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Alterations in monoamines level in discrete brain regions and other peripheral tissues in young and adult male rats during experimental hyperthyroidism

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ABSTRACT

The present study was conducted to investigate the effect of experimentally-induced hyperthyroidism on dopamine (DA), norepinephrine (NE) and serotonin (5-HT) levels in different brain regions as well as in blood plasma, cardiac muscle and adrenal gland of young and adult male albino rats (60 rats of each age). Hyperthyroidism was induced by daily s.c. injection of L-thyroxine (L-T_4, 500 μg/kg body wt.) for 21 consecutive days. Induction of hyperthyroidism caused a significant elevation in DA and 5-HT levels in most of the tissues studied of both young and adult animals after 7, 14, and 21 days. NE content significantly decreased after 21 days in most of the brain regions examined and after 14 and 21 days in blood plasma of young rats following hyperthyroidism. In adult rats, NE content decreased after 14 and 21 days in cardiac muscle and after 21 days only in adrenal gland. It may be suggested that the changes in monoamines level induced by hyperthyroidism may be due to disturbance in the synthesis, turnover and release of these amines through the neurons impairment or may attributed to an alteration pattern of their synthesis and/or degradative enzymes or changes in the sensitivity of their receptors

1. Introduction

Thyroid hormones, tri-iodothyronine (T_3) and tetra-iodothyronine (T_4) are critical in regulating the growth and differentiation of many tissues and organs. Several reports have been published on the essential role of the thyroid hormones for mammalian and non-mammalian development (Ahmed et al., 2008; Koibuchi, 2008; Leonard, 2008; Ahmed et al., 2010; Di Paola et al., 2010; Sigrun and Heike, 2010).

The influence of hyperthyroidism on developing nervous system is dramatic and has been intensively studied (Anderson et al., 2003; Kester et al., 2004; Zamoner et al., 2007; Ahmed et al., 2008, 2010; Carreon-Rodriguez and Perez-Martinez, 2012). Any increase of thyroid hormones during the developmental period may result in an irreversible impairment, morphological and cytoarchitecture abnormalities, disorganization, maldevelopment and physical retardation that are permanent (Bernal et al., 2003; Koibuchi, 2008; Ahmed et al., 2010). These effects may be responsible for the loss of neuronal vital functions and may lead, in turn, to biochemical dysfunctions (Ahmed et al., 2012). Moreover, adult-onset thyroid dysfunction is also associated with neurological abnormalities (De Groot et al., 1984), emphasizing the importance of thyroid hormones for normal functions.

It is well established that thyroid hormones are essential for maturation and function of the nervous system, however, little has been known about the effect of hyperthyroidism on classical neurotransmitters. Maturation of several central neurotransmitter systems including the serotonergic system has been reported to be under the influence of thyroid status (Vara et al., 2002; Aszalos, 2007; Ahmed et al., 2008, 2010).

The role of thyroid hormones in regulating central noradrenergic function is well demonstrated (Saravanan et al., 2006). Several lines of evidence also support a relationship between thyroid hormones and serotonergic transmission in the brain (Sandrini et al., 1996; Gur et al., 1999; Lifschytz et al., 2004). It was speculated that the serotonergic system play a role in the pathogenesis of depression by modulating thyroid hormones effect (Bauer et al., 2002), as suggested by the T_3- induced potentiation of therapeutic actions of serotonergic antidepressant (Lifschytz et al., 2006, 2012). The peripheral nervous system has also been found to be dependent on the thyroid status. Alterations in the plasma monoamines have been studied in several animal models of thyrotoxicosis (Upadhyaya et al., 1993; Cleare et al., 1995). Catecholaminergic and serotononergic activities in the sympathetic nervous system are also dependent on the thyroid state (Zwaveling et al., 1996; Mano et al., 1998).

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To gain more insight into the effects of hyperthyroidism on neurochemical changes, the present study was directed to examine the influence of experimental hyperthyroidism on the levels of DA, NE and 5-HT in different brain regions as well as in blood plasma, cardiac muscle and adrenal gland of young and adult male albino rats, besides elucidating the impact of hyperthyroidism on body weight.

2. Material and methods

2.1. Experimental animals

The experimental animals used in this study were male albino rats of Wistar origin: 60 young male rats aged 3 weeks (30–40 g) and 60 adult male rats aged 18 weeks (130–160 g). Animals were supplied by the breeding unit of the National Organization for Drug Control and Research (NODCAR). The animals were housed in plastic cages, fed ad libitum and allowed to adjust to the new environment for two weeks before starting the experiment. The animals were housed at 23 ± 2 °C dark/light cycles. Animal care and use for experimental procedure were approved by the Institutional Animal Care and Use Committee (IACUC) of NODCAR.

2.2. Induction of hyperthyroidism

Animals received a daily dose of 500 μg/kg body wt. of L-T_4 (Sigma chemical company), via s.c. injection for 21 consecutive days. L-T_4 was dissolved in alkaline saline. This dose is consistent with a previous study indicating that s.c. administration of 500 μg/kg L-T_4 induced hyperthyroidism (Wren et al., 2006). The control animals group received only vehicle solution for full period of experiment. L-T_4-treated groups and their controls were decapitated after 7, 14 and 21 days from daily s.c. injection.

2.3. Body weight measurement

Body weight was recorded daily beginning on zero time (the time prior to treatment) and continued until decapitation. The body weight was averaged for each week until the end of the treatment.

2.4. Handling of tissue samples

In all experiments done the conditions were adjusted to decapitate the animals between 3.00 and 4.00 p.m. After decapitation, two blood samples were collected from each rat. The first was allowed to coagulate at room temperature (to obtain serum). The second blood sample was collected in a heparinized centrifuge tube (to obtain plasma). All tubes were centrifuged at 3000 rpm for 15 min to separate serum and plasma. The brain, cardiac muscle and adrenal gland were rapidly excised. The brain was transferred to a dry ice-cold glass plate and dissected into the following regions: cerebral cortex, thalamus & hypothalamus, midbrain, cerebellum and pons-medulla. All tissues were plotted dry on filter paper and weighed. Tissue samples were stored at −20 °C till taken for analysis.

2.5. Determination of thyroid hormones

T_3, T_4 and TSH were determined in blood serum by ELISA using commercial kits (Diagnostic Systems Laboratories INC.) according to the methods of Wenzel (1981), Midgeley (2001) and Bravermann (1996) respectively.

2.6. Estimation of the amine levels

The estimation of DA, NE and 5-HT levels in the selected rat tissues were carried out according to the fluorometric method described by Ciarlone (1978).

2.7. Data presentation and statistical analysis

The concentration of the parameters studied in blood serum and in the selected tissues was expressed as mean ± S.E. The mean concentrations were presented as pg/ml for T_3, ng/dl for T_4, μIU/ml for TSH and μg/g fresh tissues or ml plasma for NE, DA and 5-HT levels.

Statistical significance was calculated using one-way analysis of variance (ANOVA) followed by LSD post hoc test. All calculations were performed using SPSS statistical software version 12. Values of $p < 0.05$ were considered statistically significant.

Percentage differences representing the percent of variation in concentration with respect to the control or different time intervals or young-treated rats were also calculated.

3. Results

3.1. Effect of L-thyroxine administration on thyroid hormones level

As depicted from Table 1, hyperthyroidism induced by L-T_4 was confirmed by a pronounced increase in serum concentrations of T_3 and T_4 and a decrease of TSH level in both young and adult rats throughout the three experimental periods in a time–dependent fashion.

3.2. Effect of L- thyroxine administration on body weight

Table 2 shows that, in either young or adult rats, L-T_4 did not affect the body weight after 7 days of treatment, however, after 14 and 21 days the treated groups demonstrated a parallel progressive highly significant ($p < 0.01$) decrease in their body weights compared to initial values.

3.3. Effect of L- thyroxine administration on monoamine levels

As can be noticed from Fig. 1, DA contents exhibited a nonsignificant elevation in the different brain regions of the two age groups of animals after 7 days of hyperthyroidism induction. However, after 14 and 21 days, a significant ($p < 0.05$) or highly significant ($P < 0.01$) increase in DA contents was noticed in most of the brain regions examined of both young and adult animals.

From Fig. 2 it is obvious that, DA levels in blood plasma and cardiac muscle of young rats were largely affected compared to those of adult rats following hyperthyroidism. In young rats, a significant increase was recorded in plasma after 14 days (+11.8%, $p < 0.05$) and 21 days (+23.1%, $p < 0.01$) and in cardiac muscle after all the time intervals studied. In adult rats, plasma and cardiac muscle DA contents increased significantly ($p < 0.01$) after 21 days only (+25.9% and +23.9%, respectively). Adrenal gland DA content was significantly elevated after 21 days in both young (+11.2%, $p < 0.05$) and adult (+22.0%, $p < 0.01$) animals.

Fig. 3 shows that L-T_4 treatment had a little effect on NE contents in the different brain regions of young and adult rats during the course of the experiment. However, a significant ($p < 0.05$) decrease was recorded after 21 days in midbrain (−9.5%), cerebellum (−12.8%) and pons-medulla (−17.7%) of young rats. Moreover, a significant decline was also noticed after 14 and 21 days in blood plasma of young rats (−11.1% and −12.5%, $p < 0.05$, respectively) and cardiac muscle of adult rats (−11.4% and −15.7%, $p < 0.05$, respectively), and after 21 days in adrenal gland of adult rats (−19.1%, $p < 0.01$) following hyperthyroidism (Fig. 4).