Effect of non-genomic actions of thyroid hormones on the anaesthetic effect of propofol

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Abstract. Hyperthyroidism is a common disease of the endocrine system and it is known that additional propofol anaesthesia is required during surgery for patients with hyperthyroidism compared with those with normal thyroid function. The aim of the present study was to determine the mechanism through which thyroid hormones (THs) inhibit the effect of propofol anaesthesia. Immunofluorescence techniques were used to verify the difference between the expression quantities of γ-aminobutyric acid type A ($GABA_A$) receptor subunits α2 and β2 in the dorsal root ganglions (DRGs) of rats with hyperthyroidism and those in normal rats. Perforated patch clamp recordings in the whole-cell mode were performed to detect the GABA-activated current in acutely isolated rat DRG neurons from rats with hyperthyroidism and normal rats. This method was also used to evaluate the change in the GABA-activated currents following the pre-perfusion of propofol with and without 3,3',5-L-triiodothyronine (T_3). Compared with normal rats, rats with hyperthyroidism expressed same quantities of $GABA_A$ receptor α2 and β2 subunits in DRGs. In addition, no difference in GABA-activated currents in the acutely isolated DRG neurons from the two types of rat was observed ($P>0.05$). T_3 inhibits or minimises the augmentation effect of propofol on the GABA-activated currents ($P<0.05$). The inhibitory effect of T_3 on propofol was minimised by increasing the propofol concentration ($P<0.05$). The inhibitory effect of T_3 on the anaesthetic effect of propofol is achieved through the inhibition of the function of $GABA_A$ receptors through the non-genomic actions of the THs, rather than by changing the number of $GABA_A$ receptors. This inhibitory effect can be mitigated by increasing the propofol concentration. In conclusion, rats with hyperthyroidism require a larger dose of propofol to induce anaesthesia since the non-genomic actions of THs suppress GABA receptors, which in turn inhibits the anaesthetic action of propofol.

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Abbreviations: GABA, γ-aminobutyric acid; $GABA_AR$, γ-aminobutyric acid type A receptor; T_3, 3,3',5-L-triiodothyronine; T_4, thyroxine; DRG, dorsal root ganglion

Key words: hyperthyroidism, propofol, 3,3',5-L-triiodothyronine, non-genomic actions, γ-aminobutyric acid type A receptor

Introduction

Propofol is the most widely used intravenous general anaesthetic worldwide. Hyperthyroidism is a common endocrine system disease (1-3). In clinical terms, additional propofol anaesthesia is required during surgery for patients with hyperthyroidism compared with those with normal thyroid function (4-7). Propofol is a primary intravenous general anaesthetic that is accepted and used worldwide due to its ability to enhance γ-aminobutyric acid (GABA)-mediated inhibition in the nervous system (8,9). GABA is a natural inhibitory neurotransmitter, and the GABA receptor (GABAR) comprises $GABA_AR$, $GABA_BR$ and $GABA_CR$ subclasses. Considering that $GABA_AR$ is a ligand-gated ion channel receptor, GABA can inhibit presynaptic neurotransmitter release and generate analgesia through a primary afferent depolarisation process by acting on $GABA_AR$ localised on primary afferent neurons (10,11). Approximately 19 known subunits (α1-6, β1-3, γ1-3, δ, ε, θ, π and ϱ1-3) constitute the $GABA_AR$ (10,12), and all these subunits share an integral channel, which is permeable to Cl^- ions. Dorsal root ganglions (DRGs) are nociceptive primary afferent sensory neurons, and the GABA neurotransmitter/receptor system has an important role in the modulation of spinal nociceptive information.

As basal hormones, thyroid hormones (THs) have an essential role in maintaining the functional activity of the body and in heat production, metabolism, tissue differentiation and organ growth. The majority of the biological effects of TH are mediated by nuclear TH receptors (TRs). Two kinds of receptor, namely TRα and TRβ, have been found (13). Similar to other nuclear transcription factor families, TR can combine

with other nuclear transcription factors to mediate the target gene expression. In a previous study it was found that the biological effects of THs are rapid and unaffected by inhibitors associated with genetic transcription. This fact demonstrates the importance of the non-genetic effects of THs, which can affect the functions of the $GABA_A$ receptors (14).

Materials and methods

Animals and experimental procedures. With the permission and using the protocol of the Committee of Animal Use for Research and Education of Wuhan University (Wuhan, China), male Sprague-Dawley rats (weighing 200-250 g) were purchased from the Center for Animal Experiments, Wuhan University and housed under a temperature- and light-controlled environment (22±1 h on a 12-h light/dark cycle at 60% humidity). Standard rat chow diet and water were given *ad libitum*. Rats were randomly divided into two groups: Control (n=30) and hyperthyroid (n=30). Over 14 days, hyperthyroidism was induced in the rats of the hyperthyroid group with daily injections of 3,3',5-L-triiodothyronine (T_3) [7 μg/100 g body weight (BW) in 0.01 mM NaOH, intraperitoneally], whilst only a daily injection of the vehicle was given to the control rats. Approximately 24 h following the last dose of T_3, the rats were sacrificed by decapitation without other special treatment. To evaluate the TH serum levels and confirm the hyperthyroid status of the animals, blood samples were carefully collected. Sixty rats were used in the final experiment: 20 and 10 rats from each group were utilised for the electrophysiology and immunofluorescence experiments, respectively. Propofol was dissolved in soybean oil at a concentration of 10 mg/ml. The rats in the two groups were tested to determine the propofol dosage required for successful anesthesia after 14 days of treatment. The success of the anaesthesia was monitored by righting reflex and the propofol dosage was calculated by measuring the volume of soybean oil that was administered. Chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) and stored according to the manufacturer's instructions unless otherwise specified.

Enzyme-linked immunosorbent assay of T_3 and T_4 concentrations. An enzyme-linked competitive immunosorbent assay with biotin-avidin amplification was employed (Beijing North Institute of Biological Technology Co., Ltd., Beijing, China). Serum T3 levels were determined by a competitive binding assay in which T_3 in the sample and biotin-labeled T_3 competitively bound with anti-T_3 antibodies on 96-well-microtiter plates. Once reaction equilibrium was reached after 45 min at 37˚C, horseradish peroxidase-labeled avidin was added and complexes were formed. Following the addition of substrate for colour development, optical density values were determined at 450 nm using a Bio-Rad 680 microplate reader (Bio-Rad Laboratories, Inc., Hercules, CA, USA). Their values are inversely proportional to the concentration of T_3 in the sample. The levels of T_4 were evaluated by a similar assay.

Electrophysiological recordings of DRG neurons. The DRG neurons were pulled out from the spines of the rats, immersed in extracellular fluid, cut into pieces and then soaked in the extracellular fluid with collagenase and trypsin at 37˚C for 15 min and then centrifuged at 111.8 g for 5 min. The supernatant was then removed and the neurons were stood for 30 min to reach adherence. With the aid of a whole-cell patch clamp amplifier, perforated patch-clamp recordings in the whole-cell mode were performed. Using an Axon 700B amplifier (Axon, San Jose, CA, USA) and pCLAMP 0.2 hardware and software (Axon), currents were recorded from the DRG neurons *in vitro*. The room temperature was set at 22-24˚C. The internal solution was added to micropipettes containing 150 mM KCl and 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES). Osmolarity was regulated at 320 mOsm/l with glucose. The pH was maintained at 7.2 with KOH. On the day of the experiment, amphotericin B was prepared as a stock solution by dissolving in dimethyl sulphoxide. The recording electrodes were backfilled with amphotericin B-containing solution, and the tip of the electrode was filled with amphotericin B-free solution. The experiment required 15-30 min to obtain a stable series resistance and 5-10 min to perforate the membrane. Cells were immersed in an external solution containing 2.5 mM $CaCl_2$, 2 mM $MgCl_2$, 10 mM HEPES, 10 mM D-glucose, 150 mM NaCl and 5 mM KCl. The pH was maintained at 7.4 with NaOH, and the osmolarity of the solution was maintained at 330 mOsm/l with glucose. The resistance of the recording pipette ranged from 3 to 5 MΩ. The membrane currents were recorded following adjustment of the capacitance and series resistance compensations. Without other specific indication, the holding potential was adjusted to -60 mV and the membrane currents were filtered at 10 kHz. GABA, GABA + T_3, GABA + propofol and GABA + propofol + T_3 were successively injected in the same cell at various concentrations to detect the effect of T_3 and propofol on DRG neurons.

Immunofluorescence. Following anaesthetization with sodium pentobarbital (60 mg/kg), the rats in the control and hyperthyroid groups were subjected to cardiac perfusion with physiological saline followed by 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). $Lumbar_{1-5}$ DRGs were bilaterally removed. For 4 h, DRGs were kept in a fixative state at 4˚C, and then separately soaked in 10, 20 and 30% sucrose at 4˚C until the DRGs settled at the bottom. The DRGs were then embedded in an optimal cutting temperature compound (OCT; Sakura Finetek USA, Inc., Torrance, CA, USA) and segmented using a cryostat at 10-μm thickness. The sections were kept at -80˚C prior to use. The sections were pretreated with acetone (at 4˚C), 0.3% Triton X-100 and 5% normal foetal calf serum prior to incubating overnight at 4˚C in a humid chamber with goat polyclonal primary antibodies against $GABA_A\alpha2$ (sc-7350; 1:50; Santa Cruz Biotechnology, Dallas, TX, USA) and $GABA_A\beta2$ (sc-7362; 1:50; Santa Cruz Biotechnology). The sections were incubated respectively with donkey anti-goat immunoglobulin (Ig)G conjugated with tetramethylrhodamine isothioscyanate (1:100; Santa Cruz Biotechnology) or donkey anti-goat IgG conjugated with fluorescein isothiocyanate (1:100; Santa Cruz Biotechnology) at 37˚C for 1 h following a thorough rinsing with phosphate-buffered saline (PBS). The antibodies were diluted in 0.01 M PBS. The primary antibodies were excluded from the control experiments, leading to the negative staining of all examined sections. Sections were examined under a laser confocal microscope (LSM 710;

Table I. Experimental groups at baseline and following 14 days of T_3-treatment.

	Control		Hyperthyroid	
Parameter	Day 0	Day 14	Day 0	Day 14
Body weight (g)	241.5±9.6	306.9±14.8	242.6±9.3	233.9±12.1
Free T_3 (ng/ml)		0.41±0.10		1.32±0.50[a]
Free T_4 (ng/ml)		30.8±3.26		8.9±0.71[a]

Values are expressed as mean ± standard deviation; n=30 per group. [a]P<0.05 vs. control. T_3, 3,3',5-L-triiodothyronine; T_4, thyroxine.

Carl Zeiss Microscope, Jena, Germany). Analytical software was used to quantitatively analyse the immunofluorescence (hp9001; Carl Zeiss Microscope).

Statistical analysis. Data are presented as mean ± standard error of the mean and were analysed and using SPSS software (version 17.0; SPSS, Inc., Chicago, IL, USA). In cases of homogeneity of variance, the least significant difference t-test, one-way analysis of variance and two-group comparison were performed. P<0.05 was considered to indicate a statistically significant difference.

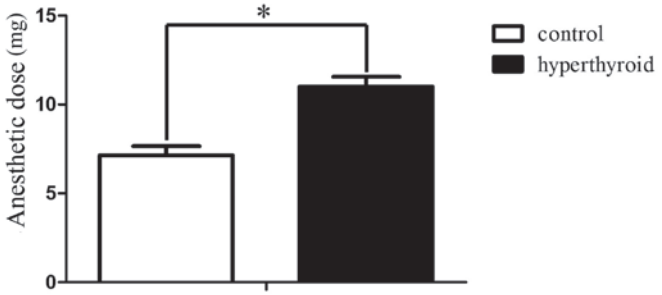

Figure 1. Anaesthetic dose in control and hyperthyroidism groups. *P<0.05 vs. control group.

Results

Validation of hyperthyroidism in experimental rat models. The serum levels of free T_3 and T_4 were measured to confirm whether hyperthyroidism was successfully induced in the T_3-treated rats. The increased T_3 and decreased T_4 serum levels observed in the T_3-treated rats are in accordance with hyperthyroidism (Table I).

Anaesthetic dose of control and hyperthyroid groups. The anaesthetic dose for the control and hyperthyroid groups was 7.14±0.51 and 11.02±0.53 mg/100 g BW (P<0.05), respectively (Fig. 1). The intraperitoneal injections of propofol anaesthesia to the rats in the control and hyperthyroid groups were successful since the righting reflex was absent.

Subunit expression differences of $GABA_A$ receptors α2 and β2. Immunofluorescence staining was used to indicate the expression of DRG $GABA_A$ receptor α2 and β2 subunits in rats in the control and hyperthyroid groups, and any differences in their expression levels were determined using quantitative analysis.

The results showed no statistical difference in the expression of either $GABA_A$ receptor subunit α2, marked by green immunofluorescence, or in $GABA_A$ receptor subunit β2, marked by red immunofluorescence (Figs. 2 and 3). The absorbance values of the DRG $GABA_A$ receptor subunits α2 and β2 of the control group were 40.5±2.05 and 38.2±1.95, respectively, whilst those of the hyperthyroid group were 41.1±2.17 and 37.8±1.84, respectively.

Comparison of GABA-activated currents. GABA induced a concentration-dependent (0.01-1,000 μM) inward current in the DRG neurons of rats in the control and hyperthyroid groups (Fig. 4).

THs inhibit GABA-evoked currents in DRGs. Using the patch clamp technique in the whole-cell configuration, the effect of T_3 on the GABA-induced currents recorded in DRG was tested. T_3 reduced the currents in a dose-dependent manner (Fig. 5). The concentration response curves showed an approximate IC_{50} of 10±3 μM for T_3. No direct T_3 channel gating was observed at any of the concentrations investigated.

T_3 inhibits the augmentation effect of propofol on the GABA-activated currents. Since T_3 inhibits GABA-activated currents in DRG, in order to determine if T_3 inhibits or minimises the augmentation effect of propofol on the GABA-activated currents, GABA, GABA + propofol and GABA + propofol + T_3 were successively injected in the same cell (Figs. 6 and 7). The following procedures were performed in the same-cell experiments: i) 100 μM GABA, which can induce an inward current, was injected. The activated current for the $GABA_AR$ was 450±35 pA; ii) 5 μM propofol was pre-perfused followed by 100 μM GABA, which induced an increase of the inward current, demonstrating that propofol has an inductive effect on GABA-activated currents and that this is the anaesthetic mechanism. The activated current for $GABA_AR$ was 860±41 pA; iii) a mixture of 10 μM T_3 and 5 μM propofol was pre-perfused, followed by 100 μM GABA, which then clearly showed that the augmentation effect of propofol on the GABA-activated currents was significantly reduced by T_3. The activated current for the $GABA_AR$ was 470±43 pA; iv) the propofol concentration was increased, and detection of the 100 μM GABA-activated currents following the pre-perfusion of the mixture of 10 μM T_3 and 10 μM propofol demonstrated that the inward current increased. This result indicated that an increased propofol concentration can partially

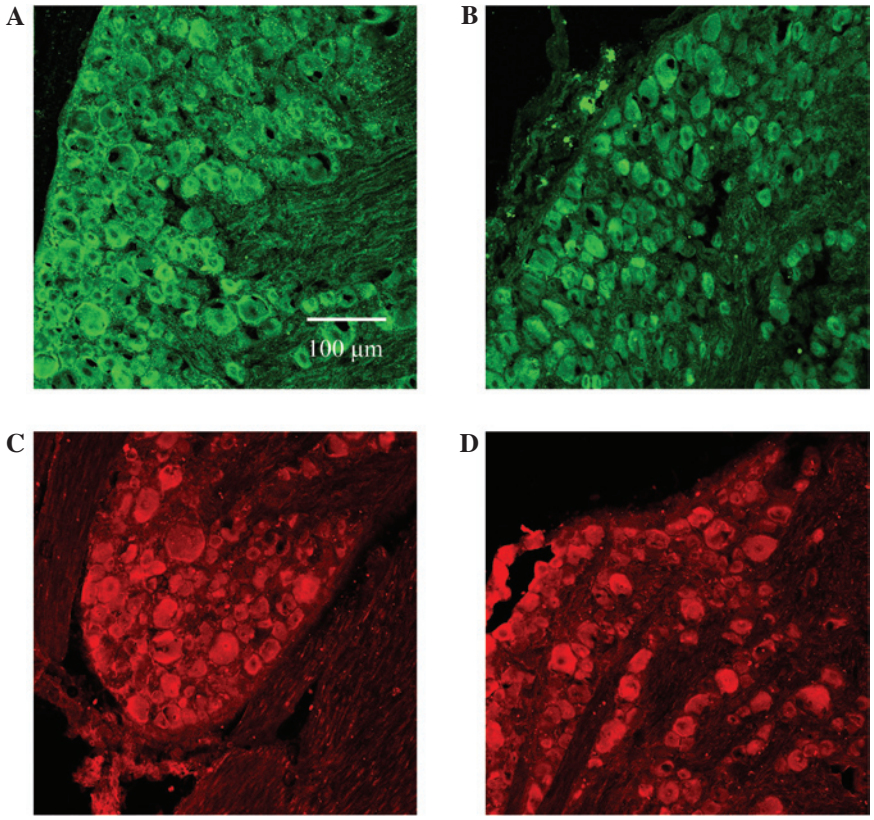

Figure 2. Confocal images (immunofluorescence staining) of $GABA_A$ receptor subunit α2 and β2 expression in the DRGs of the hyperthyroid and control groups. $GABA_A$ receptor subunit α2 and β2 immunoreactivity is visible in the DRG neuron cell membranes. Positive cells presented as green or red fluorescence, respectively. $GABA_A$ receptor subunit α2 in DRG neurons of rats in (A) the control group and (B) the hyperthyroid group. $GABA_A$ receptor subunit β2 in DRG neurons of rats in (C) the control group and (D) the hyperthyroid group. DRG, dorsal root ganglion; GABA, γ-aminobutyric acid.

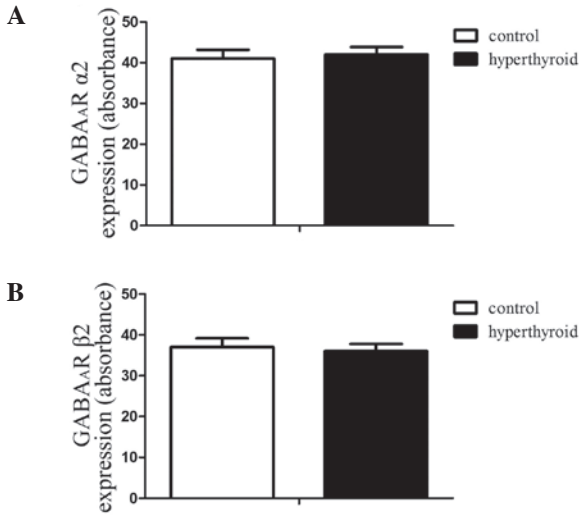

Figure 3. Bar charts showing the mean absorbance of immunofluorescently stained $GABA_AR$ α2 and β2 positive neurons from DRGs. Data are expressed as mean ± standard error of the mean (n=6). Homogeneity test for variance was performed, followed by analysis of variance and Student's t-test. No significant difference is exhibited in (A) $GABA_AR$ α2 expression levels and (B) $GABA_AR$ β2 levels between the control and hyperthyroid groups (P>0.05). GABA, γ-aminobutyric acid; $GABA_AR$, GABA receptor A; DRG, dorsal root ganglion.

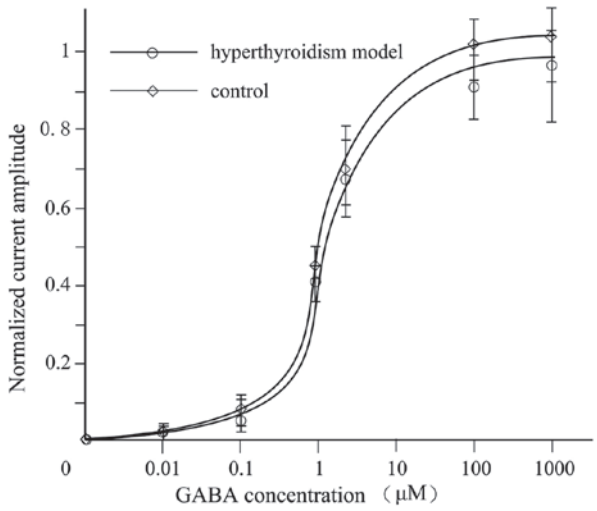

Figure 4. Comparison of GABA-activated currents in DRG neurons: Concentration-response curves for GABA activation. Data at each point represent the mean ± standard error of the mean for 12-17 neurons. The GABA-induced currents were normalised. No significant difference is observed at each point (P>0.05). GABA, γ-aminobutyric acid; DRG, dorsal root ganglion.

offset the inhibitory effect of T_3 on GABA-activated currents. The activated current for the $GABA_AR$ was 856±39 pA. The results presented in Fig. 7 show that a statistically significant difference exists in the GABA-induced current amplitude between GABA + propofol (5 μM) and GABA + propofol (5 μM) + T_3 (10 μM; P<0.05). A statistically significant difference also exists between GABA + propofol (5 μM) + T_3 (10 μM) and GABA + propofol (10 μM) + T_3 (10 μM; P< 0.05).

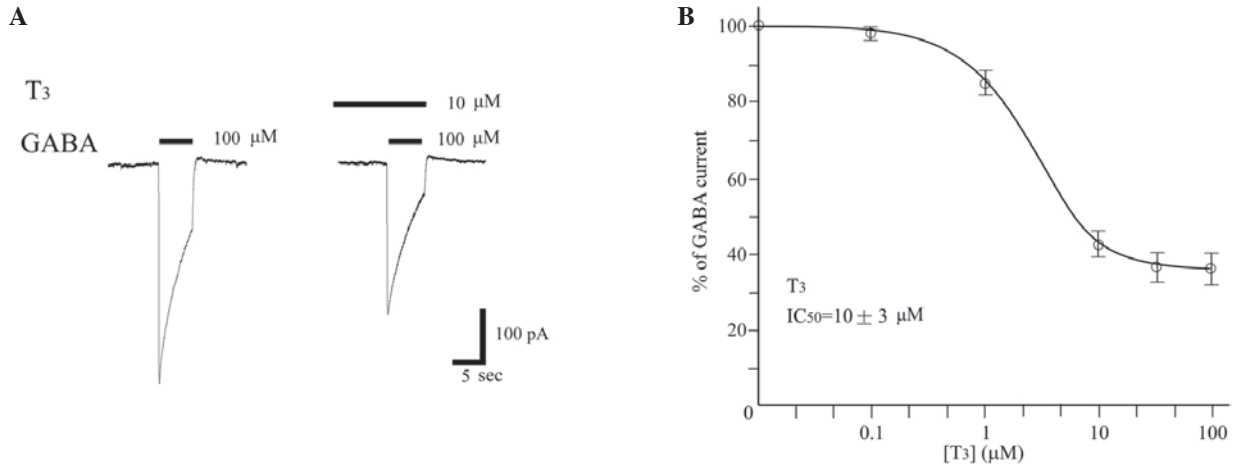

Figure 5. GABA-activated currents in DRG neurons are inhibited by T_3. (A) Whole cell recordings from neurons in DRGs show the current response to 100 μM GABA alone and with 10 μM T_3 under controlled conditions. Holding potential = -60 mV. (B) Concentration response curve of the Hill coefficient and T_3 with IC_{50}. Each data point represents the mean ± standard error of the mean of ≥6 cells. GABA, γ-aminobutyric acid; IC_{50}, half maximal inhibitory concentration; DRG, dorsal root ganglion; T_3, 3,3',5-L-triiodothyronine.

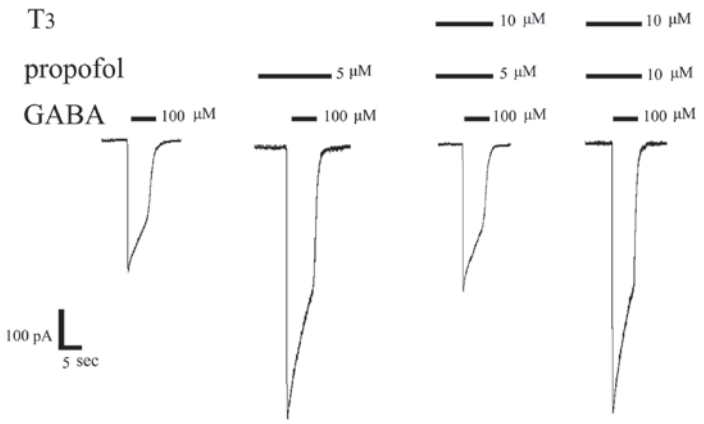

Figure 6. Current traces show that T_3 inhibits the effect of propofol on GABA-activated currents. T_3 inhibits the augmentation effect of propofol on GABA-activated currents, and increasing the propofol concentration can partially offset the inhibitory effect of T_3. T_3, 3,3',5-L-triiodothyronine; GABA, γ-aminobutyric acid.

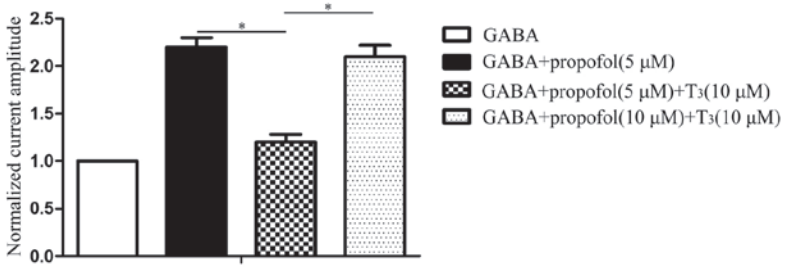

Figure 7. Bar chart of normalised current amplitude shows that T_3 inhibits the effect of propofol on GABA-activated currents. T_3 inhibits the augmentation effect of propofol on GABA-activated currents ($P<0.05$), and increasing the propofol concentration can partially offset the inhibitory effect of T_3 ($^*P<0.05$). T_3, 3,3',5-L-triiodothyronine; GABA, γ-aminobutyric acid.

Further experiments were carried out to investigate whether a higher concentration of T_3 produced a stronger inhibitory effect on the anaesthetic effect of propofol. GABA, GABA + propofol and GABA + propofol + T_3 at various concentrations were successively injected into the same cell to validate the effect of T_3. The results are shown in Figs. 8 and 9, and demonstrate that a higher concentration of T_3 produced a stronger inhibitory effect on the propofol-augmented increase in GABA-induced current.

Perfusion of 100 μM GABA produced an activated current for the $GABA_AR$ of 450±35 pA. When pre-perfusion was conducted with 5 μM propofol, the activated current for $GABA_AR$ was 860±41 pA. The activated current for the $GABA_AR$ was 628±46 pA following the perfusion of

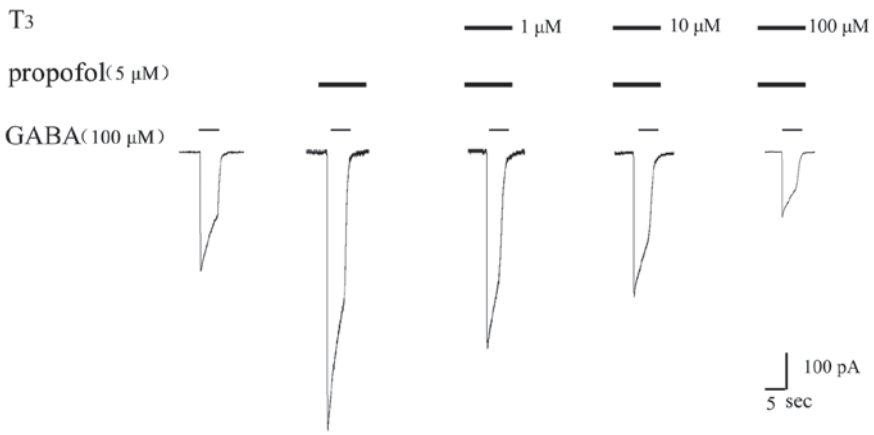

Figure 8. Current traces show the inhibitory effects of different concentrations of T_3 on propofol-augmented GABA-activated currents. Increasing the concentration of T_3 enhances the inhibition of the augmentation effect of propofol on GABA-activated currents.

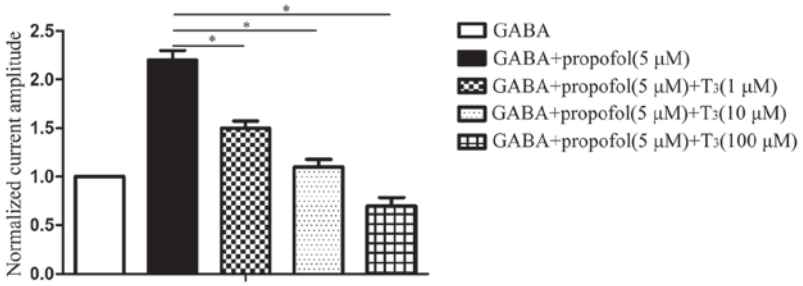

Figure 9. Bar chart of normalised current amplitude shows that T_3 inhibits the effect of propofol on GABA-activated currents in a concentration-dependent manner. Increasing the concentration of T_3 increases the inhibitory effect on the propofol-augmented GABA-activated currents (*P<0.05).

1 μM T_3 and 5 μM propofol, and was 470±43 pA following the pre-perfusion of 10 μM T_3 and 5 μM propofol. Finally, the activated current for $GABA_AR$ was 326±38 pA following the pre-perfusion of 100 μM T_3 and 5 μM propofol.

The bar chart in Fig. 9 shows that a statistically significant difference exists between GABA + propofol (5 μM) and GABA + propofol (5 μM) + T_3 (1 μM; P<0.05), and between GABA + propofol (5 μM) and GABA + propofol (5 μM)+T_3 (10 μM; P<0.05). In addition, a statistically significant difference exists between GABA + propofol (5 μM) and GABA + propofol (5 μM) + T_3 (100 μM; P<0.05).

Discussion

THs, as basal hormones, have important roles in energy utilisation, tissue differentiation, metabolism and organ growth, as well as in maintaining the functional activities of the body (15). THs are mainly involved in the development and functioning of the central nervous system (16-18). The direct transcriptional effects of TH bound to nuclear TRs mediate the majority of the TH effects. A new mechanism of TH action had been previously identified, and is a novel development of the traditional view that THs mediate their effects by controlling gene expression by binding to nuclear receptors TRα and TRβ. According to the study (19), this novel mechanism of TH action is rapid and unaffected by RNA and protein synthesis inhibitors. These facts are indicative of a non-classical nuclear TR-mediated action (19,20). Furthermore, the non-classical nuclear TR-mediated action of TH has been verified in human fibroblasts, human glioma, cardiomyocytes and osteoblasts. The GABAergic system is also an important target for the non-genomic action of THs (20-26).

Propofol is the most widely used short-acting intravenous general anaesthetic. In the classical view, the antalgic mechanism of propofol is mainly associated with an increase in the function of the $GABA_A$ receptors and the inhibitory post-synaptic potential. In clinical terms, additional propofol general anaesthesia is required during surgery for patients with hyperthyroidism compared with those with normal thyroid function. A representation of the result was provided in the present study using a hyperthyroidism model.

Rats with hyperthyroidism require propofol administration at 11.02 mg/100 g BW and control rats at 7.14 mg/100 g BW. To determine why the two groups require different doses of propofol anaesthetic, a DRG immunofluorescent assay was performed. This assay was conducted to evaluate if any changes in the distribution and number of the $GABA_A$ receptors in the DRG neuron occur and to determine if THs alter the functions of the $GABA_A$ receptors by changing their distribution and number. The results showed that the expression levels of $GABA_A$ receptor subunits α2 and β2 did not differ between the control and hyperthyroid groups (Figs. 2 and 3). Considering that the subunits α2/β2/γ2 constitute the $GABA_A$ receptor, it may be assumed that the hyperthyroid model does not change the distribution and number of the $GABA_A$ receptors. The changes in the GABA-activated currents in the DRG neurons

of the hyperthyroid and control rats were then investigated. Whole-cell patch clamp recording tests were performed on an acutely isolated DRG neuron; however, no statistical difference was found between the two groups at various doses. The results indicated that there was no significant difference between the GABA-activated currents in the TH-free interstitial fluids of the hyperthyroid and control rats (Fig. 4). The non-genomic effects of THs on the $GABA_A$ receptors were considered, and the inhibitory effect of T_3 on the GABA-activated currents in DRG neurons was examined (Fig. 5). T_3 inhibits the current-augmenting and anaesthetic effect of propofol on $GABA_A$ receptors (Fig. 6). Propofol can increase the amplitude of GABA-activated currents. The current amplitude decreased when propofol was simultaneously pre-perfused with T_3 at various concentrations, and a higher concentration of T_3 induced stronger inhibition; therefore, it appears that the non-genomic effects of THs were achieved by inhibiting the activities of the $GABA_A$ receptors to mitigate the anaesthetic effect of propofol. With increasing concentrations of THs, the inhibitory effects strengthened. Fig. 7 shows that 5 μM propofol enhanced the GABA-activated currents; however, with 10 μM T_3, the effect of propofol on the GABA-activated currents was inhibited. A higher concentration of propofol was shown to offset the inhibitory effect of T_3 through the simultaneous use of 10 μM propofol and T_3 with the same concentration.

The ideal situation is to have effective anaesthesia with less anaesthetic, but additional propofol anaesthesia during surgery is necessary for patients with hyperthyroidism compared with those with a normal thyroid function. Additional anaesthetic suggests greater anaesthesia risks and adverse reactions; therefore, according to the current study, higher levels of THs in patients with hyperthyroidism inhibit the augmentation effect of propofol on $GABA_A$ receptors. This inhibitory effect leads to less propofol-induced anaesthesia. Given that the mechanism through which T_3 inhibits the $GABA_A$ receptors is unclear, the optimum method of anaesthesia for patients with hyperthyroidism is the control of hyperthyroidism prior to surgery in order to reduce TH levels. It is expected that the mechanism through which T_3 inhibits the $GABA_A$ receptors will be determined in future research. By preventing this inhibition using a specific blocking agent, the optimum anaesthesia effect of propofol can be achieved.

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