Cognitive dysfunction associated with activation of the mTOR signaling pathway after TSH suppression therapy in rats

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Abstract. Thyroid stimulating hormone (TSH) suppression therapy after thyroid carcinoma surgery could lead to cognitive impairment. But, the possible mechanism of TSH suppression therapy impairs cognitive function is yet unknown. In this study, forty Wistar rats were randomized into the sham operation control (OC), total thyroidectomy (TD), thyroxine replacement therapy (TR), and TSH suppression therapy (TS) groups. We observed that compared to the OC group, escape latency on 1–4 days was significantly prolonged in the TD and TS groups, and the number of rats crossing the virtual platform was significantly reduced in the TD and TS groups. In the TD, TR, and TS groups, the residence time in the target quadrant was significantly decreased, while the activity distance in the target quadrant in the TD group was significantly decreased compared with OC group. In the TD and TS groups, the pyramidal cells in the hippocampal CA1 region showed a disordered arrangement. The cytoplasm was lightly stained, the cells were swollen and round, and spotty liquefaction necrosis could be observed. Compared to the OC group, hippocampal p-mTOR and p-p70s6k levels were significantly decreased in the TD group, while no significant changes were detected in the TR group. Hippocampal p-mTOR and p-p70s6k amounts in the TS group were significantly increased compared with OC group. These results indicated that TSH suppression therapy after total thyroidectomy in rats could impair cognitive function, which might be related to the activation of the mTOR signaling pathway and the damage and necrosis of hippocampal neurons.

Key words: TSH suppression therapy, Cognitive impairment, mTOR signaling pathway, Rats

THYROID CANCER is a common malignant tumor of the endocrine system with increasing incidence. After surgical resection, the oral administration of L-thyroxine (L-T4) therapy is essential for TSH suppression [1]. However, long-term TSH inhibition treatment can cause drug-induced subclinical hyperthyroidism, which affects the physical, psychological, and social life of the patients. Patients are mainly affected by the damage of the cardiovascular system, such as disrupted heart rate, ventricular hypertrophy, and diastolic dysfunction. Older patients face a severe risk of adverse reactions [2]. A previous study has shown that long-term TSH inhibition treatment significantly increases the incidence of osteoporosis and the risk of fracture in postmenopausal women [3]. Another prospective study suggested that postoperative TSH inhibition in differentiated thyroid cancer can lead to short-term memory impairment, attention deficit disorder, and word selection anomia [4]. In addition, it has been confirmed that learning and memory are inseparable from the intensity and number of synapti-
suppression treatment-related cognitive dysfunction.

Materials and Methods

Experimental animals

All research animals were treated in accordance with the Principles of Laboratory Animal Care formulated by the U.S. National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals published by the U.S. This study was approved by the biomedical ethics committee of Inner Mongolia Medical University (No. YKD2014063). The research animals were clean-grade female Wistar rats (8-week-old, 200 ± 30 g), and purchased from the Laboratory Animal Center of Inner Mongolia Medical University (Inner Mongolia, China; Production License No. SCXK (Mongolia) 2015-0001). They were housed in a specific pathogen-free (SPF) environment with a 12-h light/dark cycle and temperature-controlling. Drinking water and standard feed were freely available.

The rats were randomly divided into four groups, 10 rats in each group. ① Sham operation control (OC) group: Rats were fed standard feed and distilled water. Before experiments, the animals were anesthetized with 10% chloral hydrate solution. Then, the neck was cut open, and the thyroid gland was exposed; however, thyroidectomy was not performed before suture. ② Total thyroidectomy (TD) group: Rats were provided the same feeding condition adaptively for 1 week, followed by thyroidectomy according to our previous study [8]. A longitudinal incision was made in the middle of the neck. The neck skin and subcutaneous connective tissue were incised, and the sternohyoid muscle was directly separated along the midline to expose the thyroid glands. Then, the total thyroidectomy was undertaken. Postoperatively, standard feed and high calcium water (1% calcium gluconate) were given to the rats. The placebo was injected subcutaneously into the abdomen daily from the first day post-surgery. ③ Thyroxine replacement therapy (TR) group: After 1 week of adaptive feeding, the rats underwent total thyroidectomy according to the above procedures. Then, they were fed regular diet and high calcium water (1% calcium gluconate). The rat model of thyroxine replacement therapy was successfully established with daily subcutaneous injection of 1.4 μg/100 g*d body weight of L-T4 [8]. Morris water maze and specimen collection were conducted after 60 days of continuous injection.

Behavioral tests

Morris water maze [9] was used to evaluate the cognitive functions related to spatial learning and memory of experimental animals. This method was performed after 60 days of feeding and injection of L-T4 in TD, TR, TS, and OC groups. Adaptive training began 4 days before the end of the experiment, and each group of animals spent a fixed duration swimming in the pool without an underwater platform for 60 s daily. ① During the 4-day directional navigation experiment, the rats were placed into the water from four quadrant entry points (facing the wall when they entered the water) every day. The time to discover the hidden platform (escap e incubation period) by the animals was recorded. If the hidden platform was not found within 120 s, the researchers guided the rats to the hidden platform and left them in its center for 10 s before returning the animals to their cages. In this case, the escape incubation latency was recorded as 120 s. ② The spatial exploration experiments were as follows. On day 5, the underwater platform was removed, and each group of rats was placed into the water facing the pool wall from a fixed position in the first quadrant. The number of times the animals passed through the virtual platform, the time they stayed in the target quadrant, and the distance they moved within 120 s in the target quadrant were recorded.

Detection of serum T3, T4, and TSH levels

After the water maze experiment, all the rats were fasting for 12 h. Then, 5 mL blood was collected from the chest cavity (left ventricle) of each rat, and subjected to centrifugation at 3,000 r/min for 15 min. The supernatant samples were stored in EP tubes. Serum T3, T4, and TSH levels in the supernatant were determined by Cobas E601 automatic electrochemiluminescence immunoassay system (Roche). Previous studies successfully established the normal reference values of serum thyroid hormone in adult Wistar rats [10]: 0.73–0.98 ng/mL for T3, 4.2–8.4 ng/mL for T4, and 0.76–1.29 μIU/mL for TSH. The thyroid function status was assessed according to the standard values.

Hippocampal histopathology

Rats were killed by anesthesia overdose after heart blood sampling: 5 animals in each group. The animals were decapitated, and their skin cut open. Then, the skull, hard and soft meninges were dissected with a biting forceps, and each pair of cranial nerve root filaments was cut off. Finally, the entire brain was dissociated and
removed. Hippocampal tissues of rats were quickly extracted, placed on ice, fixed with 4% paraformaldehyde solution, followed by HE staining and pathological examination. In the above four groups, the slides of each group were placed under a 200× magnification field of view to count the normal cells, disordered cells and damaged cells in the CA1 area of the hippocampus tissues.

**Western blotting of hippocampal tissues**

Rats were executed by anesthesia overdose after withdrawing heart blood samples: 5 animals in each group. The animals were decapitated, and the samples of hippocampal tissues were extracted according to the above methods, frozen in liquid nitrogen, preserved at −80°C, and detected by Western blotting. Total tissue protein was extracted by RIPA buffer, and protein concentration was measured by Bradford method. The proteins were resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to PVDF membrane. Then, the membrane was blocked with 5% skimmed milk for 2 h, followed by overnight incubation with p-p70s6k (Thr389/412) Antibody (Medical Discovery Leader MD1400-100) and p-mTOR (Medical Discovery Leader MD6475) at 4°C. Subsequently, the membranes were probed with secondary antibodies (Medical Discovery Leader MD912565) at room temperature for 2 h. Electrochemiluminescence (ECL) method was used for the detection of the immunoreactive bands, and semi-quantitative analysis was conducted using the Odyssey software [11].

**Statistical analysis**

Statistical analysis was performed with SPSS 19.00 software, and the data are expressed as mean ± standard deviation (x ± S). Analysis of variance (ANOVA) was used to compare the groups. P < 0.05 was considered as statistically significant.

**Results**

**Serum T3, T4, and TSH levels**

Serum T3 and T4 levels were significantly lower in the TD group than in the OC group (p < 0.05), and the serum TSH level was significantly increased (p < 0.05). No difference was detected in serum T3 and TSH levels between TR and OC groups (p > 0.05), while the serum T4 level was slightly increased as compared to the OC group (p < 0.05). Also, no significant difference was observed in serum T3 level between the TS and OC groups (p > 0.05), the serum T4 level was slightly increased (p < 0.05), and the serum TSH level was significantly reduced as compared to the OC group (p < 0.05) (Table 1).

**Behavioral performance of rats**

**Orientation**

Table 2 shows that at different time points, the escape incubation period of rats in the TD and TS groups was significantly prolonged as compared to the OC group (p < 0.05). However, no significant change was detected in the escape latency in the TR group compared with OC group (p > 0.05) (Table 2).

**Spatial exploration**

Frequency of crossing the virtual platform: Compared to the OC group, the frequency of crossing the virtual platform was significantly reduced in the TD and TS

| Group    | OC group | TD group | TS group | TR group |
|----------|----------|----------|----------|----------|
| T3 (ng/mL) | 0.82 ± 0.06 | 0.57 ± 0.06* | 0.88 ± 0.04 | 0.86 ± 0.04 |
| T4 (ng/mL) | 6.13 ± 0.74 | 1.55 ± 0.11* | 13.85 ± 1.50 △ | 11.54 ± 3.20 □ |
| TSH (Uiu/mL) | 1.10 ± 0.13 | 20.47 ± 3.5* | 0.78 ± 0.09 △ | 1.05 ± 0.04 |

Note: * p < 0.05 vs. OC group; △ p < 0.05 vs. OC group; □ p < 0.05 vs. OC group; Normal reference: T3: 0.73–0.98 ng/mL; T4: 4.2–8.4 ng/mL; and TSH: 0.76–1.29 μIU/mL

| Group    | OC group | TD group | TS group | TR group |
|----------|----------|----------|----------|----------|
| The first day | 50.30 ± 36.19 | 90.77 ± 34.72* | 68.92 ± 46.13* △ | 52.52 ± 39.31 |
| The second day | 25.87 ± 16.06 | 76.11 ± 38.46* | 54.19 ± 40.72* △ | 29.23 ± 24.60 |
| The third day | 16.06 ± 12.73 | 53.23 ± 38.85* | 40.83 ± 24.67* △ | 14.92 ± 6.70 |
| The fourth day | 11.23 ± 8.33 | 46.57 ± 24.30* | 25.05 ± 18.38* △ | 12.71 ± 8.09 |

Note: * p < 0.05 vs. OC group; △ p < 0.05 vs. TD group
groups ($p < 0.05$); however, no significant change was detected in the TR group. Target quadrant residence time: Compared to the OC group, the rats in the TD, TR, and TS groups showed significantly reduced residence time in the target quadrant ($p < 0.05$); however, no significant difference was detected among the three groups ($p > 0.05$). Target quadrant activity distance: Compared to the OC group, the TD group showed a significant decrease in the target quadrant activity distance ($p < 0.05$), but no significant difference was detected in the TR group ($p > 0.05$). Also, no significant difference was observed in the range of activity of the target quadrant in the TS group ($p > 0.05$) (Table 3).

**Histopathological changes in hippocampal tissues**

In the OC group, the abundant hippocampal CA1 pyramidal cells were intact, evenly distributed, closely arranged, and the intracellular structure was distinct (Fig. 1A). In the TD group, the vertebral cells in the hippocampal CA1 area of the rats were loose, the number was reduced, the arrangement was disordered, and the individual cells showed nuclear pyknosis and nuclear fragmentation (Fig. 1B). In the TS group, the number of pyramidal cells in the hippocampal CA1 area was significantly reduced, most of the nerve cells were shrunk, the structure was loose, and the arrangement was disordered. In addition, the nucleus was deeply stained, nuclear pyknosis and nuclear fragmentation was observed, and nucleoli disappeared (Fig. 1C). In the TR group, the pyramidal cells in the hippocampal CA1 area were evenly distributed, neatly arranged, tightly ordered and complete, the nuclei were lightly colored, and the intracellular structure was clear (Fig. 1D) (Table 4).

| Group     | OC group  | TD group  | TS group  | TR group  |
|-----------|-----------|-----------|-----------|-----------|
| Number of crossing platform (times) | 6.9 ± 1.3 | 1.3 ± 0.82* | 4.9 ± 1.5* | 5.6 ± 1.58 |
| Residence time in the target quadrant (s) | 41.90 ± 7.62 | 32.93 ± 5.33* | 34.23 ± 11.0* | 34.55 ± 4.25* |
| Activity distance in the target quadrant (cm) | 605.37 ± 101.13 | 396.69 ± 163.57* | 554.92 ± 196.03 | 529.64 ± 99.86 |

Note: * $p < 0.05$ vs. OC group; † $p < 0.05$ vs. OC group; ‡ $p < 0.05$ vs. OC group

**Fig. 1** Histology of hippocampal tissues

Histology of the CA1 region of the hippocampal tissue in the OC group (A), TD group (B), TS group (C) and TR group (D). (HE200× magnification).
Expression level of mTOR-related proteins in rat hippocampus

Compared to the OC group, the expression of p-mTOR and p-p70s6k proteins in the hippocampus of the TD group was significantly decreased ($p < 0.05$); however, no significant difference was noted in the OC and TR groups ($p > 0.05$). Compared to the OC and TR groups, the expression of p-mTOR and p-p70s6k proteins in the hippocampus of rats in the TS group was significantly increased ($p < 0.05$) (Fig. 2).

Discussion

Thyroid hormone plays a major role in the occurrence, development, and maintenance of the central nervous system, and is closely related to the cognitive function [12]. Related clinical reports have confirmed that thyroid hormone has an irreplaceable biological effect on the growth and development of the body and target organs. Also, the hormone is positively correlated with the cognitive level [13]. In addition, a clinical trial confirmed that patients with thyroid cancer who received L-T4 replacement therapy had subclinical hyperthyroidism caused by the drug, which in turn, caused damage to attention, executive function, and working memory, as well as caused emotional disorders such as anxiety and depression [14]. The present study established the animal model of TSH suppression therapy after total thyroidectomy in rats. The experimental results of the navigation assay demonstrated that the escape latency of rats in the TS group was significantly longer than that in the OC group. In the space exploration experiment, the number of rats crossing the virtual platform and the target quadrant residence time of rats in the TS group were significantly reduced as compared to the OC group. These results indicated that thyroid hormone levels exert a major influence on the learning and memory ability of the brain neurons.

Hippocampus is the most abundant region of thyroid hormone receptors in the brain, including CA1, CA3, and dentate gyrus [15]. The various biological effects of synaptic transmission, neurotransmitter release, cell construction and growth, synaptic plasticity, and activation of the enzyme system in the hippocampal neurons play a critical role in learning and memory [15, 16]. The hippocampus is a component of the limbic system of the brain and is a key brain area in the central nervous system involved in learning and memory storage and spatial localization. Hippocampal neurogenesis may be closely related to cognitive dysfunction caused by aging and certain degenerative diseases. Early in the course of neurodegenerative disease, the hippocampus is the first area to be damaged, and the above-mentioned pathological changes in this area are also particularly obvious. Animal behavioral evidence indicates that structural and functional changes in hippocampal neurons, such as long-term potentiation (LTP) and changes in synaptic plasticity, are related to their important role in learning and memory [17]. Other studies have also confirmed that the application of genetic modification and genetic mutation

| Group   | OC group | TD group | TS group | TR group |
|---------|----------|----------|----------|----------|
| Number of normal cells | 18.00 ± 2.62 | 5.75 ± 1.39* | 7.50 ± 1.07* | 17.00 ± 1.51 |
| Number of disordered cells | 5.38 ± 2.00 | 9.13 ± 1.73* | 7.00 ± 1.16* | 5.04 ± 2.00 |
| Number of damaged cells | 1.00 ± 0.76 | 16.25 ± 1.98* | 16.75 ± 3.01* | 1.25 ± 0.71 |

Note: * $p < 0.05$ vs. OC group

Fig. 2 Expression levels of P-mTOR and P-p70s6k proteins in hippocampal tissues

P-mTOR and P-p70s6k protein levels in hippocampal tissues were significantly decreased in the TD group, while the levels were significantly increased in the TS group as compared to the TR and control groups (*$p < 0.05$ vs. OC group).
methods in rodent models to induce neurogenesis loss can lead to experimental animals’ spatial exploration capabilities, long-range spatial memory capabilities, spatial exploration capabilities, footprint constraints, and fear conditioning and obstacles to amnesic and reproduction [18]. Similar results were found in our experimental group. The vertebral cells in the CA1 region of hippocampal HE-stained sections of the TD group and TS group showed nuclear condensation, deep staining, and neuronal apoptosis. The vertebral cells of the OC group and the TR group were approximately normal in size and structure. The mTOR belongs to the serine/threonine protein kinase, which is widely present in mammalian cells. mTOR can coordinate and control the growth and proliferation, nutrient supply, energy conversion, and stress response inside and outside the cell [19]. Therefore, mTOR is a signaling hub that regulates cell growth, survival, apoptosis, autophagy, angiogenesis, and metabolism [20]. Under physiological conditions, mTOR plays a crucial role in regulating the morphological structure of neuronal dendritic spines and may affect the development of hippocampus that is closely related to the learning and memory function of the brain [15, 16, 21]. Jobim’s results show that memory consolidation in the hippocampus needs to be supported by the synthesis of some proteins. Injecting the mTOR inhibitor rapamycin directly into the hippocampus can impair memory formation and reconsolidation. That is, mTOR participates in the process of hippocampal memory consolidation [22]. The mTOR signaling pathway includes the upstream PI3K/Akt/mTOR signaling pathway and the downstream signaling pathway with p70S6K and eukaryotic initiation factor 4E binding protein (4E-BP) as the major effector proteins. Interestingly, mTOR plays a critical role in the PI3K/Akt/mTOR signaling pathway and is closely related to the development of various diseases in the body. A previous study demonstrated maximal expression level of Akt by Western blot after 4 h of a mechanical injury of spinal cord neurons, while the expression level decreased with inhibitor intervention, thereby indicating that the PI3K/Akt/mTOR pathway is involved in the pathological process of mechanical nerve injury [23]. N-methyl-d-aspartate (NMDA) receptor-dependent long-term potentiation (LTP) in the hippocampal CA1 region of mammals is currently the most widely studied and characteristic electrophysiological model of learning and memory. The formation of this LTP is usually caused by high-frequency stimulation (HFS) of Schaeffer collateral/commissural inputs of the radiosynaptic synapses in the hippocampal CA1 region. Studies by Vickers et al. show that dendritic activation of the mTOR-p70S6K pathway is a necessary condition for inducing hippocampal CA1 region’s NMDAr and protein synthesis-dependent synaptic plasticity. In the hippocampus, mTOR signaling initiates β-adrenergic receptors and translation initiation. The combination of mechanisms will block the induction of protein synthesis-dependent long-term potentiation (LTP) [24]. Some studies suggested that moderate mTOR activation is essential for cognitive functions such as learning and memory. However, the over-activated mTOR signaling pathway might lead to cognitive dysfunction [25].

Ribosomal p70S6K is a vital target molecule downstream of mTOR. Several pieces of evidence suggested that p70S6K controls cell growth by enhancing the mRNA translation [26]. It is speculated that activated p70S6K promotes the translation of 5′ TOP (terminal oligopyrimidine tract) mRNA, which contains a short polypyrimidine (4–14 nucleotides), closely adjacent to the 5′ cap structure; the principal member is involved in the translational translation mechanism, including all ribosomal proteins, elongation factors, and polyA binding proteins (PABP) [26-28]. Other studies have shown that the mTOR/p70S6K signaling pathway mediates neuronal apoptosis induced by multiple injury factors (such as TNFa, glutamate, UV irradiation, cadmium, or rotenone), and the over-activated mTOR signaling pathway is involved in the development and progression of cognitive dysfunction in Alzheimer’s disease [29]. Chen et al. found that cadmium induces neural cell apoptosis by activating the mTOR/p70S6K signaling pathway in PC12 and SH-SY5Y neural cell lines. The phosphorylation of p70S6K, a downstream effector molecule of mTOR, is blocked to prevent the apoptosis of cadmium-induced neuronal cells [30]. Based on the role of the mTOR signaling pathway in neuronal apoptosis, we speculated that during the TSH suppression therapy, some stimulating factors might transduce signals to mTOR or directly to the downstream effector molecule P70S6K through various cell surface receptors or target proteins. This phenomenon causes apoptosis of nerve cells and ultimately leads to cognitive impairment. These results showed that the expression of p-mTOR and p-p70s6k protein in the TS group was significantly increased as compared to that in the OC group, and the hippocampus of the rat brain group showed obvious apoptosis in the hippocampal CA1 region, which was consistent with the current hypothesis. Therefore, the cognitive impairment after TSH suppression in the TS group may be associated with the hyperactivation of the mTOR pathway in the hippocampus, leading to neuronal necrosis.

The results of the present study showed that TSH suppression therapy after total thyroidectomy in rats could lead to cognitive impairments such as learning and memory. It also confirmed that mTOR promoted the
phosphorylation of p70s6k, and the damage of cognitive function might be attributed to the excessive activation of mTOR/p70s6k signaling pathway leading to injury or necrosis of hippocampal neurons in rats.

Disclosure

The authors have nothing to disclose.

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