The Role of Peripheral Chemoreceptor Activity on the Respiratory Responses to Hypoxia and Hypercapnia in Anaesthetised Rabbits with Induced Hypothyroidism

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Abstract

The purpose of this study was to investigate the role of peripheral chemoreceptor activity on the hypoxic and hypercapnic ventilatory drives in rabbits with induced hypothyroidism. Experiments were carried out in control and hypothyroid rabbits. Hypothyroidism was induced by an administration of an iodide-blocker, methimazole in food (75 mg/100 g food) for ten weeks. At the end of the tenth week, triiodothyronine (T_3) and thyroxine (T_4) levels significantly decreased ($P<0.001$) while thyroid stimulating hormone (TSH) increased ($P<0.001$). Tidal volume (V_T), respiratory frequency (f/min), ventilation minute volume ($\dot{V}_E$) and systemic arterial blood pressure (BP) were recorded during the breathing of the normoxic, hypoxic (8% O_2 - 92% N_2) and hypercapnic (6% CO_2-Air) gas mixtures, in the anaesthetised rabbits of both groups. At the end of each experimental phase, PaO_2, $PaCO_2$, and pHa were measured. The same experimental procedure was repeated after peripheral chemoreceptor denervation in both groups. V_T significantly decreased in some of the rabbits with hypothyroidism during the breathing of the hypoxic gas mixture (nonresponsive subgroup) ($P<0.05$). After chemodenervation, a decrease in V_T was observed in this nonresponsive subgroup during normoxia ($P<0.05$). The percent decrease in V_T in nonresponsive subgroup of hypothyroid rabbits after chemodenervation was lower than that of the chemodenervated control animals ($P<0.01$). When these rabbits with hypothyroidism were allowed to breath the hypercapnic gas mixtures, increases in V_T and $\dot{V}_E$ were not significant. In conclusion, although there is a decrease in peripheral chemoreceptor activity in hypothyroidism, it does not seem to be the only cause of decrease in ventilatory drive during hypoxia and hypercapnia.

Key Words: hypothyroidism, respiratory pattern, hypoxia, hypercapnia, peripheral chemoreceptors

Introduction

Hypothyroid patients have been reported to have abnormalities in pulmonary functions and central respiratory control mechanisms (23, 24). It was declared that there were some changes in tidal volume and CO diffusion capacity in the patients with myxedema (14). The reduction of the ventilatory response to hypercapnia and hypoxia is the most important abnormality in hypothyroidism (10).

The reasons why hypothyroid patients can develop alveolar hypoventilation have not been clarified. It has been suggested that depression of respiratory centers causing a decreased inspiratory neural drive may be involved (4, 10). On the other hand, decrease in inspiratory muscle force, i.e.,

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muscle-weakness, has also been thought to play a role (11, 13). In fact, the severe myopathy described in hypothyroid adults (8) may also affect respiratory muscles (6). Laroche *et al*. (11) suggested that those respiratory changes might occur as a result of respiratory muscle weakness or neuropathy of phrenic nerve. Ladenson *et al*. (10) investigated the prevalence of impaired hypoxic and hypercapnic ventilatory responses and they evaluated the clinical and chemical parameters that might predict the presence of abnormal ventilatory control in hypothyroid patients. These authors reported that only a subset of patients may have a blunted respiratory response to either hypercapnic (34%) or hypoxic (27%) stimulation. Hypothyroid patients with higher values of serum thyroid stimulating hormone (TSH) were more likely to have impaired ventilatory responses. On the other hand, some studies present the stimulation of the respiratory center by thyrotropin releasing hormone (TRH) (15). The rostral ventrolateral medulla (RVLM) contains neurons that are important in the control of breathing. An important component of the RVLM is the retrotrapezoid nucleus (RTN) and injections of TRH to this area cause respiratory stimulation (2).

In our previous study (21) we observed hypoventilation in hypothyroid rabbits. We saw a depression in ventilation during hypoxic gas mixture breathing compared to control group. We had suggested that decrease in ventilation during hypoxia might be due to either decrease in sensitivity of peripheral chemoreceptors or depression of central mechanisms.

In this study, we investigated the effect of peripheral chemoreceptors on the ventilatory response in rabbits with induced hypothyroidism. We studied the responses of the rabbits to hypoxia and hypercapnia before and after chemodenervation.

Materials and Methods

Experiments were carried out in 12 hypothyroid and 5 control rabbits of either sex (2.5-3.5 kg body wt). The rabbits were supplied by DETAM (Medical and Biological Research Center of Istanbul University, Istanbul). The animals were permitted *ad libitum* access to standard laboratory chow and tap water. Hypothyroidism was induced by adding methimazole (Abdi İbrahim Inc, Istanbul, Turkey) which is an iodide blocker (75 mg in 100 g of food) for 10 weeks (3, 20).

Blood samples were taken before and after ten weeks of methimazole administration. Plasma thyroxine (T_4), triiodothyronine (T_3), and thyroid stimulating hormone (TSH) were determined by chemiluminescent enzyme immunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA). Decreases in T_3 and T_4 and increase in TSH were taken as criteria for hypothyroidism. Both control and hypothyroid rabbits were anaesthetised with pentothal-Na (25 mg/kg, i.v.) (Abbott, Latina, Italy). Tracheotomy was performed and a cannula was inserted into the trachea.

Both femoral arteries and the left femoral vein were catheterized. Liquemin (F. Hoffman-La Roche Ltd., Basel, Switzerland) was injected (0.2 ml/kg, i.v.) into the rabbits.

An inspiratory-expiratory valve, attached to the tracheal cannula, was connected *via* a three-way valve to a spirometer containing 8% O_2 in N_2 or 6% CO_2 in air. Thus, the animal was allowed to breathe through the inspiratory port of the valve either atmospheric air, hypoxic, or hypercapnic gas mixtures from the spirometer.

For the recording of tidal volume (V_T) and respiratory frequency (breaths/min), the expiratory outlet of the valve was connected to a Grass 7 Polygraph (West Warwick, RI, USA) by means of a pneumotachograph and a Grass PT-5 volumetric pressure transducer. For these processes 7 PI low level DC preamplifier, DC driver amplifier and 7 P10 integrator channel were used. Hence, the flow from the pneumotachograph was measured and then integrated into tidal volume.

Ventilation minute volume ($\dot{V}_E$) was calculated from the values of V_T and breaths/min (f). Systemic arterial pressure (BP) was recorded from the femoral artery by physiological pressure transducer (Statham Laboratories, Inc., Hato Rey, Puerto Rico).

To determine the effect of hypothyroidism on peripheral chemoreceptors, chemodenervation was done in both groups to eliminate the chemoreceptor impulses.

Carotid denervation was performed by bilateral section of the carotid sinus “nerve”. The surrounding tissues were damaged at the bifurcation level of the common carotid artery bilaterally (7, 17). These regions were also flushed with alcohol and then phenol, after which the sites were rinsed thoroughly with saline solution (0.9% NaCl) (5, 7, 22).

To denervate the aortic chemoreceptors, aortic nerves were isolated and cut bilaterally on middle cervical region (5, 7, 22). Chemodenervation was tested by the absence of ventilatory response to intravenous injection of potassium cyanide (40 µg/kg i.v).

At the end of each experimental phase, arterial blood samples were obtained from the femoral artery. PaO_2, $PaCO_2$ and pHa were determined using blood gas analyser (Ciba Corning 860, Medifield, MA, USA), at a temperature of 37°C.

Animals were divided into two groups, control and hypothyroid groups. During the experiment, the

hypothyroid rabbits were divided into two subgroups as responsive and nonresponsive, according to their responses to hypoxia.

The experimental procedure in both groups was as follows:

The animals were allowed to breathe atmospheric air for 15 min. Mean tidal volume and respiratory frequency were measured from the spirogram after it had attained a steady state level. Following the air breathing phase, animals were allowed to breathe hypoxic gas mixture (8% O_2- 92% N_2) for 3 min. After another phase of air breathing for 15 min to normalize the ventilatory parameters, the animals were allowed to breathe hypercapnic gas mixture (6% CO_2-94% air) for 3 min.

After peripheral chemodenervation, the same experimental procedure was followed and changes in the investigated parameters were recorded.

Statistical Analysis

The statistical significance of the differences between experimental phases for control and hypothyroid groups were determined by Wilcoxon-Matched Paired *t*-test. Mann-Whitney U test was used to determine the statistical significance between the control and hypothyroid groups.

Results

Table 1 shows the values of T_3, T_4, TSH and body weights before and ten weeks after the methimazole administration. Significant decreases in T_3 and T_4 and increase in TSH values were taken as a criterion for development of hypothyroidism.

Control Group

Responses to hypoxia – When control group rabbits were allowed to breathe the hypoxic gas mixture, f, V_T and $\dot{V}_E$ increased significantly (P<0.05, P< 0.01, P<0.001). BP also increased significantly, as expected (P<0.01). Blood gas analysis showed appropriate changes with respiratory responses. On the breathing of hypoxic gas mixture, PaO_2 and $PaCO_2$ decreased significantly (P<0.001). The decrease in $PaCO_2$ was due to hyperventilation. Consequently, an increase was observed in pHa (P<0.05).

Response to hypercapnia – When the control group was allowed to breathe hypercapnic gas mixture, V_T and $\dot{V}_E$ values increased significantly (P<0.01) while there was no change in respiratory frequency. Significant increase in BP was observed during the hypercapnic gas mixture breathing of control rabbits (P<0.01) (Table 2). PaO_2 and $PaCO_2$ increased significantly (P<0.001) while a significant decrease (P<0.001) occured in pHa (Table 2).

Table 1. Plasma levels of measured parameters and body weights of rabbits before and ten weeks after methimazole administration (Means ± SD; n=12)

	Before	After
T_3 (ng/dl)	72.96±5.26	35.57±3.94***
T_4 (μg/dl)	2.36±0.25	1.72±0.20***
TSH (μIU/mL)	0.023±0.004	0.046±0.014***
Body wt. (kg)	3.13±0.38	3.22±0.41*

As compared with before methimazole administration (P<0.05, ***P<0.001).

Hypothyroid Group

Response to hypoxia – Breathing of hypoxic gas mixture by the rabbits with induced hypothyroidism (12 rabbits), made no significant change on mean values of f, V_T or $\dot{V}_E$ (Table 2). There was no change in the BP (Table 2). PaO_2 decreased significantly (P<0.001) and the increase in $PaCO_2$ and pHa were not significant (Table 2).

However, when we looked at each of the V_T responses of the hypothyroid rabbits, 7 of the 12 hypothyroid rabbits showed a significant increase in V_T during hypoxia. This group was designated as responsive subgroup. The V_T response of the remaining 5 hypothyroid rabbits decreased significantly during hypoxia. This group was named as nonresponsive subgroup. Consequently, the rabbits with induced hypothyroidism, were divided into two groups depending on their response to hypoxia as responsive and nonresponsive subgroups.

Nonresponsive subgroup – When the nonresponsive subgroup of hypothyroid rabbits was allowed to breathe hypoxic gas mixture, V_T decreased significantly (P<0.05) during hypoxia, but the decreases in f and $\dot{V}_E$ were insignificant (Fig. 1).

Responsive subgroup – When hypoxic gas mixture was breathed by the responsive subgroup, V_T increased significantly (P<0.01), but increases in f and $\dot{V}_E$ values were insignificant (Table 3).

Responses to hypercapnia – On breathing the hypercapnic gas mixture by the rabbits with induced hypothyroidism (12 rabbits), V_T increased significantly (P<0.01). However the increases in f and $\dot{V}_E$ were not significant (Table 2). The increase in BP was found significant (P<0.01) (Table 2). PaO_2 and $PaCO_2$ increased significantly (P<0.05, P<0.01), while pHa decreased significantly (P<0.05) (Table 2).

Nonresponsive subgroup – When the nonresponsive subgroup of hypothyroid rabbits was allowed to breathe hypercapnic gas mixture, the

Table 2. The parameters of control and of the hypothyroid rabbits breathing air, hypoxic, and hypercapnic gas mixtures. (Means ± SD)

Experimental group	Experimental phase	f (breaths min^{-1})	V_T (mL)	$\dot{V}_E$ (mL/min)	BP (mmHg)	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	pHa
Control	Air	63.4±4.50	20.96±2.28	1322.58±90.79	80.01±10.26	83.6±5.9	38.0±4.7	7.35±0.05
n=5	Hypoxia	68.4±1.51*	30.07±5.08**	2052.89±325.08**	115.20±2.46**	38.9±4.7***	32.6±4.1***	7.37±0.06*
Hypothyroid	Air	76.19±15.85	15.58±6.20	1154.76±444.61	81.67±19.20	78.3±6.7	46.3±8.4	7.23±0.16
n=12	Hypoxia	75.34±14.59	15.73±6.71	1175.69±525.94	84.97±23.06	32.9±6.12***	49.0±7.4	7.21±0.12
Control	Air	65.40±1.51	27.22±8.66	1784.55±587.63	68.10±8.04	83.0±5.6	36.5±2.8	7.34±2.8
n=5	Hypercapnia	65.20±1.78	35.74±6.37**	2332.97±438.55**	87.30±6.03**	102.0±2.8***	48.5±4.2***	7.20±2.8***
Hypothyroid	Air	68.71±14.47	17.25±6.94	1201.47±580.18	68.91±21.02	66.4±8.7	48.3±6.8	7.22±0.12
n=10	Hypercapnia	71.07±14.29	19.34±7.04**	1358.12±575.57	79.01±20.93**	79.6±11.5*	60.2±5.2**	7.10±0.23*

f: Respiratory frequency. V_T: Tidal volume. $\dot{V}_E$: Respiratory minute volume. BP: Blood pressure.
As compared with pre-hypoxic or pre-hypercapnic air phase (P<0.05, **P<0.01, ***P<0.001)

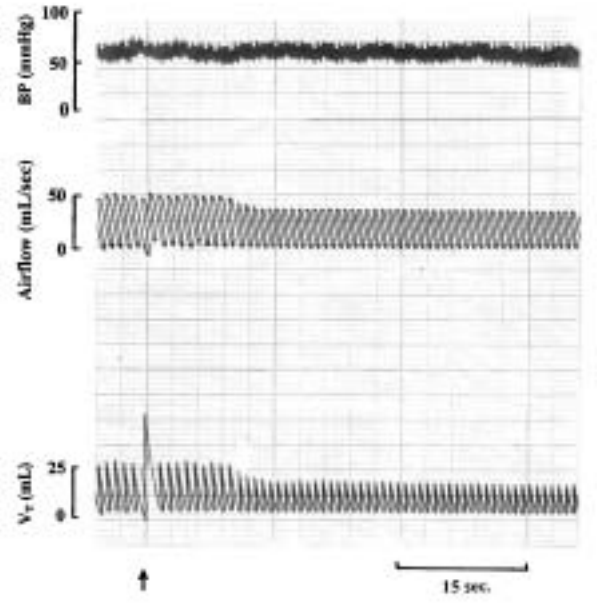

Fig. 1. Respiratory parameters and BP of hypothyroid rabbit nonresponsive to hypoxia BP: Mean arterial blood pressure; V_T: Tidal volume; The arrow indicates the beginning of the hypoxic gas mixture breathing.

changes in f, V_T or $\dot{V}_E$ were not found to be significant (Table 3). Meanwhile, in two of these rabbits no change was observed at all in f, V_T and $\dot{V}_E$ during hypercapnia.

Responsive subgroup – Breathing hypercapnic gas mixture produced significant increases in V_T (P<0.05) and $\dot{V}_E$ (P<0.05) of the responsive subgroup. The increase in f was insignificant (Table 3).

Response to Hypoxia after Chemodenervation

In the control group, during hypoxic gas mixture breathing, V_T and $\dot{V}_E$ decreased significantly (P< 0.001) while there was no change in f. In hypothyroid group there was no significant change in f while V_T decreased significantly (P<0.05). On the other hand, the decrease in $\dot{V}_E$ was not significant (Table 4).

When we compared f, V_T and $\dot{V}_E$ values of the nonresponsive subgroup of hypothyroid rabbits and control group during air breathing before chemodenervation with those after chemodenervation, significant decreases of all values in both groups were noted after chemodenervation (Table 5). When the decreases were compared as percent values, it was seen that decreases in f, V_T and $\dot{V}_E$ values in nonresponsive subgroup were less than those of the control group (P<0.05, P<0.01). The decreases in f, V_T and $\dot{V}_E$ were -6.97±1.86%, -37.43±4.84%, -41.79±5.22% and -2.07±1.49%, -12.02±6.68%, -13.86±6.39% in the control group and nonresponsive subgroup, respectively.

Responses to Hypercapnia after Chemodenervation

After chemodenervation of control and hypothyroid rabbits, on the breathing of hypercapnic gas mixture by both groups of rabbits, f, V_T, and $\dot{V}_E$ values of the control group increased significantly (P<0.01), whereas none of them showed any change in hypothyroid group (Table 4).

Discussion

The effects of hypoxia – As expected, the control animals showed significant increases in f, V_T and $\dot{V}_E$ during hypoxic gas mixture breathing. On the other hand, the increases in the f, V_T, and $\dot{V}_E$ values of the hypothyroid rabbits, were insignificant, when compared with that of the pre-hypoxic air phase. (Table 2). The augmentation in respiratory activity on breathing hypoxic gas mixture is mainly due to the stimulation of carotid chemoreceptors (16). In our study, 5 of the 12 rabbits with induced hypothyroidism were found to be nonresponsive to hypoxia. We also

Table 3. The parameters of the responsive and nonresponsive subgroups of the hypothyroid rabbits breathing air, hypoxic, and hypercapnic gas mixtures. (Means ± SD)

Experimental group	Experimental phase	f (breaths/min)	V_T (mL)	$\dot{V}_E$ (mL/min)
Nonresponsive subgroup n=5	Air	66.63±12.65	15.27±5.68	1020.24±403.34
	Hypoxia	65.90±13.50	13.96±6.46*	951.43±524.04
Responsive subgroup n=7	Air	83.0±14.50	15.80±6.75	1253.41±460.60
	Hypoxia	83.26±11.77	16.80±6.62**	1331.38±446.80
Nonresponsive subgroup n=5	Air	65.28±6.67	16.16±5.48	1057.06±368.16
	Hypercapnia	64.70±8.61	18.04±5.39	1160.13±337.54
Responsive subgroup n=5	Air	72.14±19.54	18.34±8.47	1345.88±738.32
	Hypercapnia	77.42±16.56	19.18±7.79*	1422.57±547.40*

f: Respiratory frequency. V_T: Tidal volume. $\dot{V}_E$: Respiratory minute volume.
As compared with pre-hypoxic or pre-hypercapnic air phase (P<0.05, **P<0.01)

Table 4. The parameters of chemodenervated control group and subgroups of the hypothyroid group breathing air, hypoxic, and hypercapnic gas mixtures. (Means ± SD)

Experimental group	Experimental phase	f (breaths/min)	V_T (mL)	$\dot{V}_E$ (mL/min)
Control	Air	59.60±3.20	15.94±2.84	943.69±133.85
n=5	Hypoxia	59.40±0.89	12.65±2.45***	751.85±148.67***
Hypothyroid	Air	58.53±15.94	17.38±6.36	971.72±365.75
n=10	Hypoxia	59.61±16.30	13.58±6.96*	793.03±421.42
Control	Air	59.0±3.60	23.09±6.83	1347.85±370.03
n=5	Hypercapnia	62.40±2.50**	28.04±8.76**	1735.30±514.38**
Hypothyroid	Air	56.87±28.77	17.58±9.43	887.65±402.30
n=8	Hypercapnia	55.50±24.3	20.25±11.53	1024.66±492.87

f: Respiratory frequency. V_T: Tidal volume. $\dot{V}_E$: Respiratory minute volume.
As compared with pre-hypoxic or pre-hypercapnic air phase (P<0.05, **P<0.01, ***P<0.001)

Table 5. The parameters of control and hypothyroid nonresponsive subgroup (nonresponsive to hypoxia) during air breathing before and after chemodenervation. (Means ± SD)

Experimental group	Experimental phase	f (breaths/min)	V_T (mL)	$\dot{V}_E$ (mL/min)
Control	Before denervation n=5	68.6±1.14	29.3±0.67	2010.3±69.39
	After denervation n=5	63.08±0.75**	18.32±1.48***	1168.82±95.11***
Nonresponsive subgroup	Before denervation n=5	62.4±1.98	17.32±0.66	1080.16±35.66
	After denervation n=5	57.8±1.48*	15.22±1.00*	879.4±58.90**

f: Respiratory frequency. V_T: Tidal volume. $\dot{V}_E$: Respiratory minute volume.
As compared with that of before chemodenervation (P<0.05, **P<0.01, ***P<0.001)

observed hypoventilation in these rabbits. The other 7 rabbits were slightly responsive. Although the same dose of methimazole was administered for the same period of time, there were significant differences in TSH values between the responsive subgroup and nonresponsive subgroup. TSH values were significantly higher in nonresponsive subgroup. Ladenson *et al*. (10) suggested that high serum TSH concentration was an important factor in the impairment of respiratory response in primary hypothyroidism. He declared that high TSH secretion affected the central processes and changed the sensitivity to hypoxia and hypercapnia and this effect was overcome after thyroid hormone replacement. On the other hand, the injection of TRH to the caudal medullar region, including nucleus tractus solitary and midline raphe, stimulates respiration strongly (15). Rekling *et al*. (19) described a direct postsynaptic action of TRH depolarizing a subset of inspiratory neurons in the ventral respiratory group region near the Pre-Bötzinger region. Retrotrapezoid nucleus which is an important component of the rostral ventrolateral medulla, contains neurons that fire phasically with respiratory output (18). Futhermore, the retrotrapezoid nucleus contains TRH receptors (2), chemoreceptors (1), ionotropic and metabotropic glutamate receptors (12) and cholinergic muscarinic receptors (18).

Sensitivity to hypoxia and hypercapnia decreased in our hypothyroid rabbits. This decrease of sensitivity may depend on the increase of TSH. However, there is no direct information on whether TSH crosses the blood brain barrier. Therefore, the decrease or the absence of respiratory response to hypoxia in hypothyroid group can not directly be attributed to increased plasma levels of TSH. On the other hand, the neurotransmitters or neuropeptides that are released in hypoxia and hypercapnia may also prevent the stimulating effect of TRH on respiratory neurons. The cause of activity change of the respiratory neurons in hypothyroidism is unknown.

In our previous study, we did not see any significant increase in V_T and $\dot{V}_E$ values in hypothyroid rabbits when we injected potassium cyanide (KCN) to test the sensitivity of the peripheral chemoreceptors. For that reason, we hypothesized that a decrease in the sensitivity of peripheral chemoreceptors and the resultant depression of the central mechanisms might be the cause of decreased ventilatory drive to hypoxia in hypothyroidism (21). In this study, when we performed chemodenervation to nonresponsive subgroup of hypothyroid rabbits, we obtained significant decreases in f, V_T, and $\dot{V}_E$ in normoxic condition, as compared to the values before chemodenervation (Table 5). If the sensitivity of the peripheral chemoreceptors had been completely lost in hypothyroidism, we would not have seen these decreases in f, V_T, and $\dot{V}_E$ after chemodenervation.

Peripheral chemoreceptors are active in normoxia and facilitator impulses arising from peripheral chemoreceptors, increase central inspiratory activity and tidal volume (16). After peripheral chemodenervation, central inspiratory activity decreases in normoxia due to cessation of impulses originating from peripheral chemoreceptors and hypoventilation occurs. This depression increases with the breathing of hypoxic gas mixture by its direct effect on respiratory neurons.

The f, V_T, and $\dot{V}_E$ values of both control and nonresponsive subgroup during air breathing were found to decrease significantly after chemodenervation (Table 5). However, the decrease of these parameters was less in magnitude in the nonresponsive group, when compared with that in the control group. These results show that the sensitivity of the peripheral chemoreceptors of the rabbits with induced hypothyroidism was not completely lost but just decreased.

The effects of hypercapnia – In our previous study, the ventilatory response of hypothyroid rabbits to hypercapnia was less than that of the control group (21). In the present study, the increase in V_T and $\dot{V}_E$ in response to hypercapnia in the nonresponsive subgroup was insignificant (Table 3). Furthermore, two of the hypothyroid rabbits that were non responsive to hypoxia were also nonresponsive to hypercapnia. Hypercapnic gas mixture breathing did not increase V_T and $\dot{V}_E$ values of these two rabbits of the nonresponsive subgroup. These results show that respiratory response to hypercapnia was either blunted or absent in hypothyroid rabbits that were unresponsive to hypoxia.

Hypercapnia stimulates the respiration by acting both on central and peripheral chemoreceptors, the decrease in ventilatory response cannot be explained merely by the decrease in the sensitivity of the peripheral chemoreceptors. Our results show a significant respiratory response to hypercapnia in control group after chemodenervation. On the other hand, in the hypothyroid group, no significant respiratoy response to hypercapnia was observed after chemodenervation (Table 4). This finding identifies decreased sensitivity of the central chemoreceptors in hypothyroidism. Ladenson *et al*. (10) suggested that neural factors had an important role in the nonresponsiveness against hypercapnia. Duranti *et al*. (4) observed a moderate to marked reduction in the EMG (recorded from diaphragm and intercostal muscles) response slope to carbon dioxide in hypothyroid patients with a low $\dot{V}_E$ response slope, which indicated decreased neural activation of both diaphragm and intercostal muscles. They suggested that possible reasons for this alteration may be either

central brainstem disregulation or peripheral neuropathy or both.

Although the input of peripheral and central chemoreceptors still exists in the rabbits with induced hypothyroidism, ventilatory drive decreases. This may be due to either non-responsiveness of respiratory center or insufficient response of respiratory muscles to the impulses coming from the center. Laroche *et al*. (11) showed decreased maximal respiratory mouth pressure and maximal transdiaphragmatic pressure, and suggested that there is bilateral diaphragm weakness and phrenic nerve neuropathy in hypothyroidism. Kragie *et al*. (9) showed that there was nearly 50% reduction in the number of acetylcholine receptors in hypothyroidism compared to control groups. This can be clarified by recording of phrenic nerve potential and comparing it with the potential of diaphragm.

In our study, we observed that the sensitivity of the peripheral chemoreceptors decreases, but is not completely lost in hypothyroidism. This result suggested that in addition to the decrease of the sensitivity of peripheral chemoreceptors, impairment of the neurons sensitivity of the central mechanisms and/or releasing inhibitor neuropeptide or neurotransmitter may be the cause of decreased ventilatory drive in hypoxia and hypercapnia in hypothyroidism.

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