Thermogenic and metabolic consequences of thyroid hormone treatment in brown and white adipose tissue

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Male rats were treated with triiodothyronine in the drinking water for 12 days. In vitro rates of isoprenaline stimulated lipolysis were significantly greater in brown but not white adipose tissue. Rates of \[^{14}\text{C}\]glucose incorporation into triacylglycerols were significantly reduced in BAT (brown adipose tissue) and WAT (white adipose tissue) under basal and isoprenaline stimulated conditions. In a second experiment, hyperthyroid animals showed impaired weight gain, despite increased food intake during 19 days' treatment. Energy expenditure on days 5 and 12, and BAT core temperature differences (T_{BAT} - T_{CORE}) on day 19, were significantly greater than in control animals. Epididymal white fat pad weight was reduced and interscapular brown fat pad weight increased by triiodothyronine treatment.

Previous workers have established the importance of brown adipose tissue (BAT) in the thermoregulatory response to chronic cold exposure (non-shivering thermogenesis) (1,2). Recent work with cafeteria fed rats has implicated this tissue in the thermogenic response to over-feeding (diet-induced thermogenesis) (3). These very different physiological states result in remarkably similar alterations in BAT structure and metabolism (4-6). As yet, the nature and mechanism of BAT thermogenesis is only partly understood. BAT Na\(^+\),K\(^+\)-ATPase, proton conductance pathway and a number of futile substrate cycles have all been suggested as major sites of thermogenesis (7-11). From these studies it seems unlikely that any single mechanism will prove to be entirely responsible for the degree of thermogenesis observed during cold exposure and over-eating.

A fatty-acid cycle operating between white adipose tissue (WAT) and liver was first proposed by Masoro in 1963, as a potent means of energy dissipation and heat production (10). The high rates of fatty-acid synthesis, triacylglycerol hydrolysis and fatty-acid oxidation seen in BAT (12,3,13) would enable a far greater degree of fatty acid cycling than in WAT and liver. Furthermore, the simultaneously high rates of lipid synthesis, hydrolysis and oxidation which occur in BAT (13,14) suggest major differences in hormonal and metabolic control in this tissue compared with liver and WAT.
Although the sympathetic nervous system plays a central role in the thermogenic response to cold exposure and over-eating in the rat (15,16), a number of hormones, including insulin, growth hormone, and thyroid hormones, may also play a part (17,18). In particular, thyroid hormones have long been implicated in the thermogenic response to cold exposure (19), although attempts to define a precise function for these hormones in BAT thermogenesis have proved largely unsuccessful (20,21). Recent evidence suggests triiodothyronine (T₃) may play a permissive role in catecholamine stimulation of the BAT Na⁺,K⁺-ATPase (22), although this may not be the only action of the hormone on this tissue. The stimulative effect of thyroid hormones on lipolysis and lipogenesis reported in WAT (23,24) suggests they may be important in the regulation of a futile fatty-acid cycle although there have been no investigations of these actions on BAT. In the present study we have compared the effects of chronic T₃ treatment on in vitro pathways of lipolysis and [¹⁴C]glucose lipogenesis in BAT and WAT. In addition we have studied the in vivo thermogenic response to chronic T₃ treatment.

Materials and Methods

Materials

3',5,3'-Triiodothyronine (free acid), ±-isoproterenol (isoprenaline), L-arterenol bitartrate (noradrenaline), and bovine serum albumin (Grade V) were obtained from Sigma Chemical Co. Scintillant grade toluene was obtained from BDH Chemicals. D-[U-¹⁴C]glucose (255 mCi/mmol) and the T₃ RIA kit were obtained from the Radiochemical Centre, Amersham.

Methods

Male Sprague-Dawley rats bred in the NESCOT Animal House were used in this study. Two groups of six animals (weight range 250-300 g) were selected randomly from a population, marked for identification purposes, and allowed unlimited access to drinking water and food (standard pelleted stock diet -PRD, Christopher Hill Group, U.K.). One group of rats was administered T₃ (3',5,3'-triiodothyronine) in the drinking water for a period of 12 days. The remaining six animals acted as a non-treated control group. The dose level of T₃ in the drinking water was 0.75 mg/100 ml. The mean (± S.E.M.) intake of T₃ in the treated group was calculated to be 276 ± 14.7 µg/rat/day. Water intakes were monitored daily and were not found to differ significantly between the two groups (controls 34.24 ± 0.47 ml vs T₃ treated 36.92 ± 1.98).

On the day of sacrifice (d 12), animals were killed by a blow to the head, blood collected into heparinized tubes and plasma stored frozen at -20°C for the later analysis of plasma T₃ levels (RIA kit, Amersham). The epididymal white fat pad and interscapular brown fat pad were dissected out and small pieces cut for the analysis of in vitro rates of lipolysis and [¹⁴C]glucose incorporation into triacylglycerols (see details below).

Analysis of plasma T₃ levels showed an average value of 0.28 ± 0.06 ng/ml in the control group, compared with 0.98 ± 0.27 ng/ml in the T₃ treated group. The degree of elevation of T₃ levels achieved