BIBLID: ISSN 0253-9756 Acta Pharmacologica Sinica 中国药理学报 1998 Nov; 19 (6): 554 - 556

Inhibitory effects of cyproheptadine on pituitary-thyroid axis and pancreatic β cells in rats

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KEY WORDS cyproheptadine; pituitary gland; thyroid gland; islets of Langerhans; electron microscopy

AIM: To study the influences of cyproheptadine (Cyp) on the endocrine functions of pituitary-thyroid axis and pancreatic β cells in rats. **METHODS:** The effects of Cyp on functions of pituitary-thyroid axis and pancreatic β cells were observed by radioimmunoassay, biochemical analysis, and electron microscope. **RESULTS:** Cyp 2.3 $mg \cdot kg^{-1}$ ig for 10 d decreased serum thyroid stimulating hormone (TSH) from control groups (5.3 ± 0.9) to (4.2 ± 0.9) $mU \cdot L^{-1}$ and insulin levels from (64 ± 8) to (50 ± 9) $kIU \cdot L^{-1}$ ($P < 0.05$ and 0.01). Cyp 4.6 $mg \cdot kg^{-1}$ decreased serum TSH (3.8 ± 0.5) $mU \cdot L^{-1}$, T_3 (1.2 ± 0.2) $mmol \cdot L^{-1}$, T_4 (62 ± 7) $mmol \cdot L^{-1}$, and insulin levels (42 ± 8) $kIU \cdot L^{-1}$ decreased ($P < 0.05$ or 0.01). The retrograde changes of ultrastructure of pituitary TSH cells and pancreatic β cells. **CONCLUSION:** Cyp has an inhibiting action on endocrine functions of pituitary-thyroid axis and pancreatic β cells in rats.

Cyproheptadine (Cyp), a histamine H_1 and serotonin S_2 receptor antagonist was used to treat the allergic disease of skin and mucosa, dizziness, and migraine. Cyp has effects of calcium channel antagonism, anti-shock, anti-inflammation, analgesic, myocardial protection, and anti-arrhythmia[1-6]. The goal of this study was to investigate the effects of Cyp on pituitary-thyroid axis and pancreatic β cells in rats.

MATERIALS AND METHODS

Cyp (Shanghai Tianping Pharmaceutical Factory, lot No 950303) and radioimmunoassay kits for TSH, T_3, T_4, and insulin (Department of Isotope, China Institute of Atomic Energy, Beijing). Adult ♂ Sprague-Dawley rats weighing 220 g ± *s* 15 g were provided by the Laboratory Animal Center of Weifang Medical College, and were randomly divided into 3 groups ($n = 8$): Cyp 2.3, 4.6 $mg \cdot kg^{-1}$, and equal volumes normal saline (NS) ig daily for 10 d, respectively. The rats were killed 1 h after the last ig Cyp. Blood 2.5 mL was obtained, and serum was frozen under −30 ℃ for 1 wk. The pituitary and pancreas were fixed in 2.5 % glutaraldehyde, post-fixed in 1 % osmic acid (OsO_4), dehydrated, penetrated, and embedded in Epon 812 resin. Ultrathin sections 70 nm were stained with uranyl acetate and lead citrate, and observed under JEM-100CX electron microscope. Concentrations of serum TSH, T_3, T_4, insulin, and glucose were measured with RIA and biochemical analysis.

Statistical analysis Data were expressed as $\bar{x} \pm s$ and compared by *t*-test.

RESULTS

Function of pituitary-thyroid axis in rats Cyp (2.3 $mg \cdot kg^{-1} \cdot d^{-1}$, ig for 10 d) decreased serum TSH concentrations ($P < 0.05$), but serum T_3 and T_4 levels remained unchanged ($P > 0.05$). However, after ig Cyp 4.6 $mg \cdot kg^{-1} \cdot d^{-1}$, serum TSH, T_3, and T_4 levels were markedly decreased as compared with NS group (Tab 1).

Tab 1. Effects of Cyp on functions of pituitary-thyroid axis in rats. $n = 8$, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* control.

Cyproheptadine/ $mg \cdot kg^{-1}$	TSH/$mU \cdot L^{-1}$	T_3/$mmol \cdot L^{-1}$	T_4/$mmol \cdot L^{-1}$
0	5.3 ± 0.9	1.5 ± 0.1	85 ± 10
2.3	4.2 ± 0.9^b	1.3 ± 0.3^a	79 ± 12^a
4.6	3.8 ± 0.5^c	1.2 ± 0.2^b	62 ± 7^c

Ultrastructurally, TSH cells of rat pituitary

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Received 1997-05-29 Accepted 1998-03-26

showed dilated perinuclear space and rough endoplasmic reticulum, swollen or vacuolated mitochondria, but no change was seen in cells of thyroid, which indicated that Cyp induced the retrograde changes of TSH cells of rat pituitary (Fig 1).

Function of pancreatic β cells in rats

Cyp (2.3 mg·kg^{-1}·d^{-1} ig for 10 d) decreased serum insulin level ($P < 0.01$), but blood glucose concentration was still unchanged. After ig Cyp 4.6 mg·kg^{-1}·d^{-1}, serum insulin concentration was remarkably decreased, and blood glucose level was increased (Tab 2).

Tab 2. Effect of Cyp on function of pancreatic β cells in rats. $n = 8$, $\bar{x} \pm s$. $^{a}P > 0.05$, $^{c}P < 0.01$ *vs* control.

Cyproheptadine/ mg·kg^{-1}	Insulin/kU·L^{-1}	Blood glucose/ mmol·L^{-1}
0	64 ± 8	3.8 ± 0.5
2.3	50 ± 9^{c}	3.9 ± 0.6^{a}
4.6	42 ± 8^{c}	4.5 ± 0.5^{c}

Ultrastructurally, as compared with control group, 10 d after ig Cyp, the 2 types of morphological changes were found in pancreatic β cells. The one had no obvious abnormality with only decreased cytoplasmic matrix density, big round nucleus with clear nucleolus and fewer heterochromatin, dilated slightly Golgi complex; the other cells presented degeneration, some cells had increased cytoplasmic matrix density, concentrated nucleus and fewer granules. Of them, more mitochondria or increased core density granules with large halo and swollen or vacuolated mitochondria were found; some cells were filled with vacuoles. But no change was found in A cell within the same field. Cyp induced the changes of pancreatic β cells specially, which were mainly degenerative changes (Fig 1).

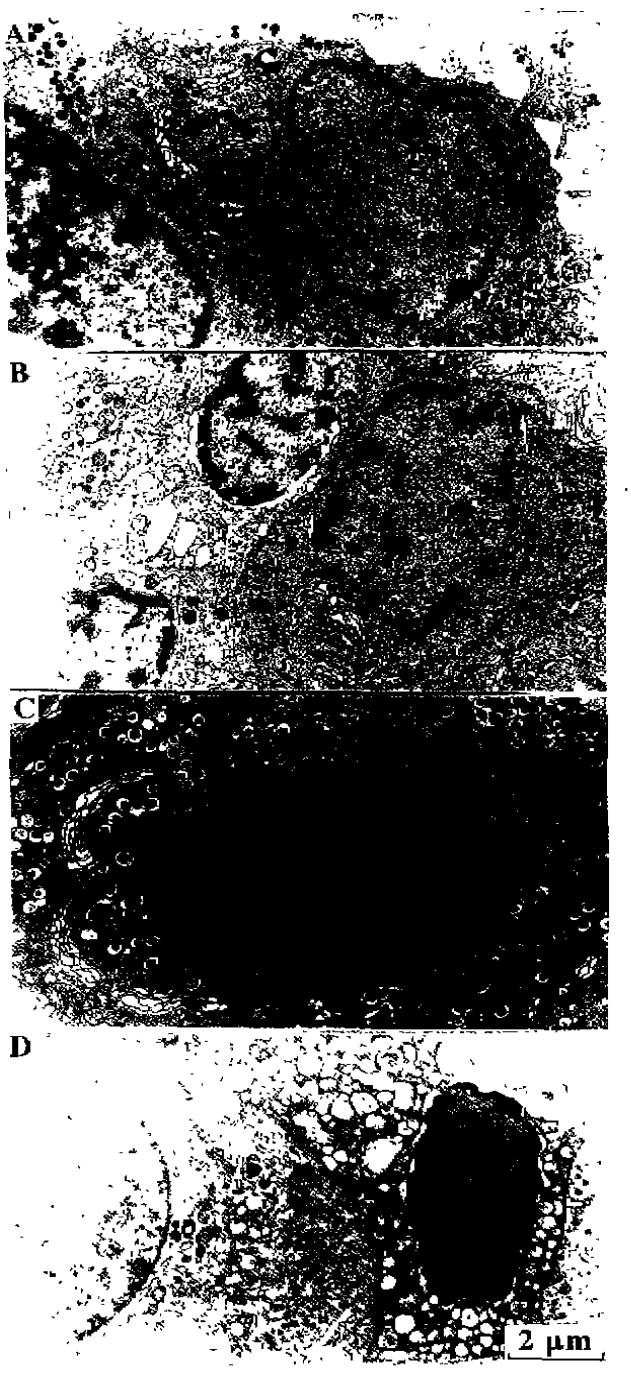

Fig 1. Effects of Cyp on TSH cells of pituitary and pancreatic β cells in rats (×6100). A) TSH cells of pituitary in control group; B) Cyp (4.6 mg·kg^{-1}, ig, 10 d), TSH cells of pituitary; C) The pancreatic β cells in control group; D) Cyp (4.6 mg·kg^{-1}, ig, 10 d), the pancreatic β cells.

DISCUSSION

The previous work proved that 5-HT concentration of central nervous system (CNS) was closely related to the endocrine function of pituitary and Cyp was a 5-*HT* S_2 receptor antagonist[7]. The present study demonstrated that Cyp (2.3 mg·kg^{-1} ig for 10 d) decreased serum TSH and insulin concentration, but serum T_3, T_4, and blood glucose levels were still unchanged. However, after ig Cyp 4.6 mg·kg^{-1}, serum TSH, T_3, T_4, and insulin levels were obviously decreased, the blood glucose level

was increased. These findings suggest that the long-term administration of Cyp first affect the TSH secretion through blocking 5-HT receptors at the pituitary level, and result in a significant decrease in the serum TSH concentration. With the regulation of the pituitary-thyroid axis, the thyroid cells reduced the synthesis of thyroid hormones. It causes a significant decrease in the serum T_3 and T_4 concentrations. Cyp also inhibited the insulin secretion in rat pancreatic β cells, and resulted in an increase of the blood sugar. By histology investigation, the retrograde changes of pituitary TSH cells and pancreatic β cells were observed. The results stated above indicated that Cyp had an inhibitory action on endocrine functions of pituitary-thyroid axis and pancreatic β cells in rats, suggesting that clinical patients treated with Cyp should be examined in serum TSH, T_3, T_4, and insulin levels regularly. In addition, Cyp should be cautiously applied for the patients with hypothyroidism, diabetes, and senility to reduce its side effects.

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554-556 (14)

赛庚啶对大鼠垂体-甲状腺轴和胰岛β细胞的抑制作用

R976

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关键词 赛庚啶; 垂体腺; 甲状腺; 胰岛; 电子显微镜检查

目的: 研究赛庚啶(Cyp)对大鼠垂体-甲状腺轴和胰岛β细胞内分泌功能的影响. **方法**: 用放射免疫测定法及生化分析法观察赛庚啶对大鼠垂体-甲状腺轴和胰岛β细胞内分泌功能的影响. **结果**: Cyp 2.3 $mg \cdot kg^{-1}$, ig 10 d, 使大鼠血清 TSH、胰岛素含量均降低, 而 T_3、T_4 及血糖水平无明显改变. Cyp 4.6 $mg \cdot kg^{-1}$引起血清 TSH、T_3、T_4 和胰岛素含量显著降低, 血糖水平明显升高; 垂体 TSH 细胞和胰岛β细胞的超微结构亦发生不同程度的退行性变化. **结论**: Cyp 对垂体-甲状腺轴和胰岛β细胞的内分泌功能有抑制作用.