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Potentiation by TRH of the effect of imipramine on the forced-swimming test

Véronique Reny-Palasse & Richard Rips

Unité de Pharmacologie Chimique de l'INSERM, 17 rue du Fer à Moulin, 75005 Paris, France

1 Discovery of the potentiation of thyrotropin releasing hormone (TRH)-induced hyperthermia in mice by antidepressants which activate α-adrenergic systems instigated investigation of other relations between TRH and antidepressants.

2 For this study the forced-swimming test using mice was chosen since this test is more sensitive for selection of antidepressants which modify catecholaminergic systems than for those affecting 5-hydroxytryptaminergic systems.

3 The effects of imipramine were potentiated by TRH. The involvement of α-adrenergic systems was then investigated in this effect since it is already known that these systems are directly implicated in the potentiation of TRH-induced hyperthermia by some antidepressants. Then the involvement of opiate systems was investigated since endogenous opiates are implicated in the action of some antidepressants, and some interactions between TRH and opiate systems are known to exist.

4 TRH made effective a completely inactive dose of imipramine as small as 2 mg kg^{-1} (i.p.) or 1 μg per mouse (i.c.v.). Pretreatment by both α_1- and α_2-adrenoceptor antagonists (phenoxybenzamine, 8 mg kg^{-1} i.p.; phentolamine, 4 mg kg^{-1} i.p.) or by a α_1-adrenoceptor antagonist (prazosin, 2 mg kg^{-1} i.p.) did not prevent this potentiation. In contrast the α_2-adrenoceptor antagonist (Yohimbine, 2 mg kg^{-1} i.p.) blocked the TRH effect. The imipramine potentiation by TRH was blocked by pretreatment with an opiate antagonist (naloxone, 1 mg kg^{-1} i.p.) and the potentiation was decreased in morphine-tolerant mice.

5 These data indicate that potentiation of the effects of imipramine on the forced-swimming test does not seem to be associated with an increase of effective levels of noradrenaline in the synaptic clefts and suggest an interaction between TRH and the opiate systems.

Introduction

There is increasing evidence that thyrotropin releasing hormone (TRH) besides having neuroendocrinological actions, such as stimulation of thyrotropin and prolactin secretion is also a centrally acting neuropeptide.

Discovery of the potentiation of TRH-induced hyperthermia by some antidepressants in mice (Desiles *et al.*, 1980; Desiles & Rips, 1981) instigated investigation of other relations between TRH and antidepressants. The potentiation of TRH-induced hyperthermia is observed only with antidepressants which activate α-adrenergic systems. To investigate a possible potentiation of one antidepressant (in this case imipramine) by TRH, we have chosen the forced-swimming test using mice since this test is more sensitive for antidepressants which modify catecholaminergic systems than for those affecting 5-hydroxytryptaminergic systems (Porsolt *et al.*, 1979; Borsini *et al.*, 1981).

Such a potentiation was found to exist between imipramine and TRH and the possible involvement of α-adrenergic systems was investigated.

In addition, the involvement of opiate systems was investigated since endogenous opioids are implicated in the action of certain antidepressants: for example the opiate antagonist (naloxone) or pretreatment with morphine, both reduce the effect of clomipramine in the mouse forced-swimming test (Devoize *et al.*, 1982; Eschalier *et al.*, 1983) and since study of the antinociceptive effect of TRH has suggested an interaction between TRH and the opiate systems (Rips *et al.*, 1983).

Methods

Animals

Male OF1 mice (Iffa-Credo, France) weighing 25–30 g on the day of the experiment were used. All animals were kept at an ambient temperature of 22 ± 1°C and a day/night cycle (12–12 h) was maintained by means of electric lighting. Experiments were carried out between 09 h 00 min and 13 h 00 min. There were 10 animals in each experimental group (except for some experimental groups which received central injections). Some experiments were repeated several times. Each animal was used only once.

Injections

The peripheral injections were given intraperitoneally (i.p.) in a volume of 0.1 ml 10 g^{-1} body wt. The control animals received the vehicle alone.

For the central injections, a cannula was implanted into the right lateral ventricle of mice at least five days before the experiment according to the method of Boschi *et al.* (1981). The drugs were injected in a volume of 0.5 µl over a period of 50 s. The control animals received 0.5 µl of saline. After the experiments had been completed, the following verification of the implantations was performed for all the treated and control animals. A solution of 0.5% methylene blue was injected via the cannula in a volume of 0.5 µl over a period of 50 s. The animals were then killed and the brains removed, sectioned frontally at the level of the cannula, and examined microscopically for the presence of dye in the ventricle. All animals without dye in the ventricle were removed.

Forced-swimming test

The procedure used was that described by Porsolt *et al.* (1977). Naive mice were forced to swim for 6 min inside a vertical plexiglass cylinder from which they could not escape (height = 25 cm, diameter = 10 cm) containing water 6 cm deep at 22 ± 1°C. The total duration of immobility during the last 4 min was recorded. A mouse was judged to be immobile whenever it remained floating in the water, in an upright position making only very small movements necessary to keep its head above water.

TRH-potentiation of the imipramine effect on the forced-swimming test

Investigation of the association between an ineffective dose of imipramine and the lowest possible dose of TRH required to induce a significant decrease in the duration of immobility of mice was carried out by use of the forced-swimming test. A completely ineffective dose of imipramine (2 mg kg^{-1} i.p.) was administered 54 min before the test. The doses of TRH 40, 20, 2, 1 and 0.5 mg kg^{-1} i.p. were administered 6 min before the test, but for TRH 10, 1 and 0.1 µg per mouse i.c.v. the doses were administered just before the start of the test. In another experiment, 2 mg kg^{-1} i.p. of TRH (the lowest dose increasing the effect of 2 mg kg^{-1} i.p. of imipramine) was administered with increasing doses of imipramine (4, 8, 16 and 32 mg kg^{-1} i.p.).

Study of α-adrenergic system involvement

To find out whether the effect induced by imipramine (2 mg kg^{-1} i.p.) + TRH (2 mg kg^{-1} i.p) on the forced-swimming test is modulated by the α-adrenergic systems, we used several different α-antagonists: phentolamine, phenoxybenzamine, prazosin and yohimbine. These drugs were given 54 min before the test in doses of 4, 8, 2 and 2 mg kg^{-1} i.p. respectively. The groups treated by α-adrenoceptor antagonists were compared to the controls. The groups treated by imipramine (2 mg kg^{-1} i.p.) + TRH (2 mg kg^{-1} i.p.) + α-antagonists were compared to both the relevant controls and the group treated with imipramine (2 mg kg^{-1} i.p.) + TRH (2 mg kg^{-1} i.p.) + vehicle.

Study of opiate systems involvement

The possible implication of opiate systems in the effect of imipramine (2 mg kg^{-1} i.p.) + TRH (2 mg kg^{-1} i.p.) on the forced-swimming test was at first investigated by use of naloxone, an opiate antagonist, at a dose of 1 mg kg^{-1} i.p., given 18 min before the test. The group treated with naloxone was compared to the controls. The group treated with imipramine (2 mg kg^{-1} i.p.) + TRH (2 mg kg^{-1} i.p.) + naloxone (1 mg kg^{-1} i.p.) was compared to the relevant controls and also to the group treated by imipramine (2 mg kg^{-1} i.p.) + TRH (2 mg kg^{-1} i.p.) + vehicle. We also investigated the effect of naloxone pretreatment (1 mg kg^{-1} i.p.) on the response produced by an effective dose of imipramine (20 mg kg^{-1} i.p.).

Given the lack of specificity of naloxone as a narcotic antagonist (Sawynock *et al.*, 1979) the effect of morphine pretreatment on the effect induced by the administration of imipramine (2 mg kg^{-1} i.p.) + TRH (2 mg kg^{-1} i.p.) on the forced-swimming test was then studied. The mice were rendered tolerant to morphine by administration of morphine 10 mg kg^{-1} (s.c.) three times a day (08 h 00 min; 14 h 00 min; 20 h 00 min) for two days. The forced-swimming test was performed on day 3. The development of tolerance to an acute dose of morphine 1 mg kg^{-1} (s.c.) was assessed by the phenyl-benzoquinone writhing test in mice. This procedure to develop morphine tolerance is the same as that described by Chescher & Chan (1977).

Drugs

TRH (Bachem, Budendorf, Switzerland) was dissolved in distilled water or saline for peripheral and central administrations respectively. Phenoxybenzamine (SKF), phentolamine methane sulphonate (Ciba-Geigy), yohimbine (Sigma), naloxone hydrochloride (Dupont) and morphine sulphate (Francopia) were dissolved in distilled water. Prazosin was dissolved in 2% w/v Tween 80 in water. Imipramine hydrochloride (Geigy) was taken from commercially available ampoules and diluted with distilled water.

Statistical analysis

The results were expressed as the mean ± s.e. mean or as a percentage relative to the respective controls. The significance of the results was calculated using the Mann-Whitney U test or the Kruskal-Wallis test.

A 50% decrease in the duration of immobility of treated animals compared with control animals represents a sign of selection for an antidepressant activity. The effective doses for 50% of the animals (ED_{50}) were calculated according to the method of Litchfield & Wilcoxon (1949) and the 95% confidence limits found.

Results

TRH-potentiation of the imipramine effect on the forced swimming test

TRH made effective a dose of imipramine (2 mg kg^{-1} i.p.) which was completely ineffective on its own. This

Table 1 Thyrotropin releasing hormone (TRH)-potentiation of the imipramine effect on the forced-swimming test: evidence of a central effect

Drugs	*Doses*	*No. of mice per experiment*	*Duration of immobility* (s) mean ± (s.e.mean)	*% change from controls*
Vehicle	—	20	152 ± 12	
Imipramine	2 mg kg^{-1} i.p.	20	152 ± 13	0
Vehicle	—	10	156 ± 25	
TRH	40 mg kg^{-1} i.p.	10	159 ± 18	↑ 2
Vehicle	—	10	170 ± 17	
TRH	20 mg kg^{-1} i.p.	10	131 ± 22	↓23
Vehicle	—	20	128 ± 13	
TRH	2 mg kg^{-1} i.p.	20	114 ± 12	↓11
Vehicle	—	10	170 ± 17	↓ 7
TRH	1 mg kg^{-1} i.p.	10	147 ± 20	↓14
TRH	0.5 mg kg^{-1} i.p.	10	158 ± 22	
Vehicle	—	10	158 ± 16	
Imip + TRH	(2 + 40) mg kg^{-1} i.p.	10	45 ± 15	↓72**
Vehicle	—	10	147 ± 23	
Imip ± TRH	(2 + 20) mg kg^{-1} i.p.	10	30 ± 14	↓80**
Vehicle	—	30	138 ± 10	
Imip + TRH	(2 ± 2) mg kg^{-1} i.p.	30	88 ± 11	↓37**
Vehicle	—	10	164 ± 10	
Imip + TRH	(2 + 1) mg kg^{-1} i.p.	10	152 ± 15	↓ 7
Imip + TRH	(2 + 0.5) mg kg^{-1} i.p.	10	144 ± 12	↓12
Vehicle	—	10	158 ± 15	
TRH	1 μg/mouse i.c.v.	10	134 ± 12	↓15
Vehicle	—	10	135 ± 29	
TRH	0.1 μg/mouse i.c.v.	9	158 ± 15	↑17
TRH	10 μg/mouse i.c.v.	7	161 ± 13	↑19
Vehicle	—	10	160 ± 10	
Imip + TRH	2 mg/kg i.p. + 1 μg/mouse i.c.v.	10	44 ± 14	↓73**
Vehicle	—	20	134 ± 13	
Imip ± TRH	2 mg/kg i.p. + 0.1 μg/mouse i.c.v.	9	139 ± 17	↑ 4
Imip + TRH	2 mg/kg i.p. + 10 μg/mouse i.c.v.	7	28 ± 10	↓79**

Imipramine (Imip) was administered 54 min before the test; TRH was administered 6 min or just before the start of the test after i.p. or i.c.v. injection, respectively. The duration of immobility was recorded during a 4 min period. $^{**}P > 0.01$; $^{*}P > 0.05$, compared with the relevant controls, Mann-Whitney U test or Kruskal-Wallis test.

result was observed with a dose of TRH as small as 2 mg kg^{-1} (i.p.). This effect has a central origin since the same effect was observed when a dose of TRH as small as 1 μg per mouse was administered intracerebroventricularly. The potentiation is even greater with larger doses of TRH (20 and 40 mg kg^{-1} i.p. or 10 μg per mouse) (Table 1).

The effect of larger doses of imipramine was also increased by TRH (2 mg kg^{-1} i.p.) except for the largest doses of imipramine used (16 and 32 mg kg^{-1} i.p.) which induced a strong effect on their own (Table 2). The ED_{50} of imipramine was 20 (16.72–23.92) mg kg^{-1} i.p. after a single injection 54 min before the test. This ED_{50} was decreased considerably when a dose of 2 mg kg^{-1} i.p. of TRH was administered 6 min before the test: ED_{50} imipramine/TRH = 2 (1.04–3.84) mg kg^{-1} i.p.

At the doses used, TRH alone i.p. or i.c.v. was not active in mice using the forced-swimming test (Table 1).

Study of α-adrenergic system involvement (Table 3)

The effect induced by imipramine (2 mg kg^{-1} i.p.) + TRH (2 mg kg^{-1} i.p.) on the forced-swimming test was not modified either by pretreatment with phenoxybenzamine (8 mg kg^{-1} i.p.) or phentolamine (4 mg kg^{-1} i.p.) which are both α_1 and α_2-adrenoceptor antagonists or by pretreatment with prazosin (2 mg kg^{-1} i.p.) which acts preferentially on α_1-receptors (Starke, 1977). In contrast, pretreatment with yohimbine (2 mg kg^{-1} i.p.) which acts preferentially on α_2-receptors (Starke *et al.*, 1975; Drew, 1976), prevented TRH-potentiation of the imipramine effect.

The α-antagonists alone at the doses investigated had no effect on the forced-swimming test.

Study of opiate systems involvement

A significant effect was induced by imipramine (2 mg kg^{-1} i.p.) + TRH (2 mg kg^{-1} i.p.) ($P<0.01$, Kruskal-Wallis test) on the forced-swimming test. This effect was completely inhibited by naloxone (1 mg kg^{-1} i.p.). Naloxone alone had no effect. However, naloxone (1 mg kg^{-1} i.p.) did not antagonize the effect induced by an effective dose of imipramine (20 mg kg^{-1} i.p.) (Table 4).

The mice treated with morphine (10 mg kg^{-1} s.c.) three times a day for two days became tolerant to an acute dose of morphine (1 mg kg^{-1} s.c.). In this case an acute dose of morphine was not effective on the phenyl-benzoquinone writhing test. The number of writhes was even increased after 1 mg kg^{-1} (s.c.) of morphine in mice that had received chronic administration of morphine (↑ 50%/controls, non significant, Kruskal-Wallis test). Whereas the number of writhes

Table 2 Potentiation of the effects of increasing doses of imipramine by thyrotropin releasing hormone (TRH) on the forced-swimming test

Drugs	*Doses* (mg kg^{-1} i.p.)	*No. of mice per experiment*	*Duration of immobility* (s) mean ± (s.e.mean)	*% change from controls*
Vehicle	—	20	142 ± 12	
Imipramine + vehicle	4	20	117 ± 15	↓18**¶
Imip + TRH	4 + 2	20	65 ± 11	↓54$^{**¶}_{*†}$
Vehicle	—	20	137 ± 15	
Imipramine + vehicle	8	20	103 ± 14	↓25*¶
Imip + TRH	8 + 2	20	60 ± 10	↓56$^{**¶}_{*†}$
Vehicle	—	20	148 ± 12	
Imipramine + vehicle	16	20	68 ± 12	↓54**¶
Imip + TRH	16 + 2	20	34 ± 8	↓77**¶
Vehicle	—	10	154 ± 10	
Imipramine + vehicle	32	10	30 ± 12	↓80**¶
Imip + TRH	32 + 2	10	29 ± 11	↓81**¶
Vehicle	—	20	128 ± 13	
Imip + TRH	2	20	114 ± 12	↓11

Imipramine and TRH were administered once 54 min and 6 min before the test respectively. The duration of immobility was recorded during a 4 min period. The groups treated by imipramine were compared to the controls (¶). The groups treated with imipramine + TRH were compared to the relevant controls (¶) or to the relevant groups treated by imipramine + vehicle (†). ** $P<0.01$; * $P<0.05$, Kruskal-Wallis test.

Table 3 Investigation of α-adrenergic system involvement in the thyrotropin releasing hormone (TRH)-induced potentiation of the imipramine effect on mice in the forced-swimming test

Drugs	*Doses* ($mg\,kg^{-1}$ i.p.)	*No. of mice per experiment*	*Duration of immobility* (s) mean ± (s.e.mean)	*% change from controls*
Vehicle	—	10	175 ± 22	
Phenoxybenzamine	8	10	172 ± 12	↓ 2
Phentolamine	4	10	176 ± 13	↑ 0.5
Vehicle	—	10	157 ± 19	
Yohimbine	2	10	168 ± 14	↑ 7
Prazosin	2	10	142 ± 12	↓ 10
Vehicle	—	10	158 ± 20	
Imip + TRH + vehicle	2 + 2	10	91 ± 25	↓ 42*¶
Imip + TRH + Pbz	2 + 2 + 8	10	70 ± 19	↓ 56**¶
Vehicle	—	10	151 ± 21	
Imip + TRH + vehicle	2 + 2	10	79 ± 16	↓ 48*¶
Imip + TRH + phent	2 + 2 + 4	10	71 ± 14	↓ 53**¶
Vehicle	—	20	154 ± 14	
Imi + TRH + vehicle	2 + 2	20	109 ± 13	↓ 29*¶
Imi + TRH + Yohimb	2 + 2 + 2	20	176 ± 8	↑ 14**†
Vehicle	—	10	166 ± 16	
Imip + TRH + vehicle	2 + 2	10	93 ± 10	↓ 44**
Imip + TRH + prazosin	2 + 2 + 2	10	80 ± 19	↓ 52**¶

Imipramine (Imip) and α-antagonists (phenoxybenzamine (Pbz), phentolamine (Phent), yohimbine (Yohimb) and prazosin) were administered 54 min before the test. TRH was administered 6 min before the test. The duration of immobility was recorded during a 4 min period. The groups treated by the α-antagonists were compared to the controls (¶). The groups treated by imipramine + TRH + α-antagonists were compared to both the relevant controls (¶) and the group treated by imipramine + TRH + vehicle (†). * $P<0.05$; ** $P<0.01$, Kruskal-Wallis test.

Table 4 Involvement of opiate systems in the thyrotropin releasing hormone (TRH)-induced potentiation of the imipramine effect on mice in the forced-swimming test

Drugs	*Doses* ($mg\,kg^{-1}$ i.p.)	*No. of mice per experiment*	*Duration of immobility* (s) mean ± (s.e.mean)	*% change from controls*
Vehicle	—	10	161 ± 13	
Naloxone	1	10	155 ± 17	↓ 4
Vehicle	—	10	178 ± 23	
Imip + TRH + vehicle	2 + 2	10	73 ± 18	↓ 59**¶
Imip + TRH + naloxone	2 + 2 + 1	10	162 ± 21	↓ 9**†
Vehicle	—	10	163 + 17	
Imipramine + vehicle	20	10	90 ± 22	↓ 45*¶
Imipramine + naloxone	20 + 1	10	87 + 28	↓ 47*¶

Naloxone, imipramine (Imip) and TRH were administered 18 min, 54 min and 6 min before the test, respectively. The duration of immobility was recorded during a 4 min period. ¶ compared with controls, † compared with the group treated by imipramine + TRH + vehicle, ** $P<0.01$; * $P<0.05$, Mann-Whitney U test or Kruskal-Wallis test.

Table 5 Decrease of the thyrotropin releasing hormone (TRH)-induced potentiation of the imipramine effect on the forced-swimming test in morphine-tolerant mice

Drugs		*No. of mice per experiment*	*Duration of immobility* (s) mean ± (s.e.mean)	*% change from controls*
Chronic treatment	*Acute treatment*			
Vehicle	Vehicle	20	159 ± 15	
Morphine 10 mg kg^{-1}	Vehicle	20	143 ± 13	↓ 10
Vehicle	Imipramine 2 + TRH 2 mg kg^{-1}	20	77 ± 12	↓ 52**¶
Morphine 10 mg kg^{-1}	Imipramine 2 + TRH 2 mg kg^{-1}	20	123 + 12	↓ 23*¶ *†

During the chronic treatment, vehicle or morphine were administered subcutaneously three times a day (08 h 00 min, 14 h 00 min, 20 h 00 min) for two days. During the acute treatment, imipramine and TRH were administered 54 min and 6 min before the test, respectively. The duration of immobility was recorded during a 4 min period. ¶ compared with controls, † compared with animals receiving chronic treatment with vehicle and acute treatment with imipramine + TRH. * $P<0.05$; ** $P<0.01$, Kruskal-Wallis test.

was significantly decreased after 1 mg kg^{-1} (s.c.) of morphine in mice which received chronic administration of distilled water (↓ 75% controls, $P<0.01$, Kruskal-Wallis test).

The potentiation of the effect of imipramine by TRH on the forced-swimming test was significantly decreased ($P<0.05$, Kruskall-Wallis test) in morphine-tolerant mice. In these animals imipramine (2 mg kg^{-1} i.p.) + TRH (2 mg kg^{-1} i.p.) decreased the duration of immobility during the forced-swimming test by 23%, whereas in non-tolerant mice the decrease was 52%.

The morphine-tolerant mice that received the vehicle alone had a similar duration of immobility to that for the non-tolerant control animals (↓ 10% controls, non significant, Kruskal-Wallis test) (Table 5).

Discussion

The forced-swimming test showed a potentiation of the effect of imipramine by TRH. Such a potentiation has been described by Plotnikoff & Kastin (1976) in depressed patients resistant to imipramine alone. Rastogi *et al.* (1980) after having found an increased turnover of catecholamines by TRH in the rat brain speculated that this potentiation could be the consequence of both an increased turnover of catecholamines by TRH, and of a blockade of their uptake in the presynaptic membrane by imipramine. The potentiation of imipramine by TRH observed on the forced-swimming test using mice does not seem to be associated with an increase of effective levels of noradrenaline in the synaptic clefts, since α-antagonists like prazosin, phentolamine or phenoxybenzamine did not prevent TRH having an effect. In contrast, yohimbine which induces an increased release of noradrenaline, blocked the potentiation of imipramine by TRH. The mechanisms involved in the potentiation of the imipramine effect on the forced-swimming test are therefore different from those involved in the potentiation of TRH-induced hyperthermia by antidepressants which activate α-adrenergic systems. The results suggest a possible interaction between TRH and the opiate systems, since naloxone (1 mg kg^{-1} i.p.) blocked the imipramine potentiation by TRH. This hypothesis is supported by the fact that imipramine potentiation is decreased in morphine-tolerant mice. It is interesting to note that the effect induced by imipramine alone was not modified by naloxone and thus activation of the opiate systems could be triggered by TRH. Interactions between TRH and the opiates have already been described. TRH antagonizes the hypothermia (Horita *et al.*, 1976; Cox *et al.*, 1976; Holaday *et al.*, 1978; Bhargava *et al.*, 1982), respiratory depression (Horita *et al.*, 1976), locomotor depression or activation (Bhargava *et al.*, 1982) and catalepsy (Holaday *et al.*, 1978) induced by opiates. It also inhibits the development of tolerance to the analgesic effect of opiates (Bhargava, 1981) and inhibits the development of physical dependence on opiates (Bhargava, 1980). Previous studies have shown that naloxone at a non-hyperalgesic dose (1 mg kg^{-1} i.p.) does not antagonize TRH-induced analgesia, but that TRH blocks the hyperalgesia induced by a hyperalgesic dose of naloxone in mice (Rips *et al.*, 1983).

It seems that TRH does not directly interact with the opiate receptors since TRH is unable to alter the binding of [^{3}H]-morphine *in vitro* or *ex vivo* in mice

(Martin *et al.*, 1977) or the binding of [^{3}H]-naloxone *in vitro* in rat brain homogenates (Tache *et al.*, 1977). It is more likely that TRH acts as a neuromodulator and modifies the opiate systems indirectly. It is already known that various systems such as dopaminergic (Narumi & Nagawa, 1983) or cholinergic (Kalivas & Horita, 1983) systems are involved in other central effects of TRH. Thus a common mechanism to explain all the TRH effects remains to be discovered.

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