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INVOLVEMENT OF A CENTRAL α-ADRENOCEPTOR SYSTEM IN ANTIDEPRESSANT POTENTIATION OF HYPERTHERMIA INDUCED BY THYROTROPIN RELEASING HORMONE

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Thyrotropin releasing hormone (TRH) causes hyperthermia in mice which is potentiated by tricyclic antidepressants (nortriptyline, imipramine, clomipramine, amitriptyline), the monoamine oxidase inhibitor, tranylcypromine, and various other antidepressants (maprotiline, nomifensin, viloxazine). Only iprindole is ineffective. The effect of mianserin, itself hypothermic, could not be interpreted. A property shared by the potentiating substances seems to be activation of a central adrenoceptor system. The potentiation of TRH-induced hyperthermia which seems to be specific to antidepressants might be used in the selection of antidepressants.

Introduction Thyrotropin releasing hormone (TRH) is one of the endogenous peptides for which an effect on the central nervous system, independent of its already known endocrine activity, has been demonstrated (Nemeroff, Loosen, Bissette, Manberg, Wilson, Lipton & Prange, 1979). Among its psychotropic effects, it causes hyperthermia in certain species (Horita & Carino, 1975).

In contrast to some other effects of TRH such as increased motor activity which appear to involve a dopaminergic system (Heal & Green, 1979), hyperthermia is inhibited by α-adrenoceptor antagonists and potentiated by α-adrenoceptor agonists (Desiles & Rips, 1980). It is not affected by agents acting on dopamine (Rips, Desiles & Puech, 1979), 5-hydroxytryptamine or GABA receptors (Desiles, Constans & Rips, 1979). This suggests specific participation of an α-adrenoceptor system. Numerous tricyclic antidepressants inhibit noradrenaline uptake. In order to confirm the role of noradrenaline, the effect of antidepressants on TRH-induced hyperthermia was investigated. The study was then extended to a series of new compounds with antidepressant activity considered 'atypical' because they do not have the classical profile of the tricyclic compounds.

Methods Female mice of the Swiss albino strain weighing between 20 and 24 g were used. All experiments were carried out between 10 h 00 min and 12 h 00 min at an ambient temperature of 21 ± 1°C. Rectal temperature was recorded with a thermistor probe, 15 min before and 15 min and 30 min after TRH (40 mg/kg i.p.) administration.

Imipramine (5, 10, 20 mg/kg i.p.), nortriptyline (1.25, 2.5, 5 mg/kg i.p.), clomipramine (5, 10, 20 mg/kg i.p.), mianserin (15, 30, 60 mg/kg i.p.) and maprotiline (5, 10, 20 mg/kg i.p.) were administered 30 min before TRH. Amitriptyline (0.75, 1.5, 3 mg/kg i.p.) was administered simultaneously with TRH. Iprindole (10, 20, 40 mg/kg i.p.), tranylcypromine (10, 20, 40 mg/kg i.p.) and nomifensine (6.25, 12.5, 25 mg/kg i.p.) were administered 1 h before TRH. Only results obtained with the lowest dose of each product are shown in Table 1. Differences between groups, at a given time after TRH injection, were determined by Student's *t* test.

Results All the tricyclic antidepressants used (nortriptyline, imipramine, clomipramine, amitriptyline), and the monoamine oxidase inhibitor (MAOI), tranylcypromine, as well as the various antidepressants, maprotiline, nomifensin and viloxazine significantly potentiated TRH-induced hyperthermia (Table 1). Potentiation followed the kinetics of TRH activity: a maximum change at 15 min, with a decrease in effect starting at 30 min. Most of the substances at the doses administered had no effect on temperature themselves. Iprindole, even at non-hypothermic doses, did not affect temperature. With mianserin, a strongly hypothermic substance, a slight decrease in TRH hyperthermia was observed, although the temperature of the animals was much higher than that of mice receiving only mianserin.

Discussion Although earlier results concerning the use of TRH as an antidepressant (Prange, Wilson, Lara & Alltop, 1974) have not been confirmed, a relationship might nevertheless, exist between TRH and depression since it seems now well established that TRH differentiates certain groups of depressed subjects (Kirkegaard, Bjorum, Cohn & Lauridsen, 1978). It is, therefore, not surprising to find one of the effects of TRH strongly potentiated by antidepressants.

The additive effects of TRH and imipramine in the Everett test have already been demonstrated (Plotnikoff, Breese & Prange, 1975). In the present study, the hyperthermic effect of TRH was significantly poten-

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tiated by all the antidepressants used, whether tricyclic, MAOI, or some of the new compounds, with the exception of mianserin and iprindole. The case of mianserin will be discussed below. As for iprindole, according to Zis & Goodwin (1979), 'There is as yet insufficient evidence to conclude that iprindole is efficacious (i.e. superior to placebo) in the treatment of major depressions'.

Among those substances causing potentiation, there were tricyclic agents thought to inhibit preferentially the uptake of noradrenaline (nortriptyline) or 5-hydroxytryptamine (5-HT) (imipramine, clomipramine, amitriptyline), maprotiline, which specifically inhibits noradrenaline uptake (Maitre, Staehelin & Bein, 1971), and nomifensine which both stimulates noradrenaline and dopamine release (Braestrup & Scheel-Kruger, 1976) and inhibits their reuptake (Hunt, Kannengiesser & Raynaud, 1974). Nomifensine has very little effect on the uptake of 5-HT (Samamin, Bernasconi & Garattini, 1975). Viloxazine inhibits noradrenaline uptake with little effect on 5-HT and dopamine (Blackburn, Foster, Greenwood & Howe, 1978).

Mianserin, which blocks presynaptic adrenoceptors, increases the activity of postsynaptic receptors (Bauman & Maitre, 1977). However, it did not potentiate TRH-induced hyperthermia, but the results are difficult to interpret since it alone produced a marked hypothermia. As for iprindole, it has no effect either on the uptake, storage or metabolism of noradrenaline (Rosloff & Davis, 1974).

If one seeks a common property among all the substances responding positively, one notes, first of all, a psychotropic and therefore a central activity. Secondly, if some of the substances act preferentially on 5-HT and dopamine systems, they all, to various degrees, block uptake of noradrenaline or increase its concentration at the level of the postsynaptic receptor. Iprindole, the only substance having no effect on the noradrenergic system, was also unable to potentiate TRH-induced hyperthermia.

Although 5-HT has been implicated in the mechanism of action of antidepressants, and in the aetiology of depression (Murphy, Campbell & Costa, 1978) and TRH increases 5-HT-mediated behavioural responses (Green & Grahame-Smith, 1974), the neurotransmitter does not appear to participate in a major way in the potentiation of TRH-induced hyperthermia since maprotiline, viloxazine and nomifensine, which have little effect on 5-HT uptake, are very active. The hypothesis that a noradrenergic system is involved is confirmed by the fact that TRH hyperthermia is antagonized by anti-adrenoceptor substances (Desiles & Rips, 1980). Also, although TRH does not modify brain noradrenaline concentrations (Hine, Sanghi & Gherson, 1973), it does increase turnover (Keller, Bartholini & Pletscher, 1974).

Do these results have any relevance to the antidepressant effect of these drugs? These results concern acute administration, whereas the clinical effect of antidepressants is generally observed after a latency period which varies with the substance. The antidepressant action may, therefore, be distinct from short-term pharmacological or biochemical effects in animals (Sulser, Vetulani & Mobley, 1978).

Chronic treatment of animals with various antidepressants results in a decrease in sensitivity of the noradrenaline-sensitive adenylate cyclase system (Vetulani, Stawarz, Dingell & Sulser, 1976), and also

Table 1 Effect of antidepressant drugs on thyrotropin releasing hormone (TRH, 40 mg/kg i.p. to mice)-induced hyperthermia

	Controls	*Antidepressant*¶	*TRH*¶	*TRH and antidepressant*†
Tricyclics				
Nortriptyline	37.7 ± 0.1	37.4 ± 0.1	38.5 ± 0.2***	39.5 ± 0.2***
Imipramine	37.7 ± 0.1	37.6 ± 0.1	38.4 ± 0.1**	39.7 ± 0.1***
Clomipramine	37.6 ± 0.1	37.4 ± 0.2	38.6 ± 0.2***	39.8 ± 0.1***
Amitriptyline	37.9 ± 0.1	37.8 ± 0.1	38.6 ± 0.2***	39.4 ± 0.1***
MAO Inhibitor				
Tranylcypromine	37.6 ± 0.1	36.2 ± 0.3***	38.5 ± 0.1***	39.5 ± 0.2***
Specific NA uptake inhibitor				
Maprotiline	37.5 ± 0.1	37.7 ± 0.1	38.2 ± 0.2**	39.4 ± 0.2***
Diverse antidepressants				
Iprindole	37.4 ± 0.1	37.6 ± 0.1	38.8 ± 0.2***	39 ± 0.2
Mianserin	37.8 ± 0.1	34.2 ± 0.3***	38.9 ± 0.1***	37.9 ± 0.2
Nomifensine	37.5 ± 0.1	37.6 ± 0.1	38.4 ± 0.2**	39.6 ± 0.1***
Viloxazine	37.9 ± 0.1	37.5 ± 0.2	38.5 ± 0.2**	39.3 ± 0.07***

Groups were composed of 12 animals (except for mianserin where 18 animals were used). Temperatures (means ± s.e. mean) were measured 15 min after TRH administration.

¶ Comparison with controls; † comparison with vehicle or TRH; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

in a decrease in the density of β-receptors (Wolfe, Kendall, Sporn & Molinoff, 1978). However, if hyposensitivity of α- or β-adrenoceptors were responsible for clinical effects, an aggravation of symptoms would be observed at the beginning of antidepressant treatment.

One cannot exclude at the present time the possibility of selecting antidepressants following acute experimentation. We have demonstrated a common property of different antidepressants which seems to be specific since neuroleptics (Rips *et al.*, 1979), anxiolytics (unpublished results), and a series of substances modifying 5-HT, GABA (Desiles *et al.*, 1979) and dopamine systems (Rips *et al.*, 1979) are inactive. Amphetamine strongly potentiates TRH hyperthermia (Desiles, Morier & Rips, 1977), but has itself antidepressant properties in clinical use (Maickel, Cox, Ksir, Snodgrass & Miller, 1970) and is well known often to act like an antidepressant in animals (Porsolt, Le Pichon & Jalfre, 1977).

In conclusion, the potentiation of TRH-induced hyperthermia which seems linked to the activation of a central α-adrenoceptor system might be used for the selection of antidepressants.

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