Enhancement of noradrenaline responses by thyrotropine-releasing hormone

Thyrotropine-releasing hormone (TRH) has been reported to have antidepressant properties (Prange & Wilson, 1972; Prange, Wilson & others 1972; Kastin, Enrensing & others, 1972; Obiols, Pujol & others, 1974). Since the tricyclic antidepressant drugs greatly potentiate the effects of noradrenaline in different preparations (Sigg, 1959; Cuenca & Valdecasas, 1965; Ursillo & Jacobson, 1965) we considered it worth-while to investigate the influence of TRH upon some of the noradrenaline responses.

We agree with Urisillo & Jacobson (1965) that the vas deferens of the rat is a suitable preparation for quantitative investigation of the potentiation of noradrenaline. In the present study the influence of TRH upon the responses elicited by noradrenaline on the rat isolated vas deferens is reported.

Cumulative dose response curves of (−)-noradrenaline were made in the presence and absence of TRH. Vasa deferentia were removed from freshly killed Wistar rats (200–250 g) and suspended in a 10 ml organ bath of Krebs solution at 31°. The solution was gassed with 5% carbon dioxide in oxygen. Changes in length of the tissues in reponse to (−)-noradrenaline were recorded kymographically on a smoked drum. Three or four dose-response curves of (−)-noradrenaline were made as controls in each experiment before adding TRH to the bath fluid. The rest time between curves was always kept constant (15 min). The noradrenaline responses obtained in the control period were converted into percentages of their maximal contraction response. None of the response curves in the control series showed a statistical difference. After the preparation had been washed, TRH was added to

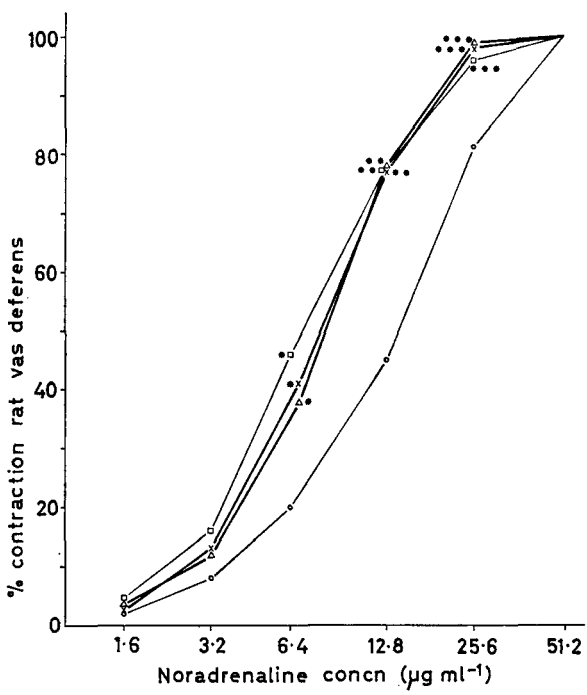

FIG. 1. Showing mean responses of rat isolated vas deferens to noradrenaline in the presence or absence of TRH, ○, control (14), TRH, g ml^{-1}: □, $2{\cdot}5 \times 10^{-6}$ (4); ×, 5×10^{-6} (5); △, 1×10^{-5} (5) (in brackets, the number of experiments). Standard errors have been omitted for simplicity. ***$=P<0{\cdot}001$; **$=P<0{\cdot}02$; *$=P<0{\cdot}05$.

the Krebs solution at $2{\cdot}5 \times 10^{-6}$ (4 experiments), 5×10^{-6} (5 experiments) and 1×10^{-5} g ml^{-1} (5 experiments.) The contact time of TRH in all experiments was 15 min. After that period new cumulative dose response curves of (—)-noradrenaline were made. The responses were converted into percentages of the maximal response which was obtained from the last curve of the control period. In this way possible potentiation of the maxima could be disregarded. However, no potentiation of the maxima was observed.

As can be seen in Fig. 1, TRH in the range of concentrations investigated cause a shift to the left of the noradrenaline dose response curves without changing the maximal response of the tissue. The differences observed at some points are statistically significant when compared with the control curve. In some experiments this enhancement lasts, after the first washing of the preparation (second dose response curve made after TRH). Lower concentrations of TRH (1×10^{-6} g ml^{-1}, not shown) are not effective. On the other hand, the highest concentration of TRH used (1×10^{-5} g ml^{-1}) did not elicit a more pronounced effect, the average response being even lower than that of the lowest concentrations used. This response prompted us to investigate the possibility that high concentrations of TRH would be antagonistic to noradrenaline. However, TRH concentrations of 6×10^{-5} and 9×10^{-5} g ml^{-1} did not modify the response of a standard concentration of noradrenaline. The lack of antagonistic properties of TRH to noradrenaline when used in large concentrations differentiates TRH from some imipramine like drugs, i.e. imipramine, desipramine (Cuenca, Rivera & others, 1967).

Finally, preliminary experiments in spinal cats show that TRH (100 μg kg^{-1}, i.v.) slightly, but significantly potentiates the blood pressure responses determined by noradrenaline.

The importance of these results regarding the mechanism of action involved in the antidepressant activity of TRH requires further work. Nevertheless, according to our results the possibility that the short-term mood elevating effect seen in pateints after TRH might be due to central sympathetic activation seems reasonable and is consistent with the catecholamine hypothesis of affective disorders (Schildkraut, Schamberg & others, 1967).

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REFERENCES

CUENCA, E. & VALDECASAS, F. G. (1965). *Neuropsychopharmac.*, **4**, 209–211.

CUENCA, E., RIVERA, P., RODRIGUEZ, L. & VALDECASAS, F. G. (1967). *Actas Soc. Esp. Cien. Fisiol.*, **10**, 127–131.

KASTIN, A. J., EHRENSING, R. H., SCHALCH, D. S. & ANDERSON, M. S. (1972). Lancet, **2**, 740–742.

OBIOLS, J., PUJOL, J., GONZALEZ, E., FERRER, J. & SARRO, R. (1974). *Med. Clin.*, 110–116.

PRANGE, A. J., & WILSON, I. C. (1972). *Psychopharmac. Suppl.*, 26, 82.

PRANGE, A. J., Jr., WILSON, I. C., LARA, P. P., ALLTOP, L. B. & BRESSE, G. R. (1972). *Lancet*, **2**, 999–1002.

SCHILDKRAUT, J. J., SCHAMBERG, S. M., BRESSE, G. R. & KOPIN, I. J. (1967). *Am. J. Psychiat.*, **124**, 600–608.

SIGG, E. B. (1959). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **18**, 144.

URSILLO, R. C. & JACOBSON, J. (1965). *J. Pharmac. exp. Ther.*, **148**, 247–251.