal commissure (A) anterior thalamus (B) and tuberal region (C).
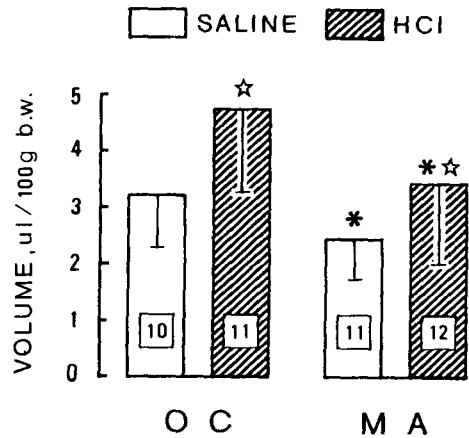

Fig. 3. Mean volume of pancreatic juice in response to intraduodenal infusion of physiological saline or 0.01 N HCl for 20 min in the operated control (OC) and the medial amygdaloid (MA) groups. Vertical bars represent 1 S.D.

* : Significantly different from values of the OC group ($P<0.05$).

☆ : Significantly different from values after saline infusion in each group ($P<0.05$).

% on the average. The additional damages besides the medial amygdaloid damage, though not severe, occurred in its adjacent area.

The medial portion of the basomedial (11 cases) and the cortical nucleus (10 cases), the hippocampus (6 cases), and the anterior amygdaloid area (5 cases) were damaged slightly and superficially. The representative coronal sections were showin in Fig. 2.

Effect of damage to medial amygdaloid nucleus on pancreatic exocrine secretion

The volume of pancreatic juice in response to the intraduodenal infusion of 0.01 N HCl or physiological saline was presented in Fig. 3. The volume of pancreatic juice in response to intraduodenal infusion of HCl and saline were 3.45 ± 1.46 and 2.46 ± 0.73 $\mu l/100$ g b.w. in the MA group, respectively. These volumes of the MA group were significantly lowered than those of the OC group (0.01 HCl: 4.77 ± 1.53, saline: 3.21 ± 0.90 $\mu l/100$ g b.w.). In the both groups, the volume of the pancreatic juice after the infusion of 0.01 N HCl into the duodenum increased significantly compared with that after the infusion of physiological saline.

The protein output in pancreatic juice in response to infusion of 0.01 N HCl and saline into the duodenum is depicted in Fig. 4. As shown in Fig. 4, the pancreatic protein output after saline infusion was significantly lowered in the MA group than in the OC group. After 0.01 N HCl infusion, however, the pancreatic protein output of the MA group tended to
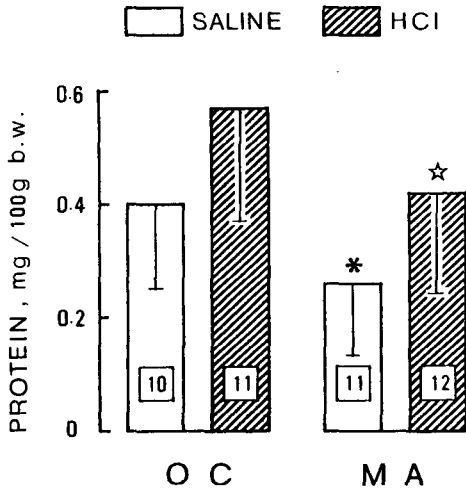
Fig. 4. Mean protein output of pancreatic juice in
response to intraduodenal infusion of saline or
0.01 N HCl in the operated control(OC) and
the medial amygdaloid(MA) groups for 20
min. Vertical bars represent 1. S.D.

  ＊ : Significantly different from value of the
OC group(P<0.05).

  ☆ : Significantly different from value after
saline infusion of the MA group (P<0.
05).

Table 1. Plasma secretin concentrations (pg/ml) after
intraduodenal infusion of physiological saline
or 0.01 N HCl into the duodenum in the
ope. .ed control(OC) and the medial amyg-
daliod(MA) groups (Mean±S.D.)

Group	Saline	0.01 N HCl
OC	16.91±4.47 (n=10)	23.52±6.79* (n=11)
MA	16.41±4.67 (n=11)	21.73±7.01* (n=12)

*Significantly different from values after saline infuion
in each group(P<0.05).

decrease compared with that of the OC group. In
both the MA and OC groups, the protein output in
response to intraduodenal infusion of 0.01 N HCl
markedly increased in comparison with that after
saline infusion.

Effect of damage to medial amygdaloid nucleus on plasma secretin concentration

The plasma secretin concentrations after infusion
of 0.01 N HCl and saline into the duodenum were
described in Table 1. The plasma secretin concentra-
tions were significantly increased by intraduodenal
infusion of 0.01 N HCl in both the MA and the OC
groups, but there was no significant difference in the
secretin levels between two groups after 0.01 N HCl
infusion as well as saline.

DISCUSSION

In the present study, the damage to the rat medial
amygdaloid nucleus caused a significant decrease in
the pancreatic secretory volume in response to
intraduodenal infusion of physiological saline. The
pancreatic protein output in response to the infusion
of saline was also markedly decreased by the damage
to the medial amygdaloid nucleus. These results are
well consistent with the results that the bilateral
electrical lesions of the medial amygdala decreased
the basal pancreatic exocrine secretion in rats(Mine
et al., 1985; Yoon & Kim, 1988). Assuming an
attenuated function following medial amygdaloid
lesion simply to be a deficiency phenomenon, we
may infer from the results of this study that the
medial amygdaloid nucleus is facilitatory to the
basal pancreatic exocrine secretion. Moreover, our
recent study using rats demonstrated that the unilat-
eral electrical stimulation of the medial amygdaloid
nucleus induced an increase in the basal pancreatic
exocrine secretion (Sim & Kim, 1988).

Following the damage to the medial amygdaloid
nucleus, intraduodenal infusion of low concentration
of hydrochloric acid (0.01 N HCl) increased signifi-
cantly the pancreatic exocrine secretion in rats, but
the magnitude of the increase in the pancreatic
secretion was significantly lower than that of the
control animals. The medial amygdaloid lesion also

markedly attenuated the increased protein output induced by intraduodenal acid. The present results are good accord with the observations of Mine and his colleagues (1985) that medial amygdalectomized rats showed a decrease in the pancreatic exocrine secretion stimulated by secretin-cholecystokinin (CCK). It is therefore suggested from results of this study and Mine et al. (1985) that the medial amygdaloid nucleus has a facilitatory influence on the pancreatic exocrine secretion in the stimulated state by acid as well as in the basal state. This suggestion is well supported by our stimulation experiment that the electrical stimulation of the rat medial amygdala increased the pancreatic exocrine secretion induced by weak hydrochloric acid. And the intraduodenal acid content used in this study is almost comparable with that after the ingestion of meal (Malagelada et al., 1976; Kim et al., 1979). Therefore it is possible to infer that the medial amygdaloid nucleus also has an augmentative effect on the pancreatic secretion in the postprandial state after the ingestion of meal. Recently, several investigators of our laboratory reported that the medial amygala increased gastric acid secretion stimulated by histamine (Lee & Choi, 1985; Koh & Choi, 1988). These reports get us to entertain misgivings that the reduction of pancreatic secretion in this study can be caused by the decrease in delivered acid into the duodenum from the stomach following the medial amygdaloid damage. But we are fully convinced that the delivered acid from the stomach might not be involved in this pancreatic secretion, because entering of gastric acid into the duodenum was prevented by the pylorus ligation in our rats.

Previously, our collaborators failed to observe the attenuating effect on pancreatic secretion induced by 0.1 N HCl in the medial amygdalectomized rats (Yoon & Kim, 1988). The discrepancy between the present study and our previous one is very likely attributable to that hydrochloric acid was too strong to discriminate the attenuating effect of the medial amygdalectomy on the pancreatic secretion.

In this study, plasma secretin concentration following the rat medial amygdaloid damage was not significantly different from that of control animals in the basal state or in the stimulated state by hydrochloric acid. The study therefore indicates that secretin release was not affected by the damage to the medial amygdaloid nucleus, and that releasing mechanism of secretin was not related to the decrease in the pancreatic secretion following the medial amygdaloid lesion. Cholinergic or vagal tone has been reported not to affect release of endogenous secretin but alter the exocrine pancreatic bicarbonate secretion stimulated by secretin (Chey et al., 1979).

In the regulation of pancreatic secretion, Mine et al. (1985) reported that different amygdaloid nuclei play different roles in rats. The medial amygdaloid nucleus was reported to modulate the lower brain stem autonomic area, directly or indirectly via preoptic-anterolateral hypothalamic area (Henke, 1980). Also the medial amygdala was known to influence the hypothalamus via other limbic structures (Kim et al., 1976; Krettek & Price, 1978). Therefore, pancreatic secretion may be influenced by the lower brain stem or indirectly by the hypothalamus, because the pancreas is innervated by the vagus from the lower brain stem which is under the influences of hypothalamus. This assumption is supported by the studies that vagotomy and a small dose of atropine decreased the pancereatic secretion (Alphin & Lin, 1959; Singer et al., 1985). The medial amygdaloid nucleus seems therefore to be facilitative to the basal pancreatic secretion via vagus nerve. Recently it has been reported that the amygdala sends fibers, directly or indirectly via the hypothalamus and the brain stem, to the spinal cord (Sandrew et al., 1986; Holstege, 1987). These projections are thought to provide the major descending drive to the sympathetic nervous system. Moreover, it have been reported that a β-adrenergic receptor antagonist, propranolol, inhibited the basal pancreatic

secretion (Jo et al., 1987) and the β-adrenoreceptor in the pancreas exerted a stimulatory influence on the exocrine secretion in rats (Furuta et al., 1978). Therefore the medial amygdala seems to regulate the pancreatic exocrine secretory function through sympathetic as well vagal mechanism.

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= 국문초록 =

흰쥐에서 내측 편도핵의 손상이 염산 자극에 의한 췌장 외분비에 비치는 영향

가톨릭대학 의학부 생리학교실

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본 연구는 십이지장내 생리 식염수와 0.01 N HCl을 주입했을때 내측 편도핵의 손상이 췌액 분비와 혈장 secretin 농도에 미치는 영향을 구명하기 위하여 44마리의 수컷 흰쥐를 사용하였다. 그 중 21마리의 흰쥐는 뇌정위 고정장치에 의해 내측 편도핵에 삽입된 전극을 통해 양측성으로 내측 편도핵을 파괴한 내측 편도핵 손상군이고, 나머지 23마리는 편도핵의 손상없이 동일한 수술 조작만을 가한 수술 대조군이다. urethan 마취후에 십이지장 근위부에 위치한 관을 통해 십이지장 내강에 0.01 N HCl 또는 생리 식염수(0.9% NaCl)를 0.18 ml/min 속도로 주입하면서 20분간 췌액을 채취하였다. 췌액 채취후 복대동맥에서 채혈하여 혈장 secretin 농도를 측정하였다.

내측 편도핵 손상군에서 십이지장내 생리 식염수는 물론 0.01 N HCl의 주입에 의한 췌액량은 수술 대조군의 것보다 유의하게 감소하였다. 내측 편도핵 손상군의 췌액내 단백질량은 생리 식염수 주입시 수술대조군의 것보다 유의하게 감소하였고, 0.01 N HCl 주입시에는 유의하지는 않지만 감소한 경향을 보였다. 그러나 기초상태 및 염산 자극에 의한 혈장 secretin 농도는 내측 편도핵의 손상에 의하여 아무런 영향을 받지 않았다.

따라서 내측 편도핵은 기초 상태 및 염산 자극에 의한 췌액의 분비에 촉진적 영향을 미치는 것으로 생각되나, secretin 분비기전이 이 촉진 영향에 관련되는 것으로는 보이지 않는다.