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Extract of *Lycopus europaeus* L. reduces cardiac signs of hyperthyroidism in rats

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Abstract

Extracts from the plant *Lycopus europaeus* L. are traditionally used in mild forms of hyperthyroidism. High doses caused a reduction of TSH or thyroid hormone levels in animal experiments, whereas in hyperthyroid patients treated with low doses of *Lycopus* an improvement of cardiac symptoms was reported without major changes in TSH or thyroid hormone concentrations.

Lycopus extract was tested in thyroxine treated hyperthyroid rats (0.7 mg/kg BW i.p.). Co-treatment with an hydroethanolic extract from *L. europaeus* L. started one week later than T_4-application and lasted 5.5 weeks. As reference substance atenolol was used. The raised body temperature was reduced very effectively even by the low dose of the plant extract, whereas the reduced gain of body weight and the increased food intake remained unaffected by any treatment. No significant changes of thyroid hormone concentrations or TSH levels were observed.

Lycopus extract and atenolol reduced the increased heart rate and blood pressure. The cardiac hypertrophy was alleviated significantly by both treatment regimes. β-Adrenoceptor density in heart tissue was significantly reduced by the *Lycopus* extract or the beta-blocking agent showing an almost equal efficacy. Although the mode of action remains unclear, these organo-specific anti-T_4-effects seem to be of practical interest, for example in patients with latent hyperthyroidism.

Keywords: *Lycopus europaeus* L.; Hyperthyroidism; Cardiac symptoms; β-adrenoceptor density; Atenolol

Introduction

Extracts from the plant *Lycopus europaeus* L. are traditionally used in mild forms of hyperthyroidism (Madaus, 1938). In addition therapeutic efficacy in mastopathy has been reported (Mohr, 1969). A considerable amount of experimental work deals with the pharmacological activities of preparations from *L. europaeus* L. or *Lycopus virginicus* L., which are used for the same therapeutic purpose. Within the pituitary–thyroidal system diverse points of attack were found by in vitro and in vivo investigations. A pronounced antithyreotropic activity was confirmed in mixed in vitro/in vivo studies (Kemper and Loeser, 1961; Kemper et al., 1961; Winterhoff et al., 1994). Extracts of *Lycopus* spec. antagonized TSH- and Graves IgG-effects in vitro as well as in vivo (Auf'mkolk et al., 1982, 1984a; Ingbar et al., 1981; Kemper et al., 1961; Sourgens et al., 1982; Winterhoff and Kemper, 1972), they reduced the TSH-plasma concentration (Sourgens, 1984; Sourgens et al., 1982; Winterhoff et al., 1994). *Lycopus* extracts diminished thyroidal secretion (Frömmling-Borges, 1990), reduced the plasma concentration of T_3 and T_4 (Winterhoff et al., 1994) and inhibited the conversion of thyroxine to triiodothyronine (Auf'mkolk et al., 1984b; Köhrle et al., 1981).

However, these effects do not fully explain the clinical findings.

1. The dose, effective in animal experiments, exceeded many times the average dose used in humans.

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2. In a clinical study an improvement of cardiac symptoms was observed at low doses (2 × 20 mg *L. europaeus* L., powdered drug, corresponding to 2 × 5 mg *Lycopus* extract) without any obvious change in thyroid hormone levels (Scheck and Biller, 2000).
3. In most experiments the drug was administered parenterally, long-term experiments with the clinical relevant oral application are not available.

Particularly in hyperthyroid patients an improvement of cardiac symptoms seems to be important, because hypertension with increased blood pressure amplitude, tachycardia or arrhythmia are frequently observed symptoms of hyperthyroidism (Klein and Ojamaa, 2001). They occur in mild forms of hyperthyroidism as well as in latent hyperthyroidism and are regarded as the cause of the increased cardiovascular morbidity and mortality (Biondi et al., 2002; Osman et al., 2002).

It was the aim of this study to investigate whether an extract of *L. europaeus* L. is able to reduce cardiac symptoms of hyperthyroidism in rats. For this purpose an experiment was performed with male Wistar rats rendered hyperthyroid by application of T_4. After one week, additional treatment with a hydroethanolic extract of *L. europaeus* L. started whilst maintaining the T_4-application. The effect was compared with that of the beta-blocking drug atenolol. During the experiments body weight increase, food consumption, rectal temperature, heart rate and blood pressure were recorded. At the end of the experiment, the thyroid hormone concentrations and TSH were measured by RIA. In addition the density of β-adrenergic receptors in the heart tissue was measured using a receptor binding assay.

Material and methods

Chemicals

L-Thyroxine sodium salt was purchased from Calbiochem (Schwalbach, Germany); ICYP from NEN Life Sciences Products GmbH (Cologne, Germany); Atenolol was obtained from ICN Biochemicals (Eschwege, Germany). All other chemicals were purchased from Sigma (Deisenhofen, Germany).

Plant material

A lyophilized ethanolic extract of *L. europaeus* L. (drug/extract ratio: 4–10:1; ethanol content of the extraction solvent: 50% m/m) was obtained from Finzelberg (Andernach, Germany). This extract contained 20% maltodextrine to avoid agglomeration. The concentration of rosmarinic acid, one of the major compounds, was 2.9%. The following dosages refer to the native plant extract.

Animals

Male Wistar (Hannover) rats (150–180 g, Harlan-Winkelmann GmbH, Borchen, Germany) were housed singly in a 12 h light/dark cycle, with lights off at 7:00 pm, at a constant temperature of 25 ± 1 °C and with free access to food (Altromin 1324, Altromin Lage, Germany) and tap water. The rats were randomly assigned to the experimental groups (n = 13/group). Food intake and body weight were measured daily. The experimental procedures used comply with the European Community's Council Directive of 24th November 1986 (86/609/EEC) and were officially approved by the local committee on animal care (Regierungspräsident, Münster, A 65/02). Animals were sacrificed between 9:00 and 11:00 am; the last drug administration was the day before between 7:00 and 8:00 pm. To measure intracardial thyroid hormone the heart was perfused with Dulbecco's PBS (pH 7.2 containing 50 IU/ml Heparin) through the right femoral vein immediately after the thorax was opened (details see below). Heart, pituitary and thyroid were dissected and weighed immediately. Left and right ventricle of the heart were rapidly prepared and handled separately for the β-receptor binding assay (details see below), one aliquot from the left ventricle was frozen in liquid nitrogen and stored at −80 °C for thyroid hormone determination. Plasma was stored at −20 °C, pituitary glands were kept frozen in BSA-buffer (1%, pH 7.6) at −20 °C for TSH determination.

Experimental design

The experiment was divided into two phases: one week of treatment with T_4 only and a second phase (five and a half week) of additional application of plant extract or beta-blocking drug resp. maintaining T_4-application. The T_4-solution (thyroxine sodium salt, dissolved in 0.01 M NaOH) was administered once daily between 11:00 and 12:00 am at a dosage of 0.7 mg T_4/kg BW/d. In preceeding own experiments oral application of 1.0 mg/T_4/kg BW/d caused marked hyperthyroid symptoms in rats (data not shown). In this experiment i.p. application was chosen to exclude an impairment of enteral absorption of T_4 by phenolic constituents of the orally given plant extract. The dosage was reduced to 0.7 mg T_4/kg BW/d as compared to 1 mg/kg when given orally to account for the increased bioavailability following i.p. application.

The one week pre-treatment period with thyroxine should ensure a hyperthyroid state at the beginning of the co-treatment. Plant extract (2 × 5 mg and 2 × 200 mg/kg BW) or beta-blocking agent atenolol (2 × 25 mg/ kg BW) resp. were administered orally (10 ml/kg body weight) by gavage twice a day between 7:00–8:00 and 19:00–20:00 h. Suspensions of the extract were prepared with water directly before use. The extracts were kept in opaque containers at −20 °C under argon atmosphere. During the application procedure the extract suspension was stirred continuously to maintain a homogenous suspension. The results were compared with those of a control group treated with water and a further group treated with the extract (2 × 200 mg/kg/d body weight). These two groups were not rendered hyperthyroid with T_4.