Brain desipramine level in relation to the anti-reserpine activity of imipramine

SIR,—The anti-reserpine activity exerted by imipramine (Garattini, 1959) is believed to be related to the formation in the body of a product of *N*-demethylation known as desipramine (Sulser, Watts & Brodie, 1962). However, Michaelis & Stille (1968) have recently postulated that the formation of desipramine would not be required to mediate the "antidepressant" action of imipramine. These authors have used for their studies the preventive effect exerted by imipramine on the tetrabenazine catalepsy and ptosis.

These findings prompted us to establish if the same conclusion would have been valid by using the test of the increase of body temperature elicited by imipramine in animals previously reserpinized (Garattini & Jori, 1967; Jori & Garattini, 1968).

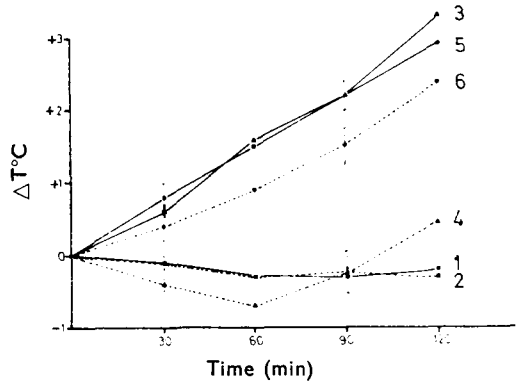

FIG. 1. Hyperthermic effect induced by imipramine and desipramine 16 hr after Reserpine (5 mg/kg i.v.). 1. Saline. 2. SKF 525 A (30 mg/kg, orally). 3. Imipramine (20 mg/kg i.p.). 4. SKF 525 A (30 mg/kg, orally) + imipramine (20 mg/kg i.p.). 5. Desipramine (15 mg/kg i.p.). 6. SKF 525 A (30 mg/kg, orally) + desipramine (15 mg/kg i.p.). The vertical bars represent the standard errors.

TABLE 1. HYPERTHERMIC EFFECT INDUCED BY IMIPRAMINE AND DESIPRAMINE IN RESERPINIZED RATS

No. of rats	Pretreatment (mg/kg/orally)	Treatment (mg/kg i.p.)	T.I. (° C) ± s.e.	Brain concentration (μg ± s.e.)	
				Desipramine	Imipramine
7	Saline	Saline	−1 ± 0·4	—	—
5	SKF 525 A 30	Saline	−1 ± 0·6	—	—
6	Saline	Imipramine 20	+7·8 ± 1·2*	5·1 ± 0·9	9·9 ± 2·1
6	SKF 525 A 30	Imipramine 20	−1 ± 0·8	1·9 ± 0·4**	37·3 ± 2·2**
6	Saline	Desipramine 15	+7·5 ± 1·4*	8·5 ± 1·2	—
6	SKF 525 A 30	Desipramine 15	+5·4 ± 1·4*	8·9 ± 1·5	—

Reserpine (5 mg/kg i.v.) was given 16 hr before the pretreatment.

SKF 525 A was given orally 1 hr before the treatment (saline, imipramine, desipramine).

T.I. = Thermic index was calculated by adding the change of body temperature induced by saline or imipramine or desipramine after 30, 60, 90 and 120 min.

Desipramine and imipramine were determined in the whole brain 2 hr after their administration.

* $P < 0.01$ versus control groups.

** $P < 0.01$ versus saline + imipramine group.

Sprague-Dawley female rats weighing 150 ± 10 g were treated with reserpine (Serpasil CIBA) (5 mg/kg i.v.) 16 hr before the experiment and kept at a room temperature of 20° with a relative humidity of 60%. Fig. 1 shows that imipramine (20 mg/kg i.p.) or desipramine (15 mg/kg i.p.) produce a similar increase of temperature in hypothermic reserpinized rats. However if SKF 525 A, a known inhibitor of microsomal enzymes (Stitzel, Anders & Mannering, 1966), was given at a dose of 30 mg/kg orally 1 hr before imipramine or desipramine, an inhibition of the imipramine but not of the desipramine effect was observed. SKF 525 A itself did not affect the body temperature in reserpinized animals.

Measurements of imipramine and desipramine in brain according to the method of Dingell, Sulser & Gillette (1964) (Table 1) are consistent with the hypothesis that the presence of desipramine in brain would be necessary to obtain the increase of body temperature. These findings are thus at variance with the results of Michaelis & Stille (1968). The reasons for this are unknown, but three major differences in the experimental conditions should be considered.

Firstly, the use of tetrabenazine or reserpine has not been proved to be equivalent, particularly if the schedule of treatment is considered. Secondly the end point used to evaluate the effect of imipramine or desipramine is different and may involve different mechanisms. In fact while the changes of body temperature induced by imipramine are currently considered as the result of an adrenergic interaction (Garattini & Jori, 1967; Ross & Renyi, 1967), symptoms such as catalepsy and ptosis seem to be more related to a cholinergic effect (Sulser, Bickel & Brodie, 1964). Imipramine shows a more pronounced anti-acetylcholine effect than desipramine (Lévy & Michel-Ber, 1965). It may be that for certain effects such as reversal of reserpine hypothermia, imipramine must be transformed into desipramine, while for other effects such as the anti-convulsant activity (Garattini, Giachetti & others, 1962) this *N*-demethylation may not be relevant because imipramine is more active than desipramine. Thirdly, the different strain of animals used by Michaelis & Stille may be a significant factor.

This work was financially supported by contract DHEW/PHS/NIH PH 43-67-83.

Istituto di Ricerche Farmacologiche "Mario Negri",
Via Eritrea, 62
20157 Milan, Italy.

A. JORI
D. BERNARDI

October 2, 1968

References

Dingell, J. V., Sulser, F. & Gillette, J. R. (1964). *J. Pharmac. exp. Ther.*, **143**, 14–22.
Garattini, S. (1959). *Schweiz. Neurol. Psychiat.*, **84**, 8–30.
Garattini, S., Giachetti, A., Jori, A., Pieri, L. & Valzelli, L. (1962). *J. Pharm. Pharmac.*, **14**, 509–514.
Garattini, S. & Jori, A. (1967). In *Antidepressant Drugs*, Proc. First Int. Symposium, Milan 1966. Editors: Garattini, S. & Dukes, M. N. G., p. 179–193, Amsterdam: Excerpta Medica Foundation.
Jori, A. & Garattini, S. (1968). *J. Pharm. Pharmac.*, **20**, 473–474.
Lévy, J. & Michel-Ber, E. (1965). *C. r. Séanc. Soc. Biol.*, **159**, 640–643.
Michaelis, W. & Stille, G. (1968). *Life Sci.*, **7**, 99–106.
Ross, S. B. & Renyi, A. L. (1967). *European J. Pharmac.*, **2**, 181–186.
Stitzel, R. E., Anders, M. W. & Mannering, G. J. (1966). *Molec. Pharmac.*, **2**, 335–340.
Sulser, F., Bickel, M. H. & Brodie, B. B. (1964). *J. Pharmac. exp. Ther.*, **144**, 321–330.
Sulser, F., Watts, J. & Brodie, B. B. (1962). *Ann. N.Y. Acad. Sci.*, **96**, 279–288.