Activity of (+)-amphetamine at different environmental temperatures in three strains of mice

Halpern, Drudi-Baracco & Bessirard in 1962 suggested a correlation of (+)-amphetamine activity and the level of catecholamines in brain, and, more recently, several experimental findings confirmed and explained this view (Glowinski & Axelrod, 1965; Weissman, Koe & Tenen, 1966; Hanson, 1967; Sulser, Owens & others, 1968).

In relation to this and to previous results showing that (+)-amphetamine induces hyperthermia and toxicity to a decreasing extent in Albino Swiss, C_{57}B1/6 and C_3H strains of mice (Dolfini, Garattini & Valzelli, 1969), we have investigated whether (+)-amphetamine depletes brain noradrenaline in a different way, in the three strains of mice. The effect of environmental temperature was considered as a variable able to influence this biochemical effect of (+)-amphetamine. This point seems to be of interest also in connection with the role attributed to noradrenaline in the central control of the thermoregulation (Feldberg & Myers, 1965; Beauvallet, Fugazza & Legrand, 1967; Simmonds & Iversen, 1969).

Male mice, 25 ± 2 g, were kept in sixes in Makrolon cages at a constant room temperature and fed a normal, balanced diet *ad libitum*. Albino Swiss mice were obtained from Alal (Milan), C_{57}B1/6 and C_3H mice from the Jackson Laboratories (Bar Harbor, Maine). (+)-Amphetamine sulphate (Recordati, Milan) was dissolved in saline and injected intraperitoneally.

Table 1. *Effect of* (+)-*amphetamine on temperature and brain noradrenaline in three strains of mice kept at a room temperature of* 4°

Strain of mice	(+)-Amphetamine sulphate mg/kg, i.p.	Body temperature °C ± s.e.			Brain noradrenaline µg/g ± s.e.		
		C	T 30 min	T 120 min	C	T 30 min	T 120 min
Albino Swiss ..	10	37·4 ± 0·1	34·0 ± 0·2	32·8 ± 0·6	0·35 ± 0·01	0·32 ± 0·01	0·30 ± 0·02*
	30	37·8 ± 0·1	34·1 ± 0·6	32·1 ± 0·9	0·43 ± 0·01	0·43 ± 0·01	0·27 ± 0·03†
	45	37·7 ± 0·1	34·1 ± 0·6	25·6 ± 0·9	0·43 ± 0·02	0·37 ± 0·03	0·27 ± 0·02†
C_{57}B1/6	10	36·7 ± 0·1	34·7 ± 0·3	32·5 ± 1·0	0·54 ± 0·02	0·52 ± 0·02	0·50 ± 0·03
	30	37·6 ± 0·2	33·9 ± 0·3	27·8 ± 0·8	0·54 ± 0·02	0·54 ± 0·01	0·46 ± 0·01*
	45	37·0 ± 0·1	33·0 ± 0·5	27·0 ± 0·9	0·60 ± 0·01	0·53 ± 0·02	0·46 ± 0·02†
C_3H/HeJ	10	37·3 ± 0·3	33·1 ± 0·2	31·9 ± 0·2	0·57 ± 0·02	0·53 ± 0·02	0·48 ± 0·02*
	30	37·1 ± 0·2	32·5 ± 0·4	20·2 ± 0·3	0·51 ± 0·02	0·44 ± 0·02	0·37 ± 0·01†
	45	38·1 ± 0·2	34·4 ± 0·2	22·4 ± 1·4	0·53 ± 0·02	0·48 ± 0·02	0·38 ± 0·02†

Controls (C) and treated (T) animals, 30 min and 120 min after (+)-amphetamine sulphate were in groups of at least 5 animals per point.

* $P = <0·05$.
† $P = <0·01$.

Table 2. *Effect of* (+)-*amphetamine on temperature and brain noradrenaline in three strains of mice kept at a room temperature of* 30°

Strain of mice	(+)-Amphetamine sulphate mg/kg, i.p.	Body temperature °C ± s.e.			Brain noradrenaline µg/g ± s.e.			Lethality %
		C	T 30 min	T120 min	C	T 30 min	T 120 min	
Albino Swiss ..	3·7	37·2 ± 0·1	40·2 ± 0·3	37·1 ± 0·3	0·42 ± 0·02	0·43 ± 0·02	0·36 ± 0·02*	0
	10	—	—	—	—	—	—	100
	15	—	—	—	—	—	—	100
C_{57}B1/6 ..	3·7	36·8 ± 0·2	36·8 ± 0·1	35·3 ± 0·3	0·58 ± 0·01	0·56 ± 0·01	0·52 ± 0·02	0
	10	36·1 ± 0·2	41·0 ± 0·2	38·9 ± 0·9	0·55 ± 0·01	0·56 ± 0·01	0·40 ± 0·05†	33
	15	36·3 ± 0·2	40·6 ± 0·3	37·7 ± 0·8	0·54 ± 0·02	0·52 ± 0·03	0·40 ± 0·01†	33
C_3H/HeJ ..	3·7	37·7 ± 0·2	37·5 ± 0·2	36·2 ± 0·3	0·55 ± 0·02	0·56 ± 0·03	0·51 ± 0·02	0
	10	37·7 ± 0·3	39·3 ± 0·2	38·2 ± 0·3	0·53 ± 0·02	0·45 ± 0·01	0·44 ± 0·02*	0
	15	36·2 ± 0·1	39·4 ± 0·3	38·5 ± 0·5	0·55 ± 0·02	0·41 ± 0·02	0·36 ± 0·02†	0

Controls (C) and treated (T) animals, 30 min and 120 min after (+)-amphetamine sulphate were in groups of at least 5 animals per point.

* $P = <0·05$.
† $P = <0·01$.

Brain noradrenaline was measured spectrofluorometrically (Shore, 1959). Temperature was recorded electrically from the rectal cavity.

(+)-Amphetamine, 7·5 and 10 mg/kg at room temperature (22°), induced the typical hyperthermic response, differing significantly ($P < 0{\cdot}05$) from control values after 30 min and accompanied by a release of brain noradrenaline significant at 120 min ($P < 0{\cdot}01$) at 10 mg/kg amphetamine, only in Albino mice while in $C_{57}B1/6$ and C_3H mice there was no effect on either parameter.

The LD50 of (+)-amphetamine sulphate (mg/kg) was 13 for Albino Swiss mice, 54 for $C_{57}B1/6$ mice and 120 for C_3H mice.

If the mice were put in a cold room immediately after administering (+)-amphetamine, the hyperthermic response of the Albino Swiss mice was found to be completely blocked while the depletion of brain noradrenaline was not present at the lower dose.

The cold environment also protected against amphetamine toxicity as was found by Askew (1961), Fink & Larson (1962) and Hohn & Lasagna (1960). In this experimental condition, $C_{57}B1/6$ and C_3H mice showed release of brain noradrenaline (Table 1).

Finally, $C_{57}B1/6$ and C_3H mice kept at 30° immediately after the administration of amphetamine showed an increased temperature in parallel with a release of brain noradrenaline (Table 2).

Thus the hyperthermic response induced by amphetamine was found to be linked both to the strain of mice as well as to the influence of the environmental temperature. The decrease of brain noradrenaline was not related with the degree of hyperthermia, at least under the experimental conditions adopted.

This work was supported by National Institutes of Health, Bethesda, Md., U.S.A., contract No. DHEW/PHS/NIH, PH 43-67-83.

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

E. DOLFINI
S. GARATTINI
L. VALZELLI

September 16, 1969

REFERENCES

ASKEW, B. M. (1961). *J. Pharm. Pharmac.*, **13**, 701–703.
BEAUVALLET, M., FUGAZZA, J. & LEGRAND, M. (1967). *C.r. Séanc. Soc. Biol.*, **161**, 2161–2165.
DOLFINI, E., GARATTINI, S. & VALZELLI, L. (1969). *Europ. J. Pharmac.*, **7**, 220–223.
FELDBERG, W. & MYERS, R. D. (1965). *J. Physiol., Lond.*, **177**, 239–245.
FINK, G. B. & LARSON, R. E. (1962). *J. Pharmac. exp. Ther.*, **137**, 361–364.
GLOWINSKI, J. & AXELROD, J. (1965). *Ibid.*, **149**, 43–49.
HALPERN, B. N., DRUDI-BARACCO, C. & BESSIRARD, D. (1962). *C.r. Séanc. Soc. Biol.*, **156**, 769–773.
HANSON, L. C. F. (1967). *Psychopharmacologia*, **10**, 289–297.
HOHN, R. & LASAGNA, L. (1960). *Ibid.*, **1**, 210–220.
SHORE, P. A. (1959). *Pharmac. Rev.*, **11**, 276–277.
SIMMONDS, M. A. & IVERSEN, L. L. (1969). *Science, N.Y.*, **163**, 473–474.
SULSER, F., OWENS, L. L., NORVICH, M. R. & DINGELL, J. V. (1968). *Psychopharmacologia*, **12**, 322–332.
WEISSMAN, A., KOE, B. K. & TENEN, S. S. (1966). *J. Pharmac. exp. Ther.*, **151**, 339–352.