J. Pharm. Pharmacol. 1989, 41: 639–641
Communicated December 20, 1988

The effect of repeated treatment with antidepressant drugs on the thyrotropin-releasing hormone (TRH)-induced hyperthermia in mice

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Abstract—The effect of acute (single dose) or repeated (twice daily, for 14 days) administration of 10 mg kg^{-1} p.o. of imipramine, amitriptyline, citalopram or mianserin has been examined on the hyperthermia induced by thyrotropin-releasing hormone (TRH) (40 mg kg^{-1} i.p., 2, or 2 and 72 h after single or last dose of antidepressants, respectively) in mice. Both imipramine and amitriptyline, given repeatedly, potentiated the TRH response, though the effect was observed 2 but not 72 h after the last dose of those drugs. Potentiation was also found after the single dose of imipramine or amitriptyline. On the other hand, citalopram and mianserin, administered either acutely or repeatedly, did not affect the TRH-induced hyperthermia.

Evidence indicates a link between antidepressant drugs and thyrotropin-releasing hormone (TRH) (Pecknold & Ban 1977; Nemeroff et al 1979). Others have recently reported that repeated antidepressant treatment reduces functional responses to the peptide. Sills & Jacobowitz (1987) found that long-term administration of desipramine or nialamide decreased the wet-dog shake response in rats induced by the TRH analogue MK-771(L-*N*-(2-oxopiperidin-6-ylcarbonyl)-L-histidyl-L-thiazolidine-4-carboxamide). Furthermore, Bennett et al (1986) showed that the hyperactivity, recovery from pentobarbitone-induced anaesthesia and reversal of both the pentobarbitone-induced hypothermia and decreased respiration—all evoked in rats by another TRH analogue, CG 3509(orotyl-histidyl-prolylamide) CG 3509—were significantly reduced following repeated treatment with amitriptyline.

Besides the above arousal effects, TRH causes hyperthermia in certain species, including mice (see Nemeroff et al 1979). Thus it was of interest to study the influence of repeated treatment with antidepressant drugs on this response to TRH. In the present paper we examined the effect of the two tricyclic antidepressants, imipramine and amitriptyline, the selective 5-hydroxytryptamine uptake inhibitor citalopram and the atypical antidepressant, mianserin.

Materials and methods

Male Albino Swiss mice (25–30 g), bought from licenced dealers, were kept at 21 ± 1°C, on a natural day-night cycle (spring), with free access to granulated rodent food (Bacutil) and tap water.

Imipramine hydrochloride (Polfa), amitriptyline hydrochloride (Polfa), citalopram hydrobromide (Lundbeck) or mianserin hydrochloride (Organon) were administered p.o. in a dose of 10 mg kg^{-1} acutely (single dose) or repeatedly (twice daily for 14 consecutive days). TRH (40 mg kg^{-1} i.p., synthesized in the Department of Chemistry, University of Gdańsk) was injected 2 h after the single dose, as well as 2 and 72 h after the last dose of the antidepressants. All the drugs were given as solution in 0·9% NaCl. Controls received the equivalent volume of saline.

The rectal body temperature was measured using an Ellab thermistor thermometer every 15 min for 1 h after TRH injection. The results are expressed as a change in the body temperature (Δt), with respect to the initial temperature measured immediately before the single or last dose of the antidepressant drugs.

Statistical significance of the results was assessed by Student's paired *t*-test.

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Results

TRH administered in doses of 10, 20, 40 and 80 mg kg^{-1} i.p. dose-dependently increased the rectal body temperature in mice with mean peak effects of 0·6, 0·8, 1·2 and 1·4°C, respectively, observed 15–30 min after its administration (results not shown). On the basis of these results the dose of 40 mg kg^{-1} of TRH was selected for the experiment with antidepressant drugs.

The hyperthermic response to TRH was potentiated in mice pretreated acutely or repeatedly with imipramine or amitriptyline, though in chronic experiment the potentiation was observed 2 but not 72 h after the last dose of antidepressants. Neither acute nor prolonged administration of citalopram or mianserin affected the TRH-induced hyperthermia (Fig. 1). None of the antidepressant drugs administered acutely, or repeatedly, affected the body temperature before TRH injection. The body temperature of mice, taken immediately before TRH injection, ranged from 36·5 to 37·1°C (results not shown).

Discussion

The present study has demonstrated that, of the four investigated antidepressant drugs, only imipramine and amitriptyline, given repeatedly, protentiated the TRH-induced hyperthermia in mice. However, this effect does not seem to result from their long-term administration, since it was observed only under drug treatment (i.e. 2 h after the last dose of the antidepressants), but not in the drug-free period (i.e. 72 h after their last administration), and since a similar potentiation—in accordance with other reports (Desiles & Rips 1980; Desiles et al 1980)—was also observed after a single dose of imipramine or amitriptyline. On the other hand, neither acute nor repeated treatment with the two other antidepressants, citalopram or mianserin, affected the response to TRH; the lack of effect of their single administration supports the results of other authors (Desiles et al 1980; Pawłowski & Nowak 1987). The potentiating effects of imipramine and amitriptyline, as well as the lack of effect of citalopram and mianserin, are in line with the results of other authors, indicating that among antidepressant drugs only noradrenaline uptake inhibitors, but not inhibitors of 5-hydroxytryptamine uptake or atypical antidepressants, potentiate the TRH-induced hyperthermia (Desiles et al 1980; Desiles & Rips 1981; Pawłowski & Kwiatek 1983).

Thus, our results show that the hyperthermic response to TRH in mice is not reduced by repeated treatment with the antidepressant drugs, though they were administered in doses which, according to Maj (1984), are sufficient to modify different behavioural responses mediated by α_1-adrenoceptors or dopamine receptors in the same species. This finding is in contrast to the literature data indicating that other functional responses to TRH (head twitch reaction, hyperactivity, arousal effects) are reduced following prolonged administration of antidepressants (Bennett et al 1986; Sills & Jacobowitz 1987). The reason for this

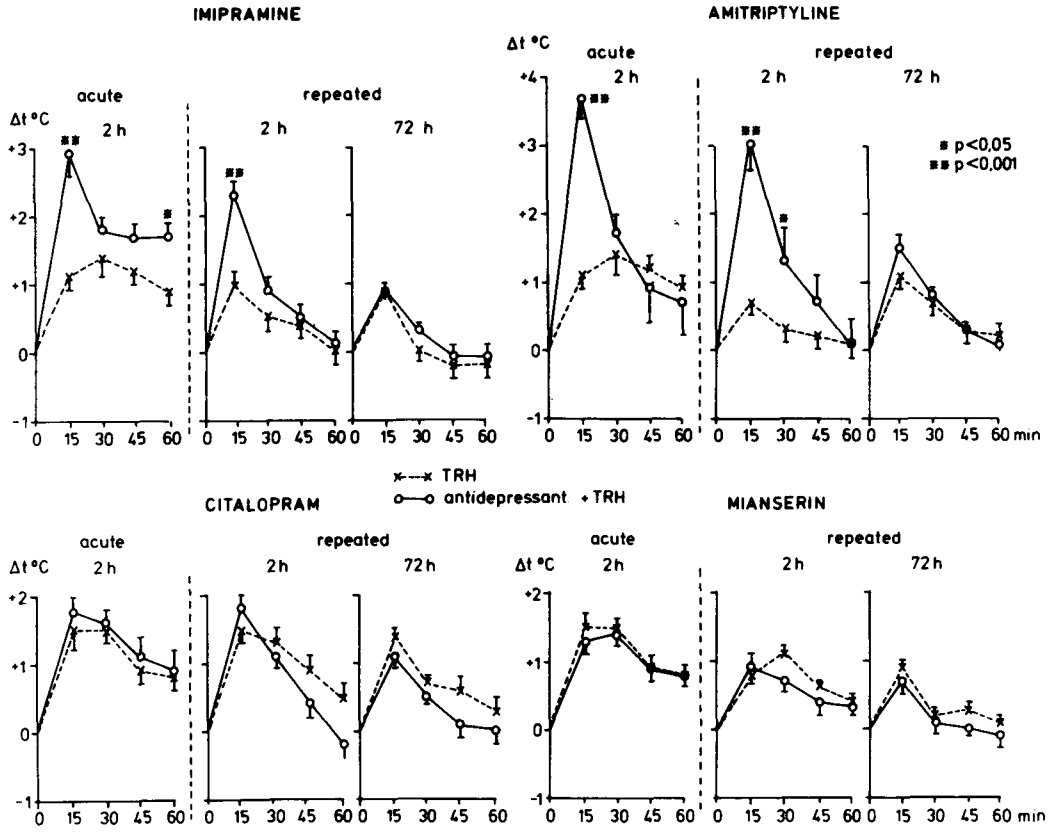

FIG. 1. The effect of acute and repeated treatment with imipramine, amitriptyline, citalopram and mianserin on the TRH-induced hyperthermia in mice.

discrepancy is unclear, though some points should be raised. (i) We studied the hyperthermic response to TRH in mice, while the head twitch reaction, hyperactivity and other arousal effects were examined in rats, hence the reduction in TRH-induced functional responses may be a species-specific phenomenon. (ii) It cannot be excluded that different (or differently localized) TRH receptors mediate different responses induced by the peptide, and that those involved in the hyperthermic response are not affected by antidepressant drugs. (iii) It has been shown that α_1-adrenoceptors participate in the hyperthermia induced by TRH in mice (Desiles & Rips 1980). On the other hand, it has been demonstrated that repeated treatment with antidepressants increases behavioural reactions mediated by α_1-adrenoceptors, e.g. the clonidine-induced aggressiveness in mice (Maj et al 1984). Thus, if long-term administration of antidepressant drugs induces subsensitivity of TRH receptors and supersensitivity of α_1-adrenoceptors, the lack of influence on the TRH-induced hyperthermia may be the net effect. However, such an explanation seems doubtful, since citalopram given repeatedly neither induces a functional supersensitivity of α_1-adrenoceptors (Maj et al 1984) nor modifies the TRH-induced hyperthermia.

In conclusion, our results demonstrate that reduction in the functional response to TRH is not a general phenomenon following repeated treatment with antidepressant drugs, as the TRH-induced hyperthermia in mice is not reduced by the drugs.

This research was supported by Grant CPBP 06.02.I.1 of the Polish Academy of Sciences. The authors wish to thank for their generosity: Lundbeck for citalopram and Organon for mianserin.

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J. Pharm. Pharmacol. 1989, 41: 641–643
Communicated January 24, 1989

Age-dependence of the effects of pinacidil on rat aorta

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Abstract—The effect of the K^+ channel opening drug, pinacidil, has been examined on aortic ring preparations from young (2 months) and aged (> 24 months) rats. The potency (neg log IC50) values for pinacidil in relaxing K^+ (20 mM)-contracted preparations were in the range expected for its K^+ channel opening (hyperpolarizing) effects but were not significantly different between young (6·34) and aged (6·31) rats. Thus, ageing does not affect the drug's potency as a K^+ channel opening drug. The more marked depression of the maximum response to noradrenaline by pinacidil (10 μM) in aged rats (85% reduction) compared with young rats (43% reduction), reflected a reduced α-adrenoceptor reserve for noradrenaline in preparations from aged rats. Pinacidil, in concentrations greater than 10 μM, was able to relax preparations contracted with 80 mM K^+ suggesting that it may have a second mechanism which does not involve hyperpolarization. It was more potent in producing this effect on the preparations from aged rats.

Vasodilator drugs are widely used in the treatment of hypertension and other cardiovascular disorders. Since these conditions are particularly common in the elderly, it is important to examine the influence of age on the responsiveness of blood vessels to vasodilator drugs. It has already been shown that ageing influences the in-vitro responses of blood vessels to different vasodilators, e.g. β-adrenoceptor agonists (Fleisch 1981; O'Donnell & Wanstall 1984, 1986), dopamine receptor agonists (Wanstall & O'Donnell 1988a) and calcium entry blocking drugs (Wanstall & O'Donnell 1988b, 1989), whilst having little or no effect on others, e.g. the nitrovasodilators (O'Donnell & Wanstall 1986; Wanstall & O'Donnell 1988a).

The aim of this study was to examine the influence of age on pinacidil, a vasodilator drug which has been suggested to have the novel mechanism of opening K^+ channels (Bray et al 1987). This drug has been examined on isolated aortic preparations from both young and aged rats. We have determined both its potency in relaxing K^+-induced contractions and its effects on concentration-response curves to noradrenaline.

Materials and methods

Male Wistar rats either 2 months old (young, 250–375 g) or 24–29 months old (aged, 440–530 g) were used.

Isolated single ring preparations (3 mm wide) of ventral aorta, from which the endothelium had been removed by gentle rubbing of the intimal surface, were set up in physiological salt solution (PSS) at 37°C, at a resting force of 10 mN, as described by Wanstall & O'Donnell (1988b). Force in the circular muscle was recorded isometrically, using a Statham Universal Transducer (UC3 and UL5).

After an initial 1h equilibration period, each preparation was contracted with K^+-depolarizing PSS (85·9 mM KCl) and relaxed with 100 μM 3-isobutyl-1-methylxanthine. After washout of this drug, one or two further contractions to K^+-depolarizing PSS were obtained. It has been found that this preliminary procedure results in preparations which have stable base-line tensions and which give consistent contractile responses for the duration of the experiment (Wanstall & O'Donnell 1988b, 1989).

Experimental protocols and expression of data. In the first series of experiments, cumulative concentration-response (contraction) curves to noradrenaline were obtained in the absence (control) and then in the presence of pinacidil (10 μM, contact time 30 min). Responses were expressed as a percentage of the maximum response to noradrenaline in the control curve so that any reduction in the maximum response could be determined. Control concentration-response curves to noradrenaline are reproducible in aorta from both young and aged rats (Wanstall & O'Donnell 1988b).

In the second series of experiments, preparations were contracted with KCl (20 or 80 mM—achieved by replacing the PSS with K^+-depolarizing PSS containing the appropriate KCl concentration). The contraction induced by 80 mM KCl was maximal, and that induced by 20 mM KCl submaximal (young 68%; aged 66% of the response to 80 mM KCl). In the absence of pinacidil, these contractions were sustained. Cumulative concentration-response (relaxation) curves to pinacidil (0·1 to 300 μM) were obtained once the spasmogenic response had reached equilibrium. Responses were expressed as % reversal of the induced contraction and were plotted against pinacidil concentration on a logarithmic scale. The concentration giving a 50% relaxant response (IC50) was interpolated and the negative log IC50 was used as an expression of relaxant potency.

Drugs and solutions. The drugs used were: 3-isobutyl-1-methylxanthine (Sigma); (−)-noradrenaline acid tartrate (Sigma) and pinacidil (gift from Leo Pharmaceuticals, Denmark). Stock solutions of noradrenaline (100 mM) and pinacidil (10 mM) were prepared in 10 mM HCl and of 3-isobutyl-1-methylxanthine (5 mM) in 10 mM NaOH. Dilutions of drugs were made in PSS.

The composition of the PSS was (mM): NaCl 118, KCl 5·9, $CaCl_2$ 1·5, $MgSO_4$ 0·72, glucose 11·7, ascorbic acid 1·14 (95% O_2/5% CO_2, pH 7·4). K^+-depolarizing PSS had the same composition as above, except that either 80 mM or 20 mM NaCl was replaced with 80 mM or 20 mM KCl (total KCl concentration = 85·9 mM or 25·9 mM).

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