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The bidirectional effects of hypothyroidism and hyperthyroidism on anxiety- and depression-like behaviors in rats

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ABSTRACT

Thyroid hormone disorders have long been linked to depression, but the causal relationship between them remains controversial. To address this question, we established rat models of hypothyroidism using ^{131}iodine (^{131}I) and hyperthyroidism using levothyroxine (LT_4). Serum free thyroxine (FT_4) and triiodothyronine (FT_3) significantly decreased in the hypothyroid of rats with single injections of ^{131}I (5 mCi/kg). These rats exhibited decreased depression-like behaviors in forced swimming test and sucrose preference tests, as well as decreased anxiety-like behaviors in an elevated plus maze. Diminished levels of brain serotonin (5-HT) and increased levels of hippocampal brain-derived neurotrophic factor (BDNF) were found in the hypothyroid rats compared to the control saline–vehicle administered rats. LT_4 treatment reversed the decrease in thyroid hormones and depression-like behaviors. In contrast, hyperthyroidism induced by weekly injections of LT_4 (15 μg/kg) caused a greater than 10-fold increase in serum FT_4 and FT_3 levels. The hyperthyroid rats exhibited higher anxiety- and depression-like behaviors, higher brain 5-HT level, and lower hippocampal BDNF levels than the controls. Treatment with the antidepressant imipramine (15 mg/kg) diminished serum FT_4 levels as well as anxiety- and depression-like behaviors in the hyperthyroid rats but led to a further increase in brain 5-HT levels, compared with the controls or the hypothyroid rats. Together, our results suggest that hypothyroidism and hyperthyroidism have bidirectional effects on anxiety- and depression-like behaviors in rats, possibly by modulating hippocampal BDNF levels.

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Introduction

Hyperthyroidism and hypothyroidism are the most common disorders affecting the hypothalamic–pituitary–thyroid (HPT) axis. The former is characterized by abnormally high levels of thyroid hormone (TH), like free triiodothyronine (FT_3) and free thyroxine (FT_4), whereas the latter is characterized by decreased TH levels. A number of clinical studies have suggested that hypothyroidism and hyperthyroidism may lead to comorbid anxiety and depression (Carvalho, 2004; Duntas and Maillis, 2013; Hage and Sami, 2012; Kamble et al., 2013). Concurrently, it has also been suggested that anxiety and depression may lead to thyroid abnormalities, due to the role of the central serotonin (5-HT) system in HPT axis function (Berent et al., 2014; Tsuru et al., 2013). However, the precise relationship between hypothyroidism and depression remains unclear (Engum et al., 2002; Jackson, 1998).

Some studies in rats have shown that hypothyroid rats display increased anxiety- and depression-like behaviors (Kulikov et al., 1997; Montero-Pedrazuela et al., 2006). Consistent with these reports, treatment with T_3, T_4 or a thyrotropin-releasing hormone analogue achieved antidepressant effects in euthyroid mice and rats (Lifschytz et al., 2006,

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2011; Paulson et al., 2003). Furthermore, a clinical study found that TH and particularly T_3 can be used as adjunct therapy to antidepressant treatment for acceleration and potentiation of clinical responses in non-responders (Goodwin et al., 1982). However, this effect was not replicated in another human study (Chang et al., 2013) nor in rats (Lifschytz et al., 2006). In contrast, hyperthyroid rats have been found to exhibit increased depression-like behaviors, whereas no significant effects were observed in hypothyroid rats (Redei et al., 2001). Together, these findings suggest a complex association between TH and anxiety/depression in humans and animals.

The etiology of depression remains poorly understood, as do the precise mechanisms underlying the action of antidepressants. Some evidence suggests that abnormal levels of central 5-HT or hippocampal brain-derived neurotrophic factor (BDNF) may play a critical role (Homberg et al., 2014) in depression. In addition, the effect of monoamine-based antidepressants including imipramine has been shown to be dependent on BDNF signaling (Ceretta et al., 2012; Reus et al., 2013). Depression is a highly heterogeneous disorder with diverse pathogenic origins, one of which may be due to abnormal TH levels that affect 5-HT or BDNF levels. This hypothesis is supported by several reports that demonstrate a close association between TH and 5-HT (Bauer et al., 2002). For example, hypothyroid rats were found to have decreased 5-HT brain levels (Ito et al., 1977; Jacoby et al., 1975; Tousson et al., 2012), whereas acute or repeated T_3 and T_4 treatments led to increased 5-HT expression in euthyroid rats (Heal and Smith, 1988; Sandrini et al., 1996). Furthermore, increased BDNF mRNA and peptide levels were observed in the cortex and hippocampus of hypothyroid rats induced by propylthiouracil (PTU) (Cortes et al., 2012). However, a previous report showed that chronic T_3 treatment or hypothyroidism had no effect on hippocampal BDNF mRNA levels (Vaidya et al., 2001).

In this study, we investigate the causal relationship between TH and depression and anxiety. To address this question, we used ^{131}iodine (^{131}I) (Harbert, 1987) and levothyroxine (LT_4) to establish hypothyroid and hyperthyroid rat models, respectively. We found that 5 mCi/kg ^{131}I and 15 μg/kg LT_4 treatments could reliably mimic the symptoms of hypothyroidism and hyperthyroidism, respectively, in human patients, particularly in respect to serum levels of free T_4 (FT_4) and free T_3 (FT_3), which are more clinically useful diagnosis indexes for thyroid axis dysfunction than total T_4 and total T_3 (Bartalena et al., 1996; Ginsberg, 2003). We assessed the body weight and water and food intake of experimental rats and then performed a number of behavioral tests such as the open field and treadmill tests to evaluate locomotor activity, the elevated-plus maze (EPM) test to assay anxiety-like behaviors, and the forced swimming test (FST) and sucrose preference test to measure depression susceptibility. In addition, we evaluated brain 5-HT and hippocampal BDNF expression levels in both hypothyroid and hyperthyroid groups. The interactions between the serum levels of the thyroid hormones and depression-like behaviors, 5-HT, BDNF were analyzed.

Materials and methods

Animals

Male Sprague–Dawley rats (Animal House Center, Kunming Medical University, Kunming), at 8–9 weeks old, weighing between 200 ~ 250 g, were used. The animals were group-housed with free access to water and food (complying with the Chinese rat food standard GB 14924.3-2001 with iodine ≥0.5 mg/kg food) and subjected to a 12 h light/dark cycle in a temperature-regulated room. The rats were acclimated to the room for one week prior to experiments. All experiments utilized different rats and were performed between 09:00 and 12:00. Experimental protocols were approved by the Animal Ethics Committee of the Kunming Institute of Zoology, Chinese Academy of Sciences.

Drug treatment

The following reagents were used: radioactive sodium iodide ($Na^{131}I$; Chengdu Gaotong Isotope Co. LTD, Chengdu, China) and L-thyroxine sodium salt pentahydrate (LT_4, Sigma-Aldrich, St. Louis, MO, USA). For the hypothyroid rat model, $Na^{131}I$ was dissolved in saline (vehicle, 2.5 or 5 mCi/ml) and injected intragastrically (I.G., 1 ml/kg). For the hyperthyroid rat model, LT_4 was dissolved in saline (5, 15 or 20 μg/ml) and injected intraperitoneally (I.P., 1 ml/kg). For the vehicle rat model, saline 1 ml/kg was injected I.G. or was injected I.P. when the hypothyroid rat or hyperthyroid rat was injected with drug, respectively, as control. If these 3 groups had experiments performed on them on the same day, the hypothyroid rat or hyperthyroid rat was injected with ^{131}I I.G. or LT_4 I.P., respectively, and the other 2 groups were correspondingly injected with saline.

FT_4, FT_3 and TSH serum levels

The rats were anesthetized using ether at all scheduled time points after drug administration, and their heart blood samples were obtained to test serum levels of FT_4, FT_3 using time-resolved fluoroimmunoassays (TRFIA) and rat thyroid-stimulating hormone (rTSH) using an enzyme-linked immunosorbent assay (ELISA). Diagnostic kits for FT_4 and FT_3 (SYM Bio Lifescience Co., LTD, Suzhou, China) were used in conjunction with a multilabel counter (Wallac Vicotor 2 TM 1420 multilabel counter, Turku, Finland) to detect thyroid hormone levels according to the manufacturer's instructions. A diagnostic kit for rTSH (Shanghai Fengshou Industrial Co., LTD, China) was used to detect rTSH. The detection ranges for FT_4, FT_3 and rTSH were 0–78 pmol/l, 0–54 pmol/l and 0.7–22 mIU/l, respectively. Whenever the concentration of a particular hormone exceeded the corresponding upper limit, the serum was further diluted with saline to achieve a measurable concentration.

HPLC assay of brain 5-HT

Brain 5-HT was tested in the hypothyroid rats at day 11 following ^{131}I administration (5 mCi/kg, I.G.), in the hyperthyroid rats at 24 h following LT_4 administration (15 μg/kg, I.P.), and in the rats given two administrations of imipramine (Sigma, 15 mg/kg, I.P., 1.5 h and 23.5 h post-LT_4 administration, the saline as the control) to rescue the effect of hyperthyroid on 5-HT.

The rats were decapitated immediately under ether anesthesia after FST on day 1 of the FST procedure (Page et al., 1999). Brain (except brain stem) supernatants were prepared as described previously (Hillert et al., 2012; Vega-Rivera et al., 2013) and stored at −80 °C. Characterization and quantification of 5-HT were carried out using a high performance liquid chromatography–electrochemical detector (HPLC–ECD, Agilent 1200, USA) as previously described (Baumann et al., 2008).

Western blot analysis of BDNF

Hippocampal BDNF was tested in hypothyroid rats at the 11th day following ^{131}I administration (5 mCi/kg, I.G.) and in hyperthyroid rats at 24 h after LT_4 administration (15 μg/kg, I.P.) without a behavioral test. Their hippocampi were dissected (Chiu et al., 2007) and immediately homogenized individually in RIPA lysis buffer modified with 1 mM phenylmethylsulfonyl fluoride and protease inhibitor (2 μg/ml aprotinin, 10 μg/ml leupeptin, 1 μg/ml pepstatin A, 5 mM EDTA, 1 mM EGTA, 10 mM sodium fluoride, 1 mM sodium or thovanadate, and 0.2 mM β-glycerophosphate) at 1:100 (v/v) in an ice surrounded homogenizer. Tissue homogenate was centrifuged at 12,000 rpm for 15 min at 4 °C and protein concentrations were determined using the bicinchoninic acid protein assay kit (Tiangen Biotech Co. LTD, Beijing, China).

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