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Effect of Thyroxie and Propylthiouracil on the Responses of Plasma Corticosterone and Brain Norepinephrine to Swim-Stress

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ABSTRACT

The circadian rhythm of spontaneous motor activity was not significantly altered by T_4 (4 mg/kg, i.p. inj. once a day for 5 days: T_4) and PTU (fed ad lib in 0.01% drinking water for 5 weeks: PTU). The plasma thyroxine level was markedly increased by T_4 but reduced by PTU, and the plasma thyrotropin level was markedly increased by PTU but moderately increased by T_4. Clonidine slightly increased the plasma CS level, but the clonidine effect was significantly enhanced by T_4-pretreatment. The brain NE and MHPG contents were little affected by T_4 but the NE content was significantly decreased by PTU. The SS-induced increase of plasma CS level was moderately decreased by PTU but increased by T_4. However, clonidine significantly inhibited the SS-induced increase, and the inhibitory effect of clonidine was not significantly affected by PTU and T_4, respectively.

The brain MHPG content and MHPG/NE ratio were significantly decreased by clonidine but increased by SS. The clonidine- and SS-induced changes of brain MHPG content and MHPG/NE ratio were not altered by T_4. PTU did not affect the SS-induced increase of brain NE turnover but significantly attenuated the clonidine-induced decrease. The SS-induced increases of brain MHPG content and MHPG/NE rtatio were markedly inhibited by clonidine, and the inhibitory effect of clonidine was not affected by T_4 and PTU, respectively.

These results suggest that the responses to swim-stress is not signigicantly affected by the alteration of thyroid function and that the hypothalamo-adenohypophysis-adrenocortical stimulation in response to swim-stress seems to be mediated via hypothalamic noradrenergic activation, and the stress response may be inhibited by the agonistic activity of clonidine on the presynaptic α_2-adrenoceptor.

Key Words: Swim-Stress, Brain norepinephrine, Plasma corticosterone, Thyroxine propylthiouracil, Clonidine

INTRODUCTION

The specific roles of hypothalamic monoamines in mediating the responses of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) to various stresses have received much attention over many years but still remain to be established (Jones *et al.*, 1976; Buckingham, 1980; Tuomisto and Mannisto, 1985).

But it is well known that the paraventricular and ventromedial nuclei (PVN and VMN) of the hypothalamus activate the adenohypophyseal-adrenocortical system (Filaretov and Filaretov, 1985; Sawchenko and Swanson, 1985; Szafarczyk *et al.*, 1985). Immunohistochemical studies (Bugnon *et al.*, 1980; Bloom *et al.*, 1982; Sawchenko and Swanson, 1985) confirmed that the area containing the PVN has a high CRH activity.

The principal region of the PVN shows a more significant role in controlling the circadian ACTH rhythm and the ACTH surge after ether stress than that of the VMN (Makara *et al.*, 1985).

The principal afferent inputs to the PVN are conveyed by ventral noradrenergic-ascending bundle (VNAB) (Sawchenko and Swanson, 1983; Szafarczyk *et al.*, 1985), which originates from the A_2 groups of medullary neurons and to a small extent from the locus ceruleus (Swanson and Sawchenko, 1983).

It has been assumed that increase of the norepinephrine (NE) neuronal activity stimulates the release of CRH from the hypothalamus (Smythe *et al.,* 1983; Szfarczyk *et al.,* 1985; Sawchenko and Swanson, 1985).

During acute stress, the decrease of brain NE content has been shown to reflect strongly enhanced NE release which exceeds the amine synthesis (Stone, 1973; Stolk *et al.,* 1974; Hedge *et al.,* 2976; Nakagawa, *et al.,* 1981). And Seo *et al.* (1988) and Hong *et al.* (1988) reported that the increase of plasma coriticosterone level in response to swim-stress (SS) was significantly inhibited by clonidine.

By the way, Prange *et al.* (1970) reported that the NE synthesis and turnover rates of the brain of hyperthyroid rats were decreased, and Sellers *et al.* (1974) proposed that a reciprocal relationship exists between the NE turnover and the level of thyroid hormone. While it has been shown that the thyroid plays an important role in circardian adrenocortical rhythm (Meier, 1976; Ottenweller and Hedge, 1981), Kamilaris *et al.* (1987) reported that the release of hypothalamic CRH and/or other ACTH secretagogues may be decreased in hypothyroidism. Therefore, the present study was undertaken to study the influence of thyroid function 1) on the circardian rhythm, 2) on the SS-induced changes of brain NE turnover and plasma CS level, and 3) on the inhibitory clonidine effect in the response to SS, in male rats pretreated with l-thyroxine or propylthiouracil.

MATERIALS AND METHODS

Materials

Propylthiouracil, l-thyroxine sodium, corticosterone acetate, norepinephrine hydrochloride, sodium octane-sulfonate, and 3-methoxy-4-hydroxyphenylglycol were purchased from Sigma. Clonidine was from Boehringer-Ingelheim. Methanol was a high performance liquid chromatographic (HPLC)-grade of Merck. Other chemicals were analytical grade.

Animal treatment

Twenty male ICR mice (weighing 18~22 g) were housed in a single cage. Food and water were given ad libitum. The room were kept at constant temperature (21±2℃) and on a schedule of 12-hr light (at 8 AM)-dark cycle.

Propylthiouracil (0.01%) dissolved in the drinking water containing 0.8% ethanol, was fed ad lib for 5 weeks, and sodium l-thyroxine (4 mg/kg) was intaperitoneally injected in an isotonic NaCl solution at 10 AM once a day for 5 days. The animals, at 10 AM on the next day after the last dose, were intraperitoneally given clonidine (500 ug/kg) 30 minutes prior to be exposed to swim-stress.

Analysis of spontaneous motor activity

The sum of spotaneous motor activities of two mice was measured in a translucent cage (23×30×17 cm), which was equipped with two horizontal infra-red beams (PL3-L photocell: Hokuyo Co., Japan) arranged at right angle (Robbins, 1977).

Methods of Swim-Stress induction

The swim-stress (SS) was given at 20±1℃ in a glass cylinder (1.D.25 cm×depth 18 cm)for 5 minutes, according to the modified method (Seo et al., 1988) originally designed by Le Fur *et al* (1979).

Plasma corticosterone measurement

The plasma corticosterone (CS) level of the blood sample obtained 30 minutes and 1 hour after the exposure to SS, was determined by Aminco-Bowman spectrofluorophotometer, according to the method of Zenker and Berstein (1958).

Radio-Immuno-Assay of plasma thyroxine and thyrotropin

The plasma thyroxine was measured by a Magic T_4 kit (CIBA Corning), and the plasma thyrotropin was measured by a Abbott TSH-RIA kit, using a packard gamma-counter.

Analysis of brain NE and MHPG

Brain NE and MHPG was extracted in 0.4 M perchloric acid, and then was analyzed by an isocratic HPLC system equipped with a Erma ERC-ODS-1262 column a Gilson 302/5 pump and a Gilson 141 electrochemical detector (Gilson), according to the ion-pairing reversed-phase HPLC method (Hong *et al.,* 1988). The HPLC

parameters were as follows; the capacity factors were MHPG: 3.91 and NE: 5.73, and the detection sensitivity were MHPG: 5.7 pg and NE: 6.2 pg.

RESULTS

Effects of PTU and T_4 plasma thyroxine and thyrotropin levels

As shown in Fig. 1, PTU (0.05%) in drinking for 5 weeks (PTU) resulted in the significant decrease of plasma T_4 level (control value: 4.62±0.87 ug/dl) down to 1.20±0.34 ug/dl and the marked increase of plasma TSH level (control value: 0.87±0.34 uIU/ml) up to 3.67±0.83 uIU/ml, while T_4 (4 mg/kg/day) i.p. injection for 5 days (T_4) resulted in the marked increase of plasma T_4 level and the significant decrease of plasma TSH level.

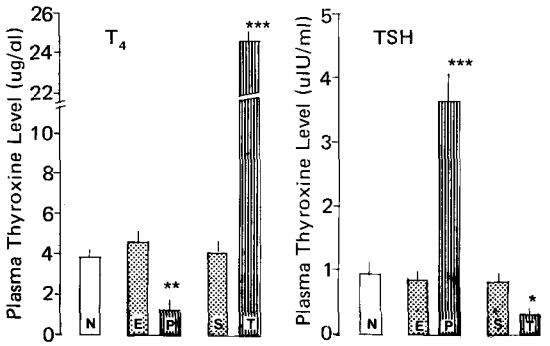

Fig. 1. Changes of plasma thyroxine (T_4) and thyrotropin (TSH) levels in the mice pretreated by propylthiouracil and l-thyroxine, respectively.
Abbreviations-N: normal, E: 0.8% ethanol, P: PTU, S: saline, T: l-thyroixine
Data indicate the mean±standard error of 4 to 6 samples. *, **, and *** indicate $p<0.05$, $p<0.02$, and $p<0.01$, respectively.

Effects of PTU and T_4 on circadian spontaneous motor activity (SMA)

The circadian pattens (Fig. 2) of SMA counts of two mice obtained by a photocel cage method showed a clear rhythm with the maxium values at early night (691-730) and the minium values at late afternoon (134-215). The circadian rhythm was well preserved even after the treatment of PTU or T_4.

Effects of PTU and T_4 on the responses of plasma corticosterone (CS) level to clonidine and swim-stress (SS)

Comparing to the control values, the plasma CS level was slightly low in the mice pretreated with PTU but significantly high in the T_4-pretreated. And the plasma CS level of the T_4 group was significantly increased by clonidine (500 ug/kg) i.p. injection (C-500), but C-500 did

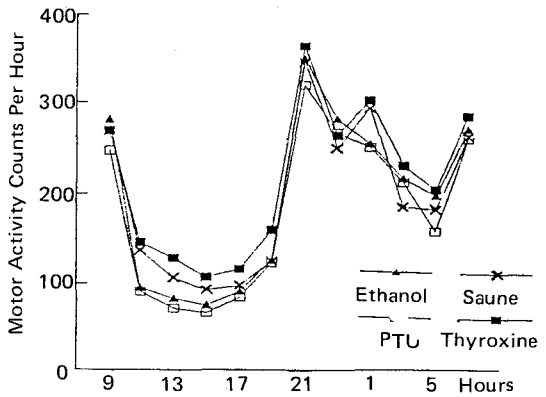

Fig. 2. Effects of PTU and T_4 on the circadian rhythm of spontaneous motor activity.

Table 1. Influence of clonidine on the plasma corticosterone level of male mice pretreated with PTU and thyroxine

Treatment	Minutes after clonidine injection		
	0	30	50
Ethanol	237.39±21.60	293.02±21.78	260.92±23.66
PTU	200.67±13.24	316.53±18.84***	220.88±18.74
Saline	223.60±21.15	264.50±25.87	206.61±12.64
Thyroxine	346.22±23.21***	453.02±37.07***	414.45±22.26

Data indicate mean±standard error (ng/ml) of 7 or more samples.
*** indicates $p<0.01$.

little affect the CS level in the PTU group, comparing to the control values (Teble 1).

Fig. 3 shows that the increase of plasma CS level in response to SS was somewhat smaller in

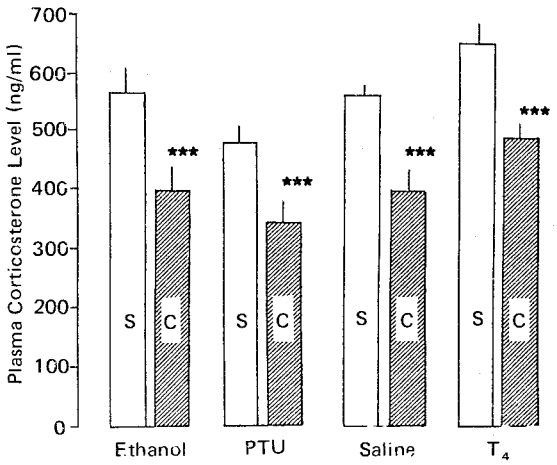

Fig. 3. Influences of PTU and T_4 on the inhibitory effect of clolidine in response of plasma corticosterone level to swim-strees at 20℃. Abbreviations-S: saline, C: clonidine

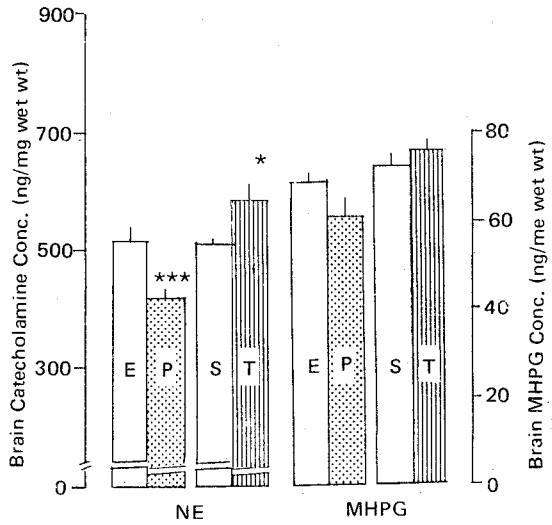

Fig. 4. Influence of PTU and thyroxine on the brain NE and MHPG contents.
* and *** indicate $p<0.05$ and $p<0.01$, respectively.

Table 2. Influence of PTU on the changes induced by swim-stress or clonidine of the brain NE, MHPG, and MHPG/NE ratio

	Treatment	NE#	MHPG#	MHPG/NE (%)§
Ethanol:	+Saline: Control	552.2±20.98	76.0±0.70	13.7±0.49
	+Clonidine	469.5±23.45	45.0±3.53^{+++}	9.5±0.40^{+++}
	+Swim-stress	517.0±25.31	86.5±1.06^{+++}	16.7±1.18
PTU:	+Saline: Control	***426.8±18.45	***60.0±3.35	14.1±0.83
	+Clonidine	*384.3± 3.78	50.0±1.53	*13.0±1.07
	+Swim-stress	445.6±26.64	$^{++}$77.7±3.28	17.4±1.38

and § indicate mean±S.E (ng/mg wet weight and MHPG/NE×100, respetively) of 7 or more samples.
* and *** indicate the significant differences: $p<0.05$ and $p<0.01$, respectively, from the corresponding level of ethanol group.

Table 3. Influence of T_4 on the changes induced by swim-stress or clonidine of the brain NE, MHPG, and MHPG/NE ratio

	Treatment	NE	MHPG	MHPG/NE (%)
Saline	+Saline: Control	607.3±24.58	73.0±2.06	12.1±0.89
	+Clonidine	526.7±15.50	41.0±2.29^{+++}	7.8±0.34^{+++}
	+Swim-stress	591.0±25.31	95.0±2.71^{+++}	16.0±1.02^{+}
T_4	+Saline: Control	621.5±32.41	79.0±2.62	12.9±1.01
	+Clonidine	535.0±21.92	50.0±2.15^{+++}	9.4±1.12
	+Swim-stress	*502.7±14.54^{+}	95.8±3.23^{++}	18.9±0.61^{+++}

* indicates the significant difference ($p<0.05$) from the corresponding level of saline group.

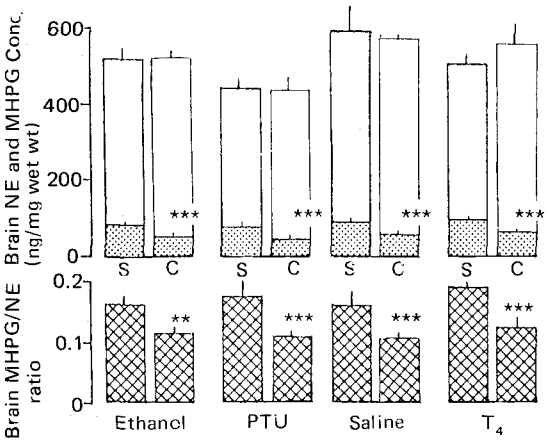

Fig. 5. Influence of clonidine on the response of brain NE, MHPG, MHPG/NE ratio to swim stress in the mice pretreated with PTU and thyroxine, respectively. ** and *** indicate $p<0.02$ and $p<0.01$, respectively.

the PTU group and was slightly enhanced in the T_4 group. However the SS-induced increases of plasma CS level in the both groups were significantly suppressed by C-500.

Effects of PTU and T_4 on the changes induced by swim-stress and clonidine of brain NE and MHPG contents

As shown in Fig. 4, the brain NE content was significantly reduced by PTU, but moderately increased by T_4. C-500 did significantly reduced the brain MHPG content as well as the MHPG/NE ratio (Table 2 and 3). But SS, in contrast to C-500, increased both the brain MHPG content and MHPG/NE ratio (Table 2 and 3). Those effects of C-500 and SS were not changed in the T_4 group (Table 3), but in the experiments of the PTU group, the brain contents of NE and MHPG, was moderately lower, and the MHPG/NE rato was little different (Table 2), comparing to those of the control: ethanol gorup (Table 2).

Effects of PTU and T_4 on the clonidine-induced inhibition on the responses to swim-stress

The SS-induced increases of both the plasma CS level (Fig. 3) and the brain MPHG content and MHPG/NE ratio (Table 2 and 3) were significantly suppressed by the pretreatment with C-500, and the inhibitory activities of clonidine were not affected by the alteration of plasma thyroid hormone level (Fig. 5).

DISCUSSION

Many of the clinical manefestations characteristic of hyperthyroidism are similar to those induced by adrenergic stimulation, and those clinical responses are often attenuated by β-adrenergic blockades (Grossman *et al.* 1971).

Williams and Lefkowitz (1977) demostrated the first direct evidence that thyroid hormone can increase the number of β-adrenoceptor. Goodkin *et al.* (1961) reported that myocardial catechlamine content revealed a singificant increase in the thyrotoxic guinea pig and a significant decrease in the hypothyroid animals. Recently, the study of Harris *et al.* (1987) showed that postnatal methimazole treatment resulted in the reduction of the hypothalamic NE synthesis rate and tyrosine content. But many investigators (Lipton *et al.*, 1968; Landsberg and Axelrod, 1968; Pranfge *et al.*, 1970; Sato *et al.*, 1986) suggested that NE synthesis and turnover rates are reduced in hyperthyroidism and vice versa in hypothyroidism, and Sellers *et al.* (1974) proposed that a reciprocal relationship exists between the NE turnover rate and the level of thyroid hormone. By the way, the hypothalamic catecholamines have been considered as a putative mediator of the stimulatory response of hypothalamo-adenohypophysis to certain conditions of stress (River and Vale, 1983; Siegel *et al.*, 1983; Szfarczyk *et al.*, 1985), although Ganong (1980) and others (Rose *et al.*, 1976; Buckingham and Hodges, 1977) have found that catecholamines released centrally inhibit stress-induced ACTH secretion. While the biological roles of thyroid hormone in the regulation of hypothalamo-pituitary-adrenal function have been received much attention but still remain to be established (Minozzi *et al.*, 1973; Ottenweller and Hedge, 1981; Smythe *et al.*, 1983; Meier, 1876; Harris *et al.*, 1987).

The present study was undertaken to study the influences of altered plasma thyroid hormone level ① on the circadian rhythm spontaneous motor activity, ② on the responses of brain NE turnover and plasma CS level to swim-stress, and ③ on the inhibitory effect of clonidine in response to SS in

male mice pretreated with T_4 and PTU.

In this study, the circadian pattern of spontaneous motor activity (Fig. 2) was not affected by the T_4 or PTU treatment, in disagreement with the previous papers (Ottenweller and Hege, 1981; Murakami *et al.*, 1984) that thyroidectomy resulted in the loss of an overt adrenocortical rhythm by decreasing the amplitude. But the amplitude of circadian aplasma CS level was moderately attenuated by the PTU-treatment, without any time-based change of the rhythm (not shown in this paper). However, any change in response of brain NE and plasma CS to swim-stress was not found.

The plasma CS level of PTU-treated group was little different from that of the control group, but in the T_4-treated group, the plams CS level was significantly high and furthermore increased by clonidine, comparing with those of the control group (Tabel 1). As shown in Fig. 3, the increase of plasma CS in response to SS was slightly attenuated by PTU but was rather enhanced by T_4. Clonidine 500 ug/kg significantly inhibited the SS-induced increase of plasma CS level, and the inhibitory effect of clonidine was not affected by the pretreatment with PTU or T_4.

These results are in agreement with the previous reports suggesting ① that the pituitary ACTH content and amplitude of circadian plasma CS were gradually decreased with time after thyroidectomy, and the decreased values were restored by T_4 to the previous ones (Murakami *et al.*, 1984), ② that the release of hypothalamic CRH and/or other ACTH secretagogues may be decreased in hypothroidism (Kamilaris *et al.*, 1987), and ③ that following pretreatment with T_4, the brain NE turnover was increased, as well as the sensitivity of adrenoceptor to clonidine (Engstrom, *et al.*, 1974).

By the way, adrenoceptor agonists, including NE and clonidine, have be assumed to stimulate the releases of hypothalami CRH (Smythe *et al.*, 1983; Szfarczyk *et al.*, 1985; Sawchenko and Swanson, 1985) and adrenohypophysial ACTH (Immura *et al.*, 1974; Giguere *et al.*, 1981, 1983; Tilders et al., 1985; Milson et al., 1986).

In the PTU-treated group (Table 2), the brain NE and MHPG contents were moderately decreased without any change of MHPG/NE ratio, and the SS-induced increases of brain MHPG conent and MHPG/NE ratio was little changed, but the clonidine-induced decrease of brain MHPG/NE ratio was singificantly attenuated by the PTU pretreatment.

The brain NE and MHPG contents and MHPG/NE ratio of the T_4-pretreatment group were not different from those of the control gorup (Table 3). However, the inhibitory effect of clonidine was not affected by the alteration of plasma thyroid hormone level (Fig.5).

The data presented here, in consideration of the previous reports showing the stimulatory effect of catecholamines on adenohypophysial ACTH release (River and Vale, 1983; Tilders et al., 1985), support ① that ventral medullary noradrenergic ascending bundle facilitates both the diurnal and stress-induced increase of ACTH release (Makare *et al.*, 1981; Filaretove and Filaretove, 1985; Szafarczyk *et al.*, 1985), ② that the inhibitory effect of clonidine on the SS-induced stimulation of the hypothalamo-adenohypophysis may be mediated by its agonist activity on the presynaptic α_2-adrenocept (Seo *et al.*, 1988; Hong *et al.*, 1988; Ganong *et al.*, 1976; Rudolph *et al.*, 1980), and ③ that although the thyroid might play a some role in circadian rhythm of blood corticosterone level (Meier, 1976; Ottenwell nd Hedge, 1981; Murakami *et al.*, 1984), the response of the hypothalamo-adenohypophysis to SS may not be under the control of the thyroid function.

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= 국문초록 =

水泳-스트레스에 의한 혈장 *Corticosterone* 함량 및 腦 *Catecholamine*代謝의 變動에 미치는 *Thyroxine* 및 *Propylthiouracil*의 영향

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수영-스트레스로 나타나는 뇌 catecholamine대사 및 혈장 corticosterone 함량의 변동에 대한 clonidine(500 ug/kg)의 억제작용을 propylthiouracil(0.01% 용액으로 5주간 마시게함) 및 l-thyrorine(4 mg/kg/day로 5일간 복강내에 주사)로 처치한 웅성-마우스에서 실험관찰하여 다음과 같은 성적을 얻었다.

마우스의 일과성 자발운동량의 변동은 갑상선-홀몬의 변동에 영향을 받지 않았고, 수영스트레스(SS)로 나타나는 혈장 corticosterone(CS)의 증가가 propylthiouracil 전처치(PTU) 및 l-thyroxine 전처치(T4)로 각각 다소의 감소 및 증강됨을 보였으나, SS에 의한 혈장 CS증가에 대한 clonidine의 억제작용은 PTU 및 T4의 영향을 받지 않았다.

SS부하로 뇌 3-methoxy-4-hydroxyphenylglycol 함량(MHPG)가 유의하게 증가되고 clonidine에 의하여는 MHPG가 현저히 감소되었으나 뇌 norepinephrine 함량(NE)은 별 변동을 보이지 않아서 MHPG/NE비는 SS와 clonidine에 의하여 각각 현저한 증가 및 감소를 나타내었다. 아울러, PTU 및 T4은 각각 뇌NE을 유의하게 감소 또는 증가시켰으나 뇌 MHPG에는 별 영향을 미치지 않았다. Clonidine은 SS에 의한 뇌 MHPG 및 MHPG/NE비의 증가를 모두 현저히 억제하였으며 그 억제작용은 PTU 및 T4에 의하여 별 영향을 받지 않았다.

이상의 성적으로 미루어서, 마우스의 일과성 자발운동양상 및 스트레스반응으로 나타나는 혈장 corticosterone의 증가현상등이 갑상선-홀몬의 변동에 별 영향을 받지 않으며, 시상하부-뇌하수체-부신계의 활성화가 시상하부의 norepinephrine성 신경-흥분에 매개되어 나타나는 바, 스트레스성 혈장 corticosterone 증가에 대한 clonidine의 억제작용이 그의 절전-α_2-adrenoceptor agonist 작용에 기인되는 것으로 사료된다.