Br. J. Pharmac. (1970), **40**, 747–758.

The effect of thyroid hormones on the action of some centrally acting drugs

P. F. COVILLE* AND J. M. TELFORD*

Department of Pharmacology, School of Pharmacy, College of Technology, Brighton, Sussex

Summary

1. The effect of administration of thyroxine or thyroidectomy on the pharmacological action of (+)-amphetamine, caffeine, hexobarbitone and morphine was determined in rats or mice.

2. Locomotor activity induced by (+)-amphetamine or caffeine was increased by hyperthyroidism and decreased by hypothyroidism.

3. The LD50s of (+)-amphetamine and caffeine in hyperthyroid rats were 1/30 and 2/5 that of control rats. With each drug, the LD50 regression lines in hyperthyroid and control rats were not parallel, suggesting that hyperthyroidism modifies the mechanism of the toxic effects. Hypothyroidism reduced toxicity to (+)-amphetamine.

4. Hexobarbitone sleeping time was prolonged in hyperthyroid male rats, but was shortened in hyperthyroid female rats. In control rats, sleeping time was approximately four times as long in females as it was in males. Ethinyloestradiol treatment and castration also prolonged sleeping time in male rats. No further prolongation was produced by combined administration of thyroxine and ethinyloestradiol, but thyroxine further prolonged the sleeping time of castrated rats indicating that its mode of action in producing these changes is not mediated via sex hormones.

5. In contrast to rats, a sex difference in the duration of action of hexobarbitone was not found in mice. Thyroxine prolonged sleeping time equally in each sex.

6. Analgesia induced by morphine in mice was unaffected by hyperthyroidism. No increase in sedative or 'Straub tail' activity could be detected, but toxicity was increased when higher doses of morphine were used.

7. The mechanism by which thyroid hormones produce these changes in sensitivity to centrally acting drugs is discussed. It is suggested that the effects of thyroxine vary according to whether the mode of action of the drug or its metabolism is modified.

Introduction

It has been demonstrated recently that treatment of rats or guinea-pigs with thyroxine modifies the sensitivity of the heart and of various smooth muscles to

* Present address: Biological Research Department, B.D.H. (Research) Ltd., Borough Road, Godalming, Surrey.

drugs (Coville & Telford, 1970). In the heart and uterus, sensitivity to drugs is enhanced, whereas in the intestine and aorta, sensitivity is depressed. Changes in the responses of the cardiovascular system of intact animals are variable. These effects are possibly related to changes in the metabolism of calcium (Coville & Telford, 1970).

The effect of thyroxine on the pharmacological actions of centrally acting drugs has not been studied, but the toxicological effects of several such drugs are known to be potentiated. For example, thyroxine increases the toxicity of monoamine oxidase inhibitors (Carrier & Buday, 1961), imipramine (Prange & Lipton, 1962), amphetamine (Halpern, Drudi-Baracco & Bessirard, 1964) and chlorpromazine (Skobba & Miya, 1969). These changes are likely to be related to peripheral effects of the hormone rather than to a local metabolic effect, since Barker (1964) has shown that thyroxine does not alter metabolic activity in the brain. The purpose of the present work was to study the effect of thyroxine on the action of several chemically unrelated drugs, all of which have a different type of pharmacological action on the central nervous system. It was hoped thereby to establish whether thyroxine non-specifically potentiates the pharmacological effects of all drugs acting on the central nervous system, or whether, as on muscle, its effects are variable.

Some of the experiments have been communicated to the British Pharmacological Society (Coville & Telford, 1969).

Methods

General

Male rats and mice were used except in experiments with hexobarbitone. The rats were Wistar albino and weighed 180–250 g, and the mice were LAC albino and weighed 20–25 g. They were housed at 21° ±0·5° C, and had free access to food (Diet 41B, Dixons) and drinking water.

Rats and mice were injected subcutaneously with (−)-thyroxine sodium dissolved in alkaline saline (0·001N NaOH in 0·9% NaCl) daily for 10 consecutive days (longer in some of the activity experiments). Dosage is indicated in the text. All experiments were performed on the day after the final day of injections. Hypothyroidism was induced by surgical removal of the thyroid in rats only, and thyroidectomized rats were used not less than 14 days from the time of operation. They were maintained for 5 days post-operatively on 1% calcium gluconate in their drinking water to avoid symptoms of tetany due to removal of parathyroid tissue. Evidence of induction of hyperthyroidism or hypothyroidism was obtained before using the animals, by measurement of basal metabolic rate as previously described (Coville & Telford, 1970). Castration of male rats for hexobarbitone experiments was performed by removal of the testes through a single midline incision. These rats were left for 21 days before commencement of thyroxine injections. Mean values and standard errors were calculated and compared by Student's *t* test.

(+)-Amphetamine and caffeine

Locomotor activity was used as a parameter of central stimulation due to (+)-amphetamine or caffeine. Rats were housed in groups of five in cages of dimensions 36 × 23 × 18 cm at 21° C and had free access to food and water. Activity

was measured (arbitrary units) by means of a Faraday-type animal activity recorder (Washington) which has the advantage of being able to screen nearly the whole of the living area for activity. Rats were tested for effects due to pretreatment with thyroxine (1 mg/kg daily) or thyroidectomy, by nightly (16 h) activity measurements. Control groups (saline treated or sham operated rats) were tested concurrently. Each day the test groups were placed in the cages previously occupied by the control groups and vice versa to avoid any errors due to recorder bias.

Groups of five hyperthyroid, control or thyroidectomized rats were injected intraperitoneally with (+)-amphetamine (0·1 mg/kg) and locomotor activity was measured continuously for 3 hours. Similarly, locomotor activity was recorded in groups of five rats following intraperitoneal injection of caffeine (20 mg/kg).

LD50 of (+)-amphetamine and caffeine

Moore (1965) showed that the LD50 of (+)-amphetamine in mice is markedly reduced by hyperthyroidism, and it was therefore necessary to determine its toxicity in rats so that in tests for central activity in this species, non-toxic doses could be employed. The LD50 of both (+)-amphetamine and caffeine was determined using ten (five + five) grouped rats per dose of drug. Percentage mortality at each dose, calculated from the number dead within 24 h, was determined for control and hyperthyroid rats, and the LD50 computed using the method of Litchfield & Wilcoxon (1949). The dose of each drug used in locomotor activity studies corresponded to about 1/10 of the LD50 in hyperthyroid rats.

Hexobarbitone

Rats and mice in groups of five of either sex were used, rats being pretreated with thyroxine 1 or 5 mg/kg daily, and mice with 5 or 10 mg/kg daily. They were then injected intraperitoneally with hexobarbitone 50 or 100 mg/kg, and the duration of action of the latter was measured as the time between loss and complete recovery of righting reflexes. Sleeping time was also measured in thyroidectomized male and female rats. During the period of narcosis, the animals were kept warm to avoid hypothermia. Further groups of male rats were also dosed orally with ethinyloestradiol (10 mg/kg daily for 10 days) alone and concurrently with thyroxine (1 mg/kg daily), or were castrated and then injected with thyroxine (1 mg/kg daily). The latter were compared with sham operated animals. The action of hexobarbitone (20, 40 and 60 mg/kg) was also examined in thyroxine treated (1 mg/kg daily) and control female rats in order to determine whether the intensity of the drug's action could be affected independently of its duration.

Morphine

Duration of analgesia was measured using the hot plate technique of Woolfe & MacDonald (1944). The hot plate was thermostatically maintained at 55° C and all mice were tested for a positive response prior to the administration of morphine, namely lifting or licking of hind paws within 30 s of being placed on the hot plate. Male mice were pretreated with thyroxine (5 or 10 mg/kg daily) and were injected intraperitoneally with either 7·5 or 15·0 mg/kg morphine. Each mouse was then tested at 10 min intervals from the injection of morphine. Mean duration of analgesia in groups of ten mice was determined, and results compared for control and thyroxine treated mice.

Drugs

(+)-Amphetamine sulphate (Smith, Kline & French); caffeine citrate, ethinyloestradiol, morphine sulphate, l-thyroxine sodium (B.D.H.); hexobarbitone sodium (May & Baker); methimazole (Lilly).

Results

Thyroid hormones and spontaneous locomotor activity

It was found that hyperthyroidism induced by thyroxine 1 mg/kg daily did not modify spontaneous locomotor activity of rats (Fig. 1). However, thyroidectomy reduced spontaneous activity to about half the control (sham operated) level (Fig. 1).

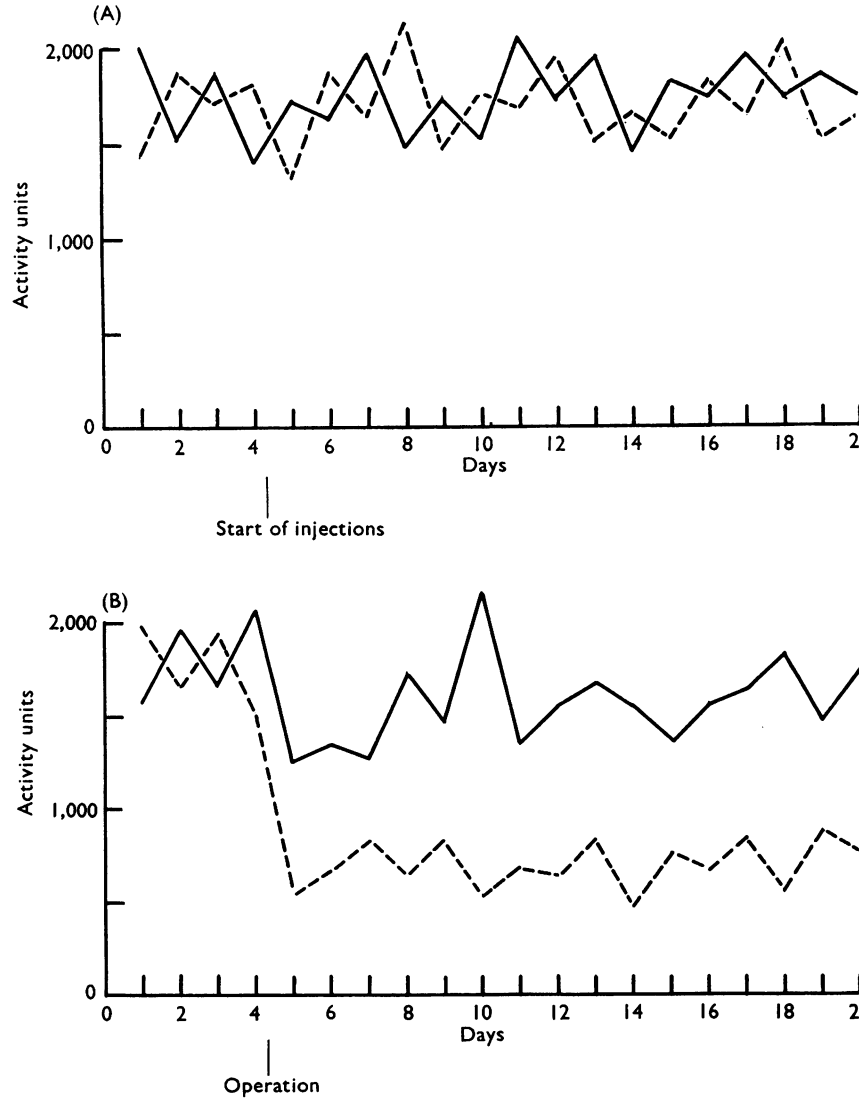

FIG. 1. Spontaneous locomotor activity of groups of five rats. Each point is the group total activity measured over a period of 16 h nightly. A, Spontaneous locomotor activity of thyroxine treated (- - - -) and control (——) rats. The dose of thyroxine was 1 mg/kg subcutaneously each day, control rats receiving saline (1 ml/kg daily). B, Spontaneous locomotor activity of thyroidectomized (- - - -) and sham operated (——) rats.

(+)-Amphetamine

The effect of a low dose of (+)-amphetamine on locomotor activity was markedly potentiated by thyroxine. This is shown in Fig. 2. The potentiation of locomotor activity was particularly marked during the first 30 min following the dose of (+)-amphetamine, locomotor activity being approximately doubled at this time. Unlike intensity of effect, the duration of the (+)-amphetamine induced locomotor activity was not increased by hyperthyroidism. Conversely, the degree of locomotor activity induced by (+)-amphetamine was not as marked in thyroidectomized rats as in

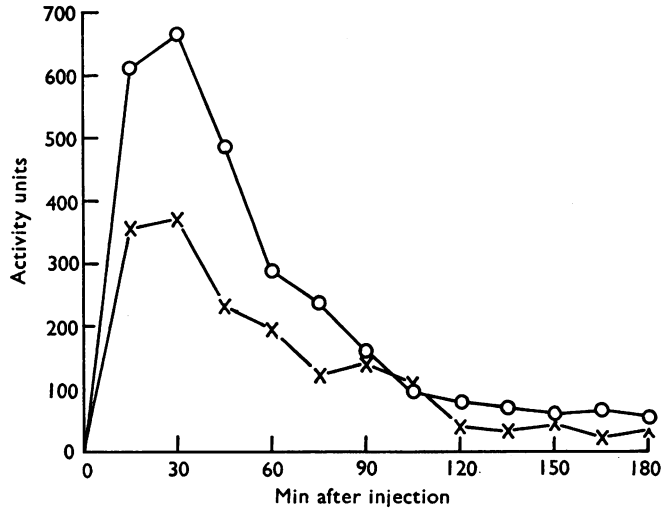

FIG. 2. Locomotor activity in grouped thyroxine treated (○——○) and saline treated (×——×) rats induced by a single intraperitoneal injection of 0·1 mg/kg (+)-amphetamine given at time 0 minutes. Each point on the graph is the mean of three determinations and is the activity count for the preceding 15 minutes.

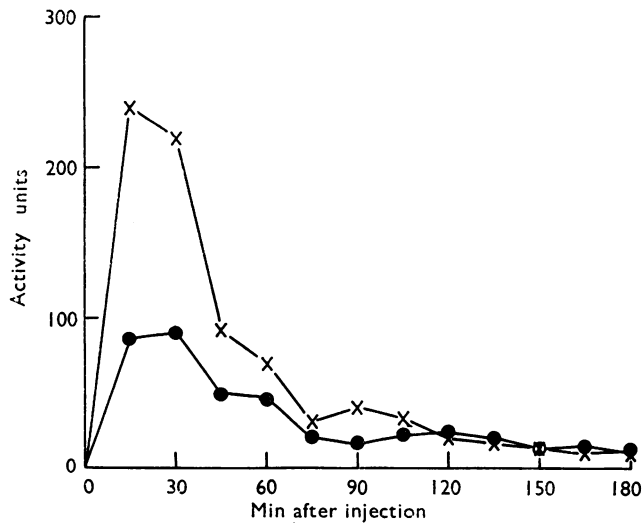

FIG. 3. Locomotor activity in grouped thyroidectomized (●——●) and sham operated (×——×) rats induced by a single intraperitoneal injection of 0·1 mg/kg (+)-amphetamine given at time 0 minutes. Each point on the graph is the mean of two determinations and is the activity count for the preceding 15 minutes.

sham operated controls. As shown in Fig. 3, the locomotor activity in thyroidectomized rats 15–30 min after a single dose of (+)-amphetamine (0·1 mg/kg) was less than half that induced by the same dose of (+)-amphetamine in control rats. Methimazole (40 mg/kg subcutaneously each day for 14 days), although having no intrinsic effect on locomotor activity, reduced the effect of (+)-amphetamine to a similar extent as that seen with thyroidectomized animals ; that is, locomotor activity was approximately half that of control rats 30 min after injection of (+)-amphetamine.

The LD50 of (+)-amphetamine in hyperthyroid rats was 0·98 mg/kg (95% fiducial limits 0·53–1·80 mg/kg) while that for control rats was 28·5 mg/kg (95% fiducial limits 26·0–31·2 mg/kg). While this represents an increase in potency of some 30-fold, an exact potency ratio could not be calculated since the slopes of the LD50 regression lines differed significantly from parallelism ($P>0·05$). This is shown in Fig. 4. Instead, the LD50 values were used to obtain an approximate

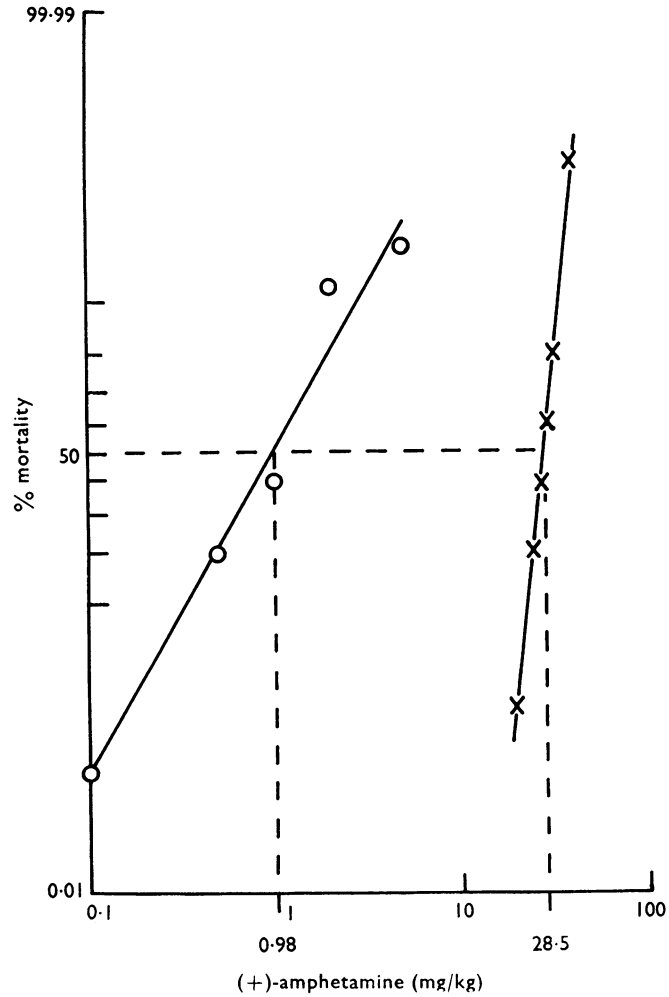

FIG. 4. LD50 of (+)-amphetamine in grouped rats. The dose/mortality regression line for thyroxine treated rats is on the left (○——○), and that for saline treated rats on the right (×——×). Each point represents the mean response for ten (five+five) rats. The LD50 for (+)-amphetamine in each case is indicated by the vertical broken lines.

potency ratio. Although an LD50 for (+)-amphetamine was not determined in thyroidectomized or methimazole treated rats, two experiments using a dose of 50 mg/kg (+)-amphetamine intraperitoneally, which is lethal in grouped control rats, produced only 60% (six out of ten) mortality in grouped hypothyroid rats. Symptoms of toxicity in all rats included excessive wetness of face, underneck and belly, defensive postures, polydipsia and tonic followed by clonic convulsions.

Caffeine

The stimulating effect of low doses of caffeine was potentiated by hyperthyroidism as shown by increase in caffeine induced locomotor activity in thyroxine treated rats. As shown in Fig. 5, the effect of a single dose of caffeine (20 mg/kg) was approximately doubled by thyroxine. As with (+)-amphetamine, thyroxine did not increase the duration of action of the drug.

The LD50 of caffeine was also markedly reduced by hyperthyroidism although there was a difference of only 2·5-fold in potency ratio. The LD50 values for hyperthyroid and control grouped rats respectively were 240 mg/kg (95% fiducial limits 171·4–336·0 mg/kg) and 645 mg/kg (95% fiducial limits 379·0–1,096·0 mg/kg). The slopes of the LD50 regression lines also differed significantly from parallelism ($P>0·05$) as shown in Fig. 6. Symptoms of toxicity were similar to those seen after (+)-amphetamine except for absence of defensive positioning.

Hexobarbitone

Rats

The results presented in Table 1 show that hexobarbitone had a more prolonged action in females than in males; in fact, a 4-fold difference was apparent.

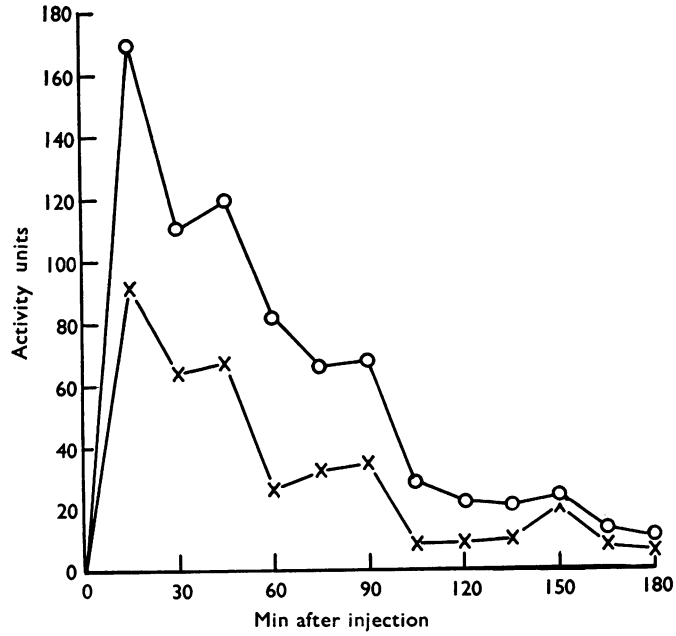

FIG. 5. Locomotor activity in grouped thyroxine treated (○——○) and saline treated (×——×) rats induced by a single intraperitoneal injection of 20 mg/kg caffeine given at time 0 minutes. Each point on the graph is the mean of three determinations and is the activity count for the preceding 15 minutes.

Thyroxine pretreatment prolonged sleeping time in males, but shortened it in females, although thyroidectomy prolonged sleeping time in each sex. Ethinyloestradiol also lengthened sleeping time in male rats, but combined ethinyloestradiol—thyroxine (10+1 mg/kg) treatment produced no further prolongation of sleeping time.

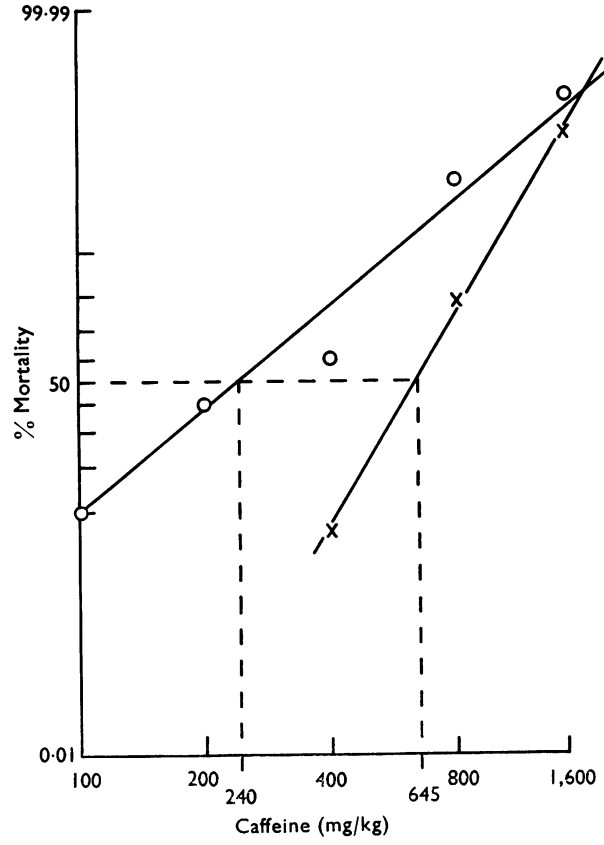

FIG. 6. LD50 of caffeine in grouped rats. The dose/mortality regression line for thyroxine treated rats is on the left (○——○), and that for saline treated rats on the right (×——×). Each point represents the mean response for ten (five+five) rats. The LD50 for caffeine in each case is indicated by the vertical broken lines.

TABLE 1. *Sleeping times in male and female rats induced by* 100 *mg/kg hexobarbitone*

Sex	Pretreatment	Dose (mg/kg)	Sleeping time (min±S.E.)	*P*	% Change
Male	Saline	–	20·5±2·6	—	100
Male	Thyroxine	1	29·8±2·9	<0·05	145·4
Male	Thyroxine	5	63·8±3·1	<0·001	311·2
Male	Ethinyloestradiol	10	74·8±4·5	<0·001	364·9
Male	Ethinyloestradiol, thyroxine	10, 1	62·6±3·7	<0·001	305·4
Male	Castration, saline	–	52·1±2·4	<0·001	254·1
Male	Castration, Thyroxine	1	94·2±4·1	<0·001	459·5
Male	Thyroidectomy	–	37·1±4·9	<0·02	181·0
Female	Saline	–	82·2±3·9	—	100
Female	Thyroxine	1	65·6±4·7	<0·05	79·8
Female	Thyroxine	5	53·4±4·4	<0·01	65·0
Female	Thyroidectomy	–	110·2±5·7	<0·01	134·1

Each result is the mean±S.E. for five rats.

Castration of male rats, like treatment with ethinyloestradiol, prolonged the effect of hexobarbitone but, in contrast, the effect of castration was potentiated by thyroxine (Table 1).

In female rats thyroxine reduced the duration of sleeping time induced by hexobarbitone, but did not modify the potency of the drug. Thus, as shown in Table 2, thyroxine had no marked effect on the number of rats sleeping following injection of smaller doses of hexobarbitone, but nevertheless decreased the duration of sleeping time in those rats in which sleep was induced.

Mice

A comparable sex difference in the response to hexobarbitone was not seen in mice (Table 3). The ratio between control male and female sleeping times was only 1 : 1·2. A similar increase in duration of sleeping time in each sex was produced by thyroxine pretreatment, unlike the differing effect in the sexes seen in rats. It was also found that in control male mice, hexobarbitone (50 mg/kg) caused sedation from which the animals could be easily aroused. However, when this dose was administered to mice pretreated with thyroxine (5 mg/kg) narcosis was produced, as shown in Table 3.

In both rats and mice, therefore, thyroxine modified the duration of action of hexobarbitone, which contrasts with its failure in rats to modify the duration of action of (+)-amphetamine and caffeine. A further contrast is that while the potency of these latter drugs in male rats was markedly increased, the potency of hexobarbitone, at least in female rats, was not. In mice, however, thyroxine increased both the potency and duration of action of hexobarbitone very considerably ($P<0·001$).

TABLE 2. *Effect of different doses of hexobarbitone on narcosis in hyperthyroid and control female rats*

Hexobarbitone (mg/kg)	Pretreatment	Number of rats sleeping (out of five)	Duration of sleeping time (min±S.E.)
20	Saline	0	0·0
	Thyroxine	0	0·0
40	Saline	2	9·5±4·5
	Thyroxine	2	18·8±2·3
60	Saline	2	38·6±4·4
	Thyroxine	5	29·0±2·7
100	Saline	5	82·2±3·9
	Thyroxine	5	65·6±4·7

TABLE 3. *Effect of thyroxine on hexobarbitone sleeping time in male and female mice*

Sex	Pretreatment	Dose (mg/kg)	Hexobarbitone (mg/kg)	Sleeping Time (min±S.E.)	*P*	% Change
Male	Saline	–	100	55·0±3·0	—	100
Male	Thyroxine	5	100	115·0±5·3	<0·001	209·1
Male	Thyroxine	10	100	158·9±7·2	<0·001	289·0
Male	Saline	–	50	0	—	—
Male	Thyroxine	5	50	35·2±5·4	<0·001	—
Female	Saline	–	100	67·2±2·6	—	100
Female	Thyroxine	5	100	142·6±7·0	<0·001	212·2
Female	Thyroxine	10	100	208·4±6·1	<0·001	310·1

Each result is the mean±S.E. for five mice.

Morphine

Thyroxine did not modify the analgesic potency of morphine. This is shown in Table 4. Also, thyroxine did not increase the incidence of sedation or 'Straub tail' induced by morphine. Morphine, therefore, differs from the other centrally acting drugs studied in these experiments in that its effects are not enhanced by thyroxine. In two experiments, morphine (20 mg/kg and 40 mg/kg) was given intraperitoneally to thyroxine treated and control mice. These doses produced, respectively, 20% (two out of ten) and 60% (six out of ten) mortality in the animals treated with thyroxine (10 mg/kg daily). Thus, the toxic effect of morphine was enhanced, even though no increase in pharmacological effect could be detected.

Discussion

These experiments indicate that thyroxine affects the responses to three different types of centrally acting drugs in three different ways. It increases the intensity of action of (+)-amphetamine and caffeine but does not prolong the duration of their effects; in contrast, thyroxine does not always increase the intensity of action of hexobarbitone, but, with the exception of female rats, increases its duration of action very markedly. In contrast again, neither the intensity nor the length of analgesia induced by morphine is altered. These results suggest that thyroxine has more than one action and since the hormone does not modify spontaneous locomotor activity or affect brain metabolism (Barker, 1964) these are likely to be peripheral.

Thyroxine markedly potentiates the central stimulant effect of (+)-amphetamine, and (+)-amphetamine is known to act by release of endogenous noradrenaline (Burn & Rand, 1958). The effect of exogenous noradrenaline on cardiac and smooth muscle is potentiated by thyroxine (Coville & Telford, 1970). The toxicological effect of (+)-amphetamine is thought to be due partly to the release of peripheral noradrenaline (Moore, 1963, 1965), and the importance of peripheral noradrenaline release is probably greater in hyperthyroidism because the slopes of the LD50 regression lines of (+)-amphetamine in hyperthyroid and control rats differ significantly from parallelism, and the pressor response to (+)-amphetamine in hyperthyroid rats is known to be greatly potentiated (Coville & Telford, 1970). In contrast, the pressor response to exogenous noradrenaline in hyperthyroid rats is not potentiated, suggesting that thyroxine facilitates the peripheral release of noradrenaline by (+)-amphetamine. However, these various considerations do not rule out the possibility that the sensitizing action of thyroxine on the stimulant effect of (+)-amphetamine is mediated by increased sensitivity to noradrenaline released locally

TABLE 4. *Effect of thyroxine on duration of morphine analgesia in mice*

Thyroxine pretreatment (mg/kg)	Morphine (mg/kg)	Duration of analgesia (min ± S.E.)
–	7·5	16·2 ± 4·4
5	7·5	18·0 ± 5·2
10	7·5	17·2 ± 3·8
–	15·0	34·6 ± 7·1
5	15·0	29·4 ± 7·5
10	15·0	31·8 ± 8·1

Each result is the mean ± S.E. for ten mice.

in the brain, or that it is due specifically to increased release of brain noradrenaline. Certainly, the release of brain noradrenaline is known to be facilitated by thyroxine (Moore, 1965 ; Dolfini, Ramirez del Angel, Garratini & Valzelli, 1970).

The effects of thyroxine on the sensitivities of rats to the central stimulant properties of (+)-amphetamine and caffeine are qualitatively and quantitatively similar, but the effect on toxicity to caffeine is less marked than on toxicity to (+)-amphetamine. This supports the conclusion that a peripheral component involving a massive release of noradrenaline plays a significant role in toxicity to the latter drug. The mode of action of thyroxine in increasing the central nervous system stimulant properties of these two drugs is not clear, but a common link between them is that both may increase tissue levels of cyclic adenosine 3′,5′-monophosphate (cyclic AMP). Caffeine inhibits phosphodiesterase and so inhibits destruction of this nucleotide (Butcher & Sutherland, 1962). (+)-Amphetamine releases noradrenaline, which activates adenyl cyclase (Murad, Chi, Rall & Sutherland, 1962) and so increases formation of cyclic AMP. Thyroid hormones have themselves been shown to increase tissue levels of cyclic AMP by inducing adenyl cyclase (Brodie, Davies, Hynie, Krishna & Weiss, 1966) and by inhibiting phosphodiesterase (Mandel & Kuehl, 1967). It is possible, therefore, that thyroxine potentiates the stimulant effects of (+)-amphetamine and caffeine indirectly by causing accumulation of cyclic AMP. Bartelstone, Nasmyth & Telford (1967) using smooth muscle have provided evidence that drugs which increase the tissue levels of cyclic AMP also increase responses to sympathomimetic amines, and that the reverse is also true. The implication of the present experiments is that tissue levels of cyclic AMP may likewise be related to the action of central stimulants.

Thyroxine is known to modify the activity of several hepatic drug-metabolizing enzymes and changes in sensitivity or toxicity to centrally acting drugs and in the duration of their effects may also be related to this property. For example, increased toxicity to morphine may be due to the known ability of thyroxine to reduce N-demethylation in the liver (Cochin & Sokoloff, 1960).

Conney & Garren (1961) have shown that thyroxine prolongs hexobarbitone induced sleeping time in male rats. The present results confirm their findings, but show that thyroxine has the opposite effect in female rats. These unusual results may be explicable in terms of a sex difference in the effect of thyroxine on the activity of the hexobarbitone-metabolizing enzyme in the liver, because Kato, Takanaka, Takahashi & Onoda (1969) have reported recently that thyroxine reduces hexobarbitone hydroxylase activity in male rats, but enhances it in female rats. It is likely, however, that these effects of thyroxine on sleeping time are mediated independently of the sex hormones themselves since the longer sleeping time of female rats is reduced by thyroxine, and in male rats, thyroxine and ethinyloestradiol administered either alone or together increase sleeping time. Furthermore, thyroxine is still able to potentiate sleeping time in castrated animals.

The results show that in mice, thyroxine prolongs hexobarbitone induced sleeping time in males and females alike, and it is known that the hormone also reduces hepatic hexobarbitone hydroxylase activity in each sex in this species (Kato *et al.*, 1969). In male mice, thyroxine also increases the intensity of action of hexobarbitone, a lower dose of hexobarbitone producing narcosis in thyroxine treated mice which in control mice produces only sedation. However, the results also show that duration of action and intensity of action do not always parallel each other.

Thus, in female rats treated with thyroxine the duration of sleeping time is reduced, but the number of rats which are induced to sleep is not.

It is concluded from these studies that thyroxine does not non-specifically potentiate all centrally acting drugs, but that its effects are variable. It is proposed that the nature of the effects depends on whether a process involved in the mode of action of the drug is modified, or whether the hormone affects the metabolism of the drug, or both.

We are grateful to Smith, Kline & French for their gift of (+)-amphetamine, and to Lilly for their gift of methimazole.

REFERENCES

BARKER, S. B. (1964). Physiological activity of thyroid hormones and analogues. In *The Thyroid Gland*, ed. Pitt-Rivers, R. & Trotter, W. R., vol. **1**, pp. 199–236. London:Butterworth & Co. Ltd.

BARTELSTONE, H. J., NASMYTH, P. A. & TELFORD, J. M. (1967). The significance of adenosine cyclic 3′,5′-monophosphate for the contraction of smooth muscle. *J. Physiol., Lond.*, **188**, 159–176.

BRODIE, B. B., DAVIES, J. I., HYNIE, S., KRISHNA, G. & WEISS, B. (1966). Interrelationship of catecholamines with other endocrine systems. *Pharmac. Rev.*, **18**, 273–289.

BURN, J. H. & RAND, M. J. (1958). The action of sympathomimetic amines in animals treated with reserpine. *J. Physiol., Lond.*, **144**, 314–336.

BUTCHER, R. W. & SUTHERLAND, E. W. (1962). Adenosine 3′,5′-phosphate in biological materials. I. Purification and properties of cyclic 3′,5′-nucleotide phosphodiesterase and use of this enzyme to characterize adenosine 3′,5′-phosphate in human urine. *J. biol. Chem.*, **237**, 1244–1250.

CARRIER, R. N. & BUDAY, P. V. (1961). Augmentation of toxicity of monoamine oxidase inhibitor by thyroid feeding. *Nature, Lond.*, **191**, 1107.

COCHIN, J. & SOKOLOFF, L. (1960). Effects of administration of l-thyroxin on liver N-demethylating activity in normal and morphine-treated rats. *Proc. Soc. exp. Biol. Med.*, **104**, 504–506.

CONNEY, A. H. & GARREN, L. (1961). Contrasting effects of thyroxine on zoxazolamine and hexobarbital metabolism. *Biochem. Pharmac.*, **6**, 257–262.

COVILLE, P. F. & TELFORD, J. M. (1969). Changes in drug sensitivity in hyperthyroidism. *Br. J. Pharmac.*, **36**, 189*P*.

COVILLE, P. F. & TELFORD, J. M. (1970). Influence of thyroid hormones on the sensitivity of cardiac and smooth muscle to biogenic amines and other drugs. *Br. J. Pharmac.*, **39**, 49–68.

DOLFINI, E.. RAMIREZ DEL ANGEL, A., GARRATINI, S. & VALZELLI, L. (1970). Brain catecholamine release by dexamphetamine in three strains of mice. *Eur. J. Pharmac.*, **9**, 333–336.

HALPERN, B. N., DRUDI-BARACCO, C. & BESSIRARD, D. (1964). Exaltation of toxicity of sympathomimetic amines by thyroxine. *Nature, Lond.*, **204**, 387–388.

KATO, R., TAKANAKA, A., TAKAHASHI, A. & ONODA, K. (1969). Species differences in the alteration of drug-metabolising activities of liver microsomes by thyroxine treatment. *Jap. J. Pharmac.*, **19**, 5–18.

LITCHFIELD, J. T. JR. & WILCOXON, F. (1949). A simplified method of evaluating dose-effect experiments. *J. Pharmac. exp. Ther.*, **96**, 99–113.

MANDEL, L. R. & KUEHL, F. A. JR. (1967). Lipolytic action of l-triodothyronine—a cyclic 3′,5′-AMP phosphodiesterase inhibitor. *Fedn Proc.*, **26**, 810.

MOORE, K. E. (1963). Toxicity and catecholamine releasing actions of d- and l-amphetamine in isolated and aggregated mice. *J. Pharmac. exp. Ther.*, **142**, 6–12.

MOORE, K. E. (1965). Amphetamine toxicity in hyperthyroid mice: effects on endogenous catecholamines. *Biochem. Pharmac.*, **14**, 1831–1837.

MURAD, F., CHI, Y. M., RALL, T. W. & SUTHERLAND, E. W. (1962). Adenyl cyclase. III. The effect of catecholamines and choline esters on the formation of adenosine 3′,5′-phosphate by preparations from cardiac muscle and liver. *J. biol. Chem.*, **237**, 1233–1238.

PRANGE, A. J. JR. & LIPTON, M. A. (1962). Enhancement of imipramine mortality in hyperthyroid mice. *Nature, Lond.*, **196**, 588–589.

SKOBBA, T. & MIYA, T. S. (1969). Hyperthermic responses and toxicity of chlorpromazine in l-thyroxine sodium treated rats. *Toxic. appl. Pharmac.*, **14**, 176–181.

WOOLFE, G. & MACDONALD, A. D. (1944). The evaluation of the analgesic action of pethidine hydrochloride (Demerol). *J. Pharmac. exp. Ther.*, **80**, 300–307.

(*Received May* 26, 1970)