reference) are similar (Horn & Rodgers 1976). Further, a bimethylene chain projects in front of the aromatic plane when this is orientated in relation to the heterocyclic ring as it is in the benzomorphan (see views looking down on the molecules). In the dextro antipodal forms, projection of heterocyclic carbons in front of the aromatic plane is less extensive and this différence may be a key factor in determining the degree of interaction with the opiate receptor either in the provision of binding sites (perhaps to fit the 'cavity' originally proposed in 1954 by Beckett & Casy) or avoidance of a receptor area intolerant to non-polar elements. An alternative model for (−)-I and (−)-II is the 1-aza analogue of the benzomorphan of Fig. 1 (with N and C-1 interchanged) which, as a racemate, has a half to a third the potency of pethidine in mice antinociceptive tests and is significantly active in a binding assay (Iorio & Casy 1975; Iorio & Klee unpublished results). These facts demonstrate that the anionic site of the opiate receptor herein involved has some degree of tolerance to the siting of the cationic centre of the ligand (Fries & Portoghese 1976).

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Thyroid hormones do not alter rat brain benzodiazepine receptor function in-vivo

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It has recently been reported that thyroid hormones and their derivatives inhibit benzodiazepine receptor binding in a stereospecific manner in rat brain membranes in-vitro (Nagy & Lajtha 1983). The endocrinologically inactive isomer D-thyroxine was found to be the most potent inhibitor with both L-thyroxine (L-T_4) and L-triiodothyronine (L-T_3) being considerably less potent. It was also of interest that audiogenic-seizure susceptible mice (DBA/2J) have both high serum thyroxine concentrations (Seyfried et al 1978, 1979) and increased benzodiazepine receptor binding (Robertson 1980) during the seizure-susceptible period of development. These reports prompted us to investigate whether these thyroid hormones possess anticonvulsant properties in mature rats since they might have clinical relevance in the treatment of epilepsy. Furthermore, since high affinity benzodiazepine receptor ligands that antagonize the anticonvulsant effect of benzodiazepines have recently been reported (Hunkeler et al 1981; Nutt et al 1982) we have investigated whether these drugs modify in any way the anticonvulsant effects of the water-soluble benzodiazepine, flurazepam, and the proconvulsant properties of FG 7142, the methylamide of ethyl β-carboline 3-carboxylate, which also acts via the benzodiazepine receptor (Petersen et al 1982).

* Correspondence

Method

Seizure thresholds were measured using an intravenous infusion method (Nutt et al 1980) at various times following the acute or chronic administration of either D-thyroxine (D-T_4) or L-triiodothyronine (L-T_3) or their respective vehicles. In addition the effects of these compounds on the flurazepam-induced increase and the FG 7142-induced decrease in seizure threshold were evaluated (for details see Table 1). Rats weighed 130–150 g for the acute experiments and 190–210 g at the end of the chronic treatment.

Results and discussion

From Table 1, it can be seen that very large doses (approximately 100 times the dose required to restore thyroid function in hypothyroid rats) of the thyroid hormones had no effect on pentetrazol seizure thresholds, a system which is quite sensitive to the anticonvulsant effect of benzodiazepines (Nutt et al 1982). Seizure thresholds were unaltered at times when brain penetration was thought to be maximal (Ford & Cramer 1977; Vigoroux et al 1979) and 24 h later. Furthermore, the failure of these hormones to alter in any way the anticonvulsant effects of various doses of flurazepam or the proconvulsant effects of FG 7142 argued against their having any benzodiazepine receptor antagonist

Table 1. Effect of thyroid hormones on pentetrazol seizure thresholds in rats (n = no of rats/group).

Treatment protocol	Drug	T_3/T_4 Dose	Seizure threshold mg kg^{-1}	n
Acute L-T_3 and D-T_4				
(i) 1 Dose	L-T_3 (L-triidothyronine)	100 μg kg^{-1}	38 ± 2	9
Test 24 h later	D-T_4 (D-thyroxine)	100 μg kg^{-1}	40 ± 2	6
	Control	—	40 ± 2	8
(ii) 1 Dose.	L-T_3	1 mg kg^{-1}	33 ± 2	6
Test 2 h later	D-T_4	1 mg kg^{-1}	31 ± 2	6
	Control	—	30 ± 2	6
(iii) 1 Dose.	L-T_3	1 mg kg^{-1}	38 ± 2	6
Test 30 min later	D-T_4	1 mg kg^{-1}	39 ± 2	6
	Control	—	39 ± 2	6
Acute D-T_4 + Flurazepam (FZP)				
D-T_4 given 2 h pre-	Control	—	34 ± 1	6
and FZP given 30	FZP (10 mg kg^{-1})	—	49 ± 1*	6
min pre-infusion	L-T_4 + FZP (10)	1 mg kg^{-1}	49 ± 2	6
	FZP (20 mg kg^{-1})	—	80 ± 4*	6
	L-T_4 + FZP (20)	1 mg kg^{-1}	91 ± 6	6
Acute D-T_4 + FG 7142				
D-T_4 given 2 h pre-	Control	—	39 ± 2	8
and FG 7142 15 min	FG 7142 (40 mg kg^{-1})	—	22 ± 2†	6
pre-infusion	L-T_4 + FG 7142 (40 mg kg^{-1})	1 mg kg^{-1}	25 ± 2	6
Chronic				
1 × daily for 10 days.	L-T_3	100 μg kg^{-1}	33 ± 2	6
Test 24 h after last			(0.29 ± 0.018)‡	(7)
dose	Control	—	36 ± 2	6
			(0.37 ± 0.024)‡	(7)

(a) * significantly different from control group ($P<0.01$), but not from FZP + T_4 groups (*t*-test)
† significantly different from control group ($P<0.001$), but not significantly different from T_4 + FG 7142 group.
(b) None of the results for T_3 or T_4 in chronic or acute experiments significantly different from control groups.
(c) All results given as mean ± s.e.m.
(d) Seizure threshold (mg kg^{-1}) calculated from time to first myoclonic jerk, using an infusion of pentetrazol (10 mg ml^{-1}) in 0·9% NaCl Infusion rate 2·22 ml min^{-1}.
(e) All thyroid analogues were dissolved in 0·02M NaOH and injected subcutaneously.
(f) Rats received 4 ml kg^{-1} of FZP in water (2·5 or 5 mg ml^{-1}) by i.p. injection.
(g) ‡ Bicuculline (0·05 mg ml^{-1} in pH 3 0·9% NaCl) used as convulsant. Infusion parameters as in (d).
(h) FG 7142 prepared as a 10 mg ml^{-1} suspension in distilled water with 2 drops of Tween 80. Controls received water/Tween 80 only.

properties such as are shown by the imidazodiazepine RO15—1788 (Hunkeler et al 1981; Nutt et al 1982).

In addition, chronic treatment with T_3 using doses which render the animals hyperthyroid (100 μg kg^{-1} once daily for 10 days) and which have been shown to alter the monoamine transmitter systems in the brain (see Atterwill 1981) had no effects on seizure thresholds to either petetrazol or bicuculline.

These results show firstly that using an in-vivo model of benzodiazepine receptor function we could detect no benzodiazepine agonist or antagonist-like activity after the hormones, despite their relatively high affinity for the receptor in-vitro. Secondly, experimental hyperthyroidism does not seem to alter benzodiazepine/GABA function as revealed by seizure thresholds in mature rats. One cannot necessarily extrapolate these findings to other pharmacological actions of the benzodiazepines e.g. their anxiolytic and myorelaxant properties, although the sedative effects of flurazepam were not obviously altered by any of the treatments. Interestingly, the locomotor effects produced by hyperthyroidism in rats have been shown to be antagonized by benzodiazepines (Rastogi et al 1979).

These data further emphasize the difficulty in predicting in-vivo pharmacological effects from in-vitro binding phenomena and demonstrate that ligands with micromolar affinity for the receptor (Nagy & Lajtha 1983) may be devoid of pharmacological action.

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