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Effects of amiodarone and thyroid dysfunction on myocardial calcium, serum calcium and thyroid hormones in the rat

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1 Myocardial calcium content was found to be elevated and serum calcium reduced in hypothyroid rats.

2 Treatment of rats with amiodarone at either 30 mg kg^{-1} or 150 mg kg^{-1} daily did not result in any significant changes in myocardial or serum calcium.

3 The administration of amiodarone to hypothyroid rats attenuated the changes in serum but not myocardial calcium, suggesting that amiodarone may exert a thyroid hormone-like effect in the hypothyroid state.

4 The administration of amiodarone to thyroid hormone-treated rats resulted in attenuation of the effects on serum calcium and calculated intracellular calcium; this was consistent with an antagonistic interaction between amiodarone and thyroid hormones.

5 Administration of amiodarone resulted in significant changes in circulating thyroid hormone levels in the rat; triiodothyronine was reduced and basal thyrotrophin elevated compared to euthyroid controls. Serum thyroxine was not changed; this is in contrast to the effects in man.

6 Amiodarone does not exert its anti-arrhythmic action via changes in total myocardial calcium content in the euthyroid rat; nonetheless the described interactions between the drug and thyroid hormones may be involved in its mechanism of action.

Introduction

The anti-arrhythmic drug amiodarone is an iodinated, benzofuran derivative with predominantly class III activity (Singh & Vaughan Williams, 1970). Whilst it is very effective in the treatment of tachyarrhythmias of both supraventricular and ventricular origin, its use has been limited by a wide spectrum and relatively high incidence of side effects (Rotmensch *et al.*, 1982; McKenna *et al.*, 1983). The mode of action of amiodarone at the cellular level is understood poorly, but the combination of its effects on peripheral thyroid hormone metabolism (Burger *et al.*, 1976; Melmed *et al.*, 1981) and the demonstration of inhibition of binding of triiodothyronine (T3) to its nuclear receptor (Franklyn *et al.*, 1985), together with the similarity between the electrophysiological effects of hypothyroidism and amiodarone treatment (Singh & Vaughan Williams, 1970), have led to the hypothesis that the drug may act by antagonism of T3 effects within the myocardial cell. This hypothesis is supported by a report of competitive interaction between binding of amiodarone and T3 to the myocardial nuclear receptor for thyroid hormones (Wiersinga & Broenik, 1983).

Alteration in thyroid status and the availability of thyroid hormones have been shown to exert considerable influence on calcium turnover (Bijlsma *et al.*, 1983), serum calcium concentration (Gammage & Logan, 1986), intracellular distribution of calcium (Kim & Smith, 1985) and the activity of calcium-activated ATPase in the heart (Suko, 1971). As the prolongation of the monophasic action potential seen with both hypothyroidism and amiodarone treatment involves the period during which influx of calcium ions is occurring, alterations in the availability or distribution of calcium within the cardiac myocyte may be involved in the mechanism of action of amiodarone.

In order to explore these hypotheses and to examine the similarities between the effects of amiodarone on the myocardium and the changes induced by hypothyroidism, myocardial calcium content, serum calcium and serum thyroid hormones (thyroxine (T4), triiodothyronine (T3)) and thyrotrophin (TSH) were

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measured in rats treated with amiodarone and the results compared to those seen in euthyroid, hypothyroid and thyroid hormone-treated animals. Myocardial water content was measured and intracellular ($[Ca]_i$) and extracellular calcium ($[Ca]_o$) concentrations calculated from published methods and data (Liu & Overman, 1964; Polimeni, 1974a,b).

Methods

Home-bred male Sprague-Dawley rats (Department of Physiology, University of Birmingham), age 8 weeks at onset of treatment, weight 250–300 g, were used in these studies; all animals were maintained on a standard diet (Rat and Mouse Breeding Diet, Pilsbury's Ltd), housed in a warm, well-lit animal house and allowed food and water *ad libitum*.

Treatment regimes:

Induction of hypothyroidism Rats were rendererd hypothyroid by subcutaneous injection of 40μCi (1.48 MBq) ^{131}I (as sodium iodide in 0.9% NaCl) and by administration of propylthiouracil (PTU) 60 mg $litre^{-1}$ in drinking water for 10 weeks (Cooper *et al.*, 1983).

Thyroid hormone treatment Rats were treated with L-thyroxine (T4) 100 μg and L-triiodothyronine (T3) 50 μg by subcutaneous injection thrice weekly for three weeks.

Low-dose amiodarone regime Amiodarone (donated by Sanofi U.K. Ltd), 50 g, was dissolved in 1 litre of distilled water at 70°C and allowed to cool to room temperature. This stock solution remained stable for up to 4 weeks if protected from light and was diluted further to produce a solution of 200 mg $litre^{-1}$ which was administered in drinking water for 10 weeks. This gave an estimated daily dose of 10 mg per rat (approximately 30 mg kg^{-1} per day); the therapeutic dose range in man is 200–800 mg per day or approximately 3–11 mg kg^{-1} daily. This dose did not, however, result in adequate 'therapeutic' serum levels of the drug; mean serum amiodarone was less than 0.1 mg $litre^{-1}$ and its first metabolite desethyl amiodarone was undetectable.

High-dose amiodarone regime As a result of data from serum levels of amiodarone, a higher dose of the drug was given to a second group of rats and the results compared to those obtained from euthyroid controls and hypothyroid animals.

The high dose regime consisted of amiodarone (50 g $litre^{-1}$ solution) given by gavage, 0.5 ml (25 mg) twice daily for 4 weeks (approximately 150 mg kg^{-1} daily). This regime resulted in mean serum levels of amiodarone of 2.56 ± 0.45 mg $litre^{-1}$ and of desethylamiodarone 0.61 ± 0.15 mg $litre^{-1}$ (mean ± s.e.mean). These concentrations are within the therapeutic range defined in man (approximately 1.5–3.5 mg $litre^{-1}$) (Holt *et al.*, 1983).

Myocardial calcium extraction

Animals were rendered unconscious with light ether anaesthesia and killed by decapitation. The chest was opened immediately, the heart removed intact, placed in ice-cold phosphate-buffered saline (PBS) (composition, $g\,l^{-1}$: $Na_2HPO_4.12H_2O$ 5.98, $NaH_2PO_4.2H_2O$ 0.52, NaCl 6.8 KCl 0.4 and glucose 0.9, pH 7.35) and flushed three times with this solution. The atria, great vessels and valve ring were trimmed off, leaving only ventricular myocardium. This was flushed again with fresh ice-cold PBS, blotted dry, divided into two portions and weighed. One sample was transferred to 10 ml of ice-cold extraction medium for calcium assay (5.85 g La_2O_3, 25 ml concentrated HCl, 40 ml n-butanol made up to 1 litre with distilled water) (Tew *et al.*, 1981), the other to 10 ml of sodium deoxycholate (4 g $litre^{-1}$) solution for solubilization before protein assay. This procedure was complete within 3 min of decapitation of the rat. The samples of ventricular myocardium were then homogenized in the extraction or solubilization medium at approximately 12,000 r.p.m. for 2 periods of 45 s in an Ultra-Turrax TP 18–10 homogenizer. The homogenate was centrifuged at 12,000 *g*, 0°C for 20 min and the supernatant decanted into polyethylene tubes.

Serum preparation

Blood was collected after decapitation of the animal. Whole blood was centrifuged in polyethylene tubes at 600 *g* for 15 min and the serum removed immediately. A 200 μl aliquot of serum was diluted with 4 ml of lanthanum stock solution (La_2O_3 18 mmol l^{-1}, 116 mmol l^{-1} HCl) and made up to 20 ml with distilled water.

Calcium assay

Myocardial and serum calcium were assayed by Atomic Absorption Spectrophotometry (AAS) using a Pye-Unicam SP9 Spectrophotometer with absorption peak set at 422.7 nm. Calibration was against calcium standards made up in identical extraction medium and lanthanum stock solution. Lanthanum ions are required during the assay of physiological fluids for calcium by AAS in order to suppress phosphate interference.

The myocardial calcium assay was validated by

correlation of myocardial calcium measured in a standard volume of extraction medium against wet weight of ventricular tissue assayed in 23 normal animals; there was a strong positive correlation with an r value of 0.939 ($P < 0.001$) (data not shown).

Protein assay

Myocardial protein was assayed according to the method of Lowry *et al.* (1951) using an Ultrospec 4050 spectrophotometer (LKB Biochrom) reading at 750 nm.

Assessment of thyroid status

Basal serum thyrotrophin (TSH) levels were measured by specific radioimmunoassay (reagents provided by the National Hormone and Pituitary Program, Baltimore, MA, U.S.A.: reference preparation was NIADDK-rat-TSH-RP2). Serum thyroxine (T4) and triiodothyronine (T3) were measured by an in-house radioimmunoassay.

Serum amiodarone and desethylamiodarone measurement

Concentrations of amiodarone and desethylamiodarone (the primary metabolite) were measured in serum by high performance liquid chromatography by courtesy of Dr D. Holt, New Cross Hospital, London (Storey & Holt, 1982).

Assessment of myocardial waters

In order to calculate myocardial water content, hearts taken from 5 control (euthyroid) animals, 5 hypothyroid animals, 5 thyroid hormone treated animals, 5 animals receiving low dose amiodarone and 5 animals receiving high dose amiodarone were weighed in a microbalance (Sartorius 4503 MP6) and dried at 100°C in an oven to constant weight in order to assess myocardial water content. Myocardial water content was calculated as:

$$\frac{\text{Wet weight} - \text{Dry weight}}{\text{Wet weight}}$$

and expressed as litre kg^{-1} wet weight and litre kg^{-1} tissue protein.

Calculation of intracellular and extracellular calcium

In order to allow for the effects that changes in extracellular fluid and extracellular calcium content of myocardial tissue might have on total myocardial calcium, extracellular and intracellular calcium concentrations were calculated according to the distribution of water between the extracellular and intracellular compartments using the data and methods of Liu & Overman (1964) and Polimeni (1974a,b), assuming no significant change from euthyroid distribution in the amiodarone-treated hearts as no change in overall tissue water was detected (control $= 0.775 \pm 0.001$ litre kg^{-1} wet weight, low-dose amiodarone $= 0.775 \pm 0.001$, high-dose amiodarone 0.776 ± 0.001, mean $\pm$ s.e.mean, N.S). Extracellular calcium was calculated from the data for serum calcium using a correction factor of 0.946 to allow for differences in protein content of extracellular fluid (Polimeni, 1974a,b).

Statistical analysis

All results are expressed as mean $\pm$ s.e.mean and were analysed by analysis of variance with the exception of the comparison of the effects of low and high-dose amiodarone on serum TSH where unpaired Student's t test was used due to unequal group sizes.

Study design

In the first series of experiments, the effects of low-dose amiodarone treatment, hypothyroidism, thyroid hormone treatment and the combination of amiodarone and thyroid hormone treatment were compared to euthyroid controls ($n = 8$ in each group). Animals in the group receiving both amiodarone and thyroid hormones were treated with amiodarone for 10 weeks with the addition of thyroid hormone for the last 3 weeks of amiodarone treatment.

In the second series of experiments, results were compared in high-dose amiodarone-treated, hypothyroid and euthyroid control animals ($n = 10$ in each group). In addition, 10 hypothyroid rats received amiodarone for the last 4 weeks of the PTU treatment period.

Results

Low-dose amiodarone treatment

A significant increase in total myocardial calcium content was found in hypothyroid animals compared to controls but no change was found in amiodarone-treated animals (Table 1). Similar results were obtained when myocardial calcium content was expressed per weight of myocardial protein. Treatment of rats with amiodarone and/or thyroid hormones had no significant effect on myocardial calcium content. In accord with the results for myocardial calcium content, serum calcium concentration was reduced significantly in hypothyroid rats but was unaffected by amiodarone. In contrast to myocardial calcium content, however, treatment with thyroid

Table 1 Myocardial calcium, serum calcium and calculated extracellular and intracellular calcium in euthyroid controls, hypothyroid, low-dose amiodarone treated, thyroid hormone-treated and low-dose amiodarone plus thyroid hormone-treated rats

	Myocardial calcium (mmol kg^{-1} wet weight)	*Myocardial calcium* (mmol kg^{-1} protein)	*Serum calcium* (mmol $litre^{-1}$)	$[Ca]_o$ (mmol $litre^{-1}$)	$[Ca]_i$ (mmol $litre^{-1}$)
Control	0.78 ± 0.01	3.59 ± 0.10	2.44 ± 0.02	2.31 ± 0.02	0.59 ± 0.02
Hypothyroid	0.96 ± 0.01**	4.10 ± 0.02**	2.09 ± 0.03**	1.98 ± 0.03**	0.95 ± 0.02**
Amiodarone	0.79 ± 0.01	3.79 ± 0.12	2.44 ± 0.03	2.31 ± 0.03	0.64 ± 0.02
Thyroid hormone-treated	0.77 ± 0.01	3.65 ± 0.12	2.59 ± 0.03**	2.45 ± 0.03**	0.40 ± 0.02**
Amiodarone + thyroid hormone treated	0.80 ± 0.01	3.79 ± 0.08	2.49 ± 0.04†	2.36 ± 0.04†	0.48 ± 0.04

Values are mean ± s.e.mean, $n = 8$ in each group.
** = $P < 0.01$ compared to control; † = $P < 0.02$ compared to thyroid hormone-treatment.

Table 2 Myocardial calcium, serum calcium and calculated extracellular and intracellular calcium in euthyroid controls, hypothyroid, high-dose amiodarone-treated and high-dose amiodarone-treated hypothyroid rats

	Myocardial calcium (mmol kg^{-1} wet weight)	*Myocardial calcium* (mmol kg^{-1} protein)	*Serum calcium* (mmol $litre^{-1}$)	$[Ca]_o$ (mmol $litre^{-1}$)	$[Ca]_i$ (mmol $litre^{-1}$)
Control	0.74 ± 0.02	3.42 ± 0.11	2.44 ± 0.02	2.31 ± 0.02	0.55 ± 0.04
Hypothyroid	1.02 ± 0.03**	4.35 ± 0.13**	2.02 ± 0.03**	1.95 ± 0.03**	1.05 ± 0.04**
Amiodarone	0.79 ± 0.03	3.33 ± 0.13	2.49 ± 0.04	2.36 ± 0.04	0.61 ± 0.04
Hypothyroid + amiodarone	1.00 ± 0.03**	3.99 ± 0.16**	2.14 ± 0.02**†	2.03 ± 0.02**†	0.98 ± 0.06**

Values are mean ± s.e.mean, $n = 10$ in each group.
** = $P < 0.01$ compared to control; † = $P < 0.05$ compared to hypothyroid.

Table 3 Basal serum thyrotrophin (TSH) in euthyroid control, hypothyroid, low-dose amiodarone-treated, thyroid hormone-treated and low-dose amiodarone plus thyroid hormone-treated rats

	Serum TSH (ng ml^{-1})
Control	2.14 ± 0.50
Hypothyroid	44.42 ± 2.06**
Amiodarone-treated	4.33 ± 0.40**
Thyroid hormone-treated	0.37 ± 0.06**
Amiodarone + thyroid hormone-treated	0.42 ± 0.16††

Values are mean ± s.e.mean, $n = 8$ in each group.
** = $P < 0.01$ compared to control; †† = $P < 0.01$ compared to amiodarone-treatment.

hormones resulted in an increase in serum calcium. This increase was abolished in animals treated with amiodarone in addition to thyroid hormones (Table 1). Calculated extracellular calcium concentrations, of course, showed identical trends to serum calcium concentrations. Calculated intracellular calcium content was elevated in hypothyroid animals compared to controls but was unchanged in amiodarone-treated animals. Rats treated with thyroid hormones showed a significant reduction in intracellular calcium; animals receiving both amiodarone and thyroid hormones showed no significant change from control (euthyroid) values (Table 1).

High-dose amiodarone treatment

Similar effects of hypothyroidism on myocardial calcium content (total and intracellular) and on serum calcium were observed. High-dose amiodarone treatment, as with low-dose treatment, did not result in any significant changes in the parameters measured (Table 2). The increase in myocardial calcium content (total and intracellular) seen with hypothyroidism was not affected by administration of amiodarone. The changes in serum and extracellular calcium were, however, significantly less marked in hypothyroid animals receiving amiodarone.

Thyroid function

Low-dose amiodarone A marked increase in serum TSH was evident in ^{131}I- and PTU-treated animals, confirming the development of hypothyroidism. A significant, but less marked, rise in serum TSH was also seen in amiodarone-treated rats when compared to controls. A reduction in serum TSH was found in rats treated with thyroid hormones but this reduction was less marked in animals receiving amiodarone in addition to thyroid hormones (Table 3).

High-dose amiodarone A significant increase in serum TSH was again seen in amiodarone-treated animals; this was greater than the rise in those given low-dose treatment. The marked increase in serum TSH in hypothyroid animals was attenuated by the simultaneous administration of amiodarone. Amiodarone treatment also resulted in marked changes in T4 and T3 in the rat although these differed from the changes seen in man (Franklyn *et al.*, 1985). Amiodarone-treatment resulted in a significant reduction in T3 but no significant change in T4 compared to euthyroid controls. Hypothyroid animals showed marked reductions in both T4 and T3 but these reductions were again attenuated in the hypothyroid animals receiving amiodarone (Table 4).

Discussion

The similarity between the effects of amiodarone and those of thyroidectomy on the duration of the monophasic action potential was first described by Singh & Vaughan Williams (1970). A number of other features

Table 4 Serum thyroxine (T4), triiodothyronine (T3) and thyrotrophin (TSH) in euthyroid control, hypothyroid, high-dose amiodarone-treated and hypothyroid plus high-dose amiodarone-treated rats

	T4 (nmol litre^{-1})	*T3* (nmol litre^{-1})	*TSH* (ng ml^{-1})
Control	61.0 ± 9.6	0.86 ± 0.06	2.24 ± 0.26
Hypothyroid	14.8 ± 2.6**	0.13 ± 0.01**	42.8 ± 1.89**
Amiodarone	50.1 ± 8.7	0.48 ± 0.09**	6.21 ± 1.09**†
Hypothyroid plus amiodarone	26.6 ± 8.0**^{a}	0.26 ± 0.04**^{aa}	28.0 ± 4.32**^{aa}

Values are mean ± s.e.mean, $n = 10$ in each group.
** = $P < 0.01$ compared to control; * = $P < 0.05$ compared to control; † = $P < 0.05$ compared to low-dose amiodarone (see Table 3); ^{a} = $P < 0.05$ compared to hypothyroid; ^{aa} = $P < 0.01$ compared to hypothyroid.

of the action of the drug on the heart, resembling those of hypothyroidism, have been described since 1970; the reduced heart rate (Charlier, 1970; Ferrero *et al.*, 1981) appears to result from a direct electrophysiological effect on the pacemaker cells of the sinus node although the non-specific adrenergic blocking activity of the drug may also be involved (Polster & Broekhuysen, 1976). A decrease in the density of β-adrenoceptors at the myocardial cell surface (Nokin *et al.*, 1983; Sharma & Corr, 1983) and a reduction in myocardial oxygen consumption (Harris *et al.*, 1986) have been demonstrated: the latter has been shown to be dose-related in the dog. Other effects include an increase in the ratio of V3 to V1 myosin heavy chain isoenzymes (this could be reversed by the administration of T3) (Wiegand *et al.*, 1984), a reduction in cardiac myosin-ATPase (Sogol *et al.*, 1983) and a reduction in Na^+, K^+-ATPase activity in rabbit and guinea-pig heart (Broekhuysen *et al.*, 1972; Clinet & Broekhuysen, 1972).

Conflicting with these data, however, are the observations that neither anti-thyroid drugs such as PTU, carbimazole or methimazole nor drugs that inhibit 5'monodeiodinase (such as the radiographic contrast medium iopanoic acid) have significant anti-arrhythmic activity (Sogol *et al.*, 1983; Lindenmeyer *et al.*, 1984). This does not, of course, exclude the possibility that the anti-arrhythmic action of amiodarone may involve a number of effects, only some of which may be similar to hypothyroidism.

In the present studies we have explored further this relationship between amiodarone and thyroid hormones by comparing and contrasting the effects of hypothyroidism and amiodarone administration on myocardial calcium content (both total and calculated intracellular) and on serum calcium concentration. We have also studied the effects of amiodarone on myocardial and serum calcium and circulating thyroid hormone levels in hypothyroid and thyroid hormone-treated animals in order to examine the possibility of agonist/antagonist interactions between the drug and thyroid hormones.

In the first series of experiments, amiodarone was administered in a dose that is similar to that used in the first few weeks of therapy in man ('loading dose'). Despite this, serum levels in the rat were found to be much lower than the clinical therapeutic range defined in man (approximately 1.5–3.5 mg $litre^{-1}$) (Holt *et al.*, 1983). It is of interest, however, that this dose did result in a significant change in basal serum TSH. The results of serum drug levels prompted an increase in the dose of amiodarone administered in the second series of experiments and required a change in technique of administration (to gavage). This resulted in adquate 'therapeutic' serum levels of amiodarone and desethyl-amiodarone.

Early animal studies using 'therapeutic' doses (e.g. 10 mg kg^{-1} daily by intraperitoneal injection for 10 days in rats) did not find any alteration in thyroid hormone levels. It was only at higher, prolonged dosage (200 mg kg^{-1} daily for one year in the rat) that evidence of thyroid overactivity was described (Harris *et al.*, 1986); this was assumed to be the result of the enormous iodine load. All subsequent studies have shown significant rises in reverse T3 (rT3) levels, consistent with the inhibition of 5'monodeiodinase, but the effects on T4 and T3 have varied both within and between laboratory animals (Sogol *et al.*, 1983; Lindenmeyer *et al.*, 1984; Kannan *et al.*, 1984; Venkatesh *et al.*, 1986). In animals studies where drug levels have been recorded (Kannan *et al.*, 1984; Venkatesh *et al.*, 1986) very high doses (in comparison to man) have been needed in small mammals in order to obtain 'therapeutic' serum levels. This problem of the difference in the rate of metabolism and/or absorption between man and small mammals may account for some of the differences in effects of amiodarone reported in the present study (i.e. no elevation of T4 in the rat) and the discrepancies between animal studies with variable effects on T3, T4 and TSH levels according to the dose.

Many animal studies have experienced problems with the difficulty in presenting amiodarone in a stable solution without the presence of the vehicle Tween 80 (polyoxyethylene (20) sorbitan monooleate) which is used in the commercial, parenteral preparation. This vehicle is known to have significant negative inotropic effects in both man and the dog when given intravenously (Sicart *et al.*, 1977; Newton *et al.*, 1981) and has also been shown to produce a calcium-dependent prolongation of atrial action potential duration in the rat isolated heart (Northover, 1984). We have been able to overcome the problem of administration by dissolving amiodarone as recommended by Kannan *et al.* (1984) to produce a solution of 50 g $litre^{-1}$ which can be administered by gavage.

The present studies have demonstrated marked effects of hypothyroidism on both serum calcium and myocardial calcium content. These are in accord with our previous findings using similar techniques (Gammage & Logan, 1986; Gammage *et al.*, 1986) but the calculation of intracellular calcium content in this study takes account of the alterations in tissue and extracellular water content which may bias changes in total calcium content via changes in extracellular calcium. This allows the confirmation of a rise in myocardial calcium content with hypothyroidism. Despite these results, however, amiodarone cannot be shown to exert any effect on myocardial calcium content at either low or high dose. These data do not, therefore, lend support to the hypothesis that amiodarone exerts its anti-arrhythmic effect by inducing similar changes in the myocardium to those resulting from hypothyroidism. Nonetheless, it is

interesting to note that in the first series of experiments the increase in serum calcium resulting from thyroid hormone treatment was attenuated by the simultaneous administration of amiodarone. Similarly, the decrease in intracellular calcium content found with thyroid hormone treatment was attenuated by amiodarone, although this change did not reach statistical significance ($P = 0.08$). These results are consistent with an antagonistic interaction between amiodarone and thyroid hormones (Singh & Vaughan Williams, 1970). In accord with the results of the first series of experiments, no effect of high-dose amiodarone on serum or myocardial calcium was evident. It was of interest in these experiments that the changes in serum and myocardial calcium concentrations induced by hypothyroidism were less marked in hypothyroid animals treated with amiodarone. These findings suggest that amiodarone is exerting a thyroid hormone-like or agonistic effect in the hypothyroid state. A similar influence on TSH was evident in that the rise in serum TSH in hypothyroid rats was significantly less marked in the amiodarone-treated hypothyroid group. This result again suggests a thyroid agonistic influence of the drug. It must be noted, however, that serum T3 was significantly higher in the amiodarone-treated hypothyroid animals than in the untreated hypothyroid animals; the influence of amiodarone on TSH may, therefore, reflect partly a change in circulating concentration of T3.

We have demonstrated previously a competitive interaction between amiodarone and T3 for binding to the nuclear receptor for thyroid hormones in the rat anterior pituitary cell (Franklyn *et al.*, 1985). Other workers have demonstrated inhibition of T3 binding to the nuclear receptor in the rat myocardial cell (Wiersinga & Broenik, 1983). The influence of amiodarone on basal serum TSH in both low and high dose studies is consistent with our previous report of the effects of the drug in man (Franklyn *et al.*, 1985); amiodarone treatment resulted in an increase in basal serum TSH compared to euthyroid control rats and this was significantly greater with the high-dose regime. The reduced serum T3 seen with amiodarone treatment reflects the inhibition of 5'monodeiodinase as described in other studies, both in man and other animals (Sogol *et al.*, 1983; Kannan *et al.*, 1984; Franklyn *et al.*, 1985).

The mechanisms underlying the observed interactions between thyroid hormones and amiodarone include effects on 5'monodeiodination and on nuclear receptor binding of T3, effects which may occur in the pituitary, myocardium and possibly other tissues. The influence of the drug in terms of thyroid hormone agonistic and antagonistic effects may reflect the relative affinity of the drug and thyroid hormones for binding to the thyroid hormone nuclear receptor and the relative concentrations of drug and thyroid hormones within the cell.

In summary, it does not appear that the effects of thyroid status on serum calcium or myocardial calcium content are mimicked by administration of amiodarone. Nonetheless, the data provide evidence for an interaction between amiodarone and thyroid hormone effects, an interaction that may contribute to the therapeutic action of the drug.

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