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

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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 $^{131}$I and hyperthyroidism using levothyroxine (LT4). Serum free thyroxine (FT4) and triiodothyronine (FT3) 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. LT4 treatment reversed the decrease in thyroid hormones and depression-like behaviors. In contrast, hyperthyroidism induced by weekly injections of LT4 (15 μg/kg) caused a greater than 10-fold increase in serum FT4 and FT3 levels. The hyperthyroid rats exhibited higher anxiety- and depression-like behaviors, higher brain 5-HT levels, and lower hippocampal BDNF levels than the controls. Treatment with the antidepressant imipramine (15 mg/kg) diminished serum FT4 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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I n t r o d u c t i o n

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 (FT3) and free thyroxine (FT4), 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-Pedrazueta et al., 2006). Consistent with these reports, treatment with T3, T4 or a thyrotropin-releasing hormone analogue affected antidepressant effects in euthyroid mice and rats (Lifschi tz et al., 2006,
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.

Materials and methods

Drug treatment

The following reagents were used: radioactive sodium iodide (Na131I; Chengdu Gaotong Isotope Co. LTD, Chengdu, China) and l-thyroxine sodium salt pentahydrate (LT4, Sigma-Aldrich, St. Louis, MO, USA). For the hypothyroid rat model, Na131I was dissolved in saline (vehicle, 2.5 or 5 mCi/ml) and injected intragastrically (l., 1 ml/kg). For the hypothyroid rat model, LT4 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 131I I.G. or LT4 I.P., respectively, and the other 2 groups were correspondingly injected with saline.

HPLC assay of brain 5-HT

Brain 5-HT was tested in the hypothyroid rats at day 11 following 131I administration (5 mCi/kg, I.G.), in the hyperthyroid rats at 24 h following LT4 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-LT4 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 131I administration (5 mCi/kg, I.G.) and in hyperthyroid rats at 24 h after LT4 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 aprotonin, 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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