interest in the present work. They would also like to acknowledge the assistance rendered by Mr. S. C. Datta.

Department of Physiology,
Calcutta University College of Science,
92 Acharya Prafulla Chandra Road,
Calcutta-700 009 India.

AJAY K. CHATTERJEE
AMITABHA D. RAY

May 16, 1973

REFERENCES

APPELT, G. D. & HEIM, H. C. (1968). *J. pharm. Sci.*, **57**, 1428–1430.
BELLER, B. M. (1968). *Circulation Res.*, **22**, 501–505.
CHANG, H. Y., YNAN, C. J., MO, P. S. & CHUNG, H. L. (1966). *Chem. Abstr.*, **65**, 14222.
CHATTERJEE, A. K., ROY, A. D., DUTTA, S. C. & GHOSH, B. B. (1970). *Experientia*, **26**, 1077–1078.
CHATTERJEE, A. K., ROY, A. D., DATTA, S. C. & GHOSH, B. B. (1971). *Ind. J. Physiol.*, **25**, 43–46.
CHATTERJEE, A. K., DATTA, S. C. & GHOSH, B. B. (1972). *Br. J. Pharmac.*, **44**, 810–813.
CHATTERJEE, A. K., JAMDAR, S. C. & GHOSH, B. B. (1966). *Experientia*, **22**, 794–795.
DEITRICH, R. A. & HEIM, H. C. (1956). *J. Am. pharm. Assoc.*, **45**, 562–563.
GROLLMAN, A. P. (1966). *Proc. natn. Acad. Sci. U.S.A.*, **56**, 1867–1874.
GROLLMAN, A. P. (1968). *J. biol. Chem.*, **243**, 4089–4094.
GROLLMAN, A. P. (1970). *The Ohio State J.*, **66**, 257–259.
JONDORF, W. R. & SZAPARY, D. (1968). *Archs Biochem. Biophys.*, **126**, 892–904.
MARINO, A. & MAGLIULO, S. (1961). *Archs int. Pharmacodyn. Thér.*, **132**, 331–338.
TONHAZY, N. E., WHITE, N. G. & UMBREIT, W. W. (1950). *Arch. Biochem.*, **28**, 36.

Effect of some lipid-soluble derivatives of amphetamine on amphetamine levels in rat brain

Jonsson & Gunne (1972) observed that amphetamine levels in brain after injection of (+)-amphetamine into rats were higher when the rats had been pretreated with fenfluramine. Jonsson (1972) showed that fenfluramine, norfenfluramine, and *N*-(2-benzoyloxyethyl) norfenfluramine inhibited the *para*-hydroxylation of amphetamine. The lipid-soluble character of the drugs seemed to be a factor in the inhibition but two other lipid-soluble derivatives of amphetamine (4-chloroamphetamine and 4-chloromethamphetamine) were unable to block the *para*-hydroxylation of amphetamine, a finding that led Jonsson to propose that both lipid-solubility and an unoccupied *para* position on the ring were requirements for inhibition.

We have compared 2-chloro, 3-chloro-, and $\beta\beta$-difluoro-amphetamine, which are lipid-soluble derivatives with an unoccupied *para* position, fenfluramine, 4-chloroamphetamine and 3-trifluoromethyl-α-methylbenzylamine, the next lower homologue of norfenfluramine, on amphetamine levels in tissues.

Male albino Wistar rats, 130–155 g, were given (+)-amphetamine sulphate (SKF) (5 mg kg^{-1}, i.p.) to which (+)-[^{3}H] amphetamine sulphate (New England Nuclear) had been added to give a specific activity of 2 μCi mg^{-1}. Two h later, the rats were decapitated, and the brain, liver, and whole blood were immediately removed. Amphetamine levels were measured by extraction of the radioactive amine from

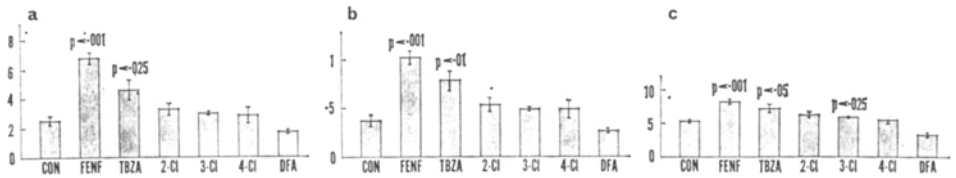

FIG. 1. Amphetamine levels in rat tissues 2 h after 5 mg kg^{-1} i.p. of (+)-[^{3}H]amphetamine sulphate. Mean amphetamine levels in μg of amphetamine per g (wet weight) of tissue (ordinate) with s.e. are shown for 5 rats per group. Drugs that had been injected at 10 mg kg^{-1}, i.p. 1 h before the amphetamine were: Control = saline, FENF = fenfluramine, TBZA = 3-trifluoromethyl-α-methylbenzylamine, 2-Cl = 2-chloroamphetamine, 3-Cl = 3-chloroamphetamine, 4-Cl = 4-chloroamphetamine, and DFA = $\beta\beta$-difluoroamphetamine.

a. Brain. b. Blood. c. Liver.

alkaline aqueous medium into benzene followed by liquid scintillation spectrometry (Fuller & Hines, 1967). Deaminated and ring hydroxylated metabolites are not extracted by this procedure. The test drug (at a dose of 10 mg kg^{-1}) or saline was given intraperitoneally 1 h before the amphetamine. All injection volumes were 1 ml kg^{-1}. Fenfluramine was from A. H. Robins, and 4-chloroamphetamine was from Regis Chemical Company. All other compounds were synthesized in The Lilly Research Laboratories.

Fig. 1 shows amphetamine levels in brain, blood, and liver. Both fenfluramine and 3-trifluoromethyl-α-methylbenzylamine significantly increased the levels of amphetamine in rat brain (Fig. 1a) and blood (Fig. 1b) and also in liver (Fig. 1c) but these increases were smaller although statistically significant.

The fact that amphetamine levels were increased by fenfluramine and by 3-trifluoromethyl-α-methylbenzylamine in all three tissues supports the idea that the effects were due to an inhibition of amphetamine metabolism. The inability of the chloroamphetamines to act similarly indicates that lipid-solubility and an unoccupied *para* position alone are not sufficient to interfere with the metabolism of amphetamine. $\beta\beta$-Difluoroamphetamine, a derivative of amphetamine so highly lipid-soluble that it localizes chiefly in adipose tissue *in vivo* (Fuller & Molloy, 1971) also was without effect on amphetamine levels. On the other hand, 3-trifluoromethyl-α-methylbenzylamine having one methylene unit less than norfenfluramine in the side chain, was able to elevate amphetamine levels. These results suggest that inhibition of amphetamine metabolism is not simply a consequence of the structural similarity of the two inhibitors to that of amphetamine but is a property that they share with agents like imipramine, desipramine, and chlorpromazine, all of which are known to retard the transport of other monoamines across cellular membranes and to inhibit amphetamine metabolism. A common mechanism of action by which all of these drugs inhibit amphetamine metabolism may involve antagonism of amphetamine transport across a membrane to the locus of hydroxylation.

The Lilly Research Laboratories,
Eli Lilly and Company,
Indianapolis, Indiana U.S.A.

RAY W. FULLER
HAROLD D. SNODDY
BRYAN B. MOLLOY

April 26, 1973

REFERENCES

FULLER, R. W. & HINES, C. W. (1967). *Biochem. Pharmac.*, **16**, 11–16.
FULLER, R. W. & MOLLOY, B. B. (1971). *The Pharmacologist*, **13**, 294.
JONSSON, J. (1972). *J. Pharm. Pharmac.*, **24**, 821–823.
JONSSON, J. & GUNNE, L.-M. (1972). *Eur. J. Pharmac.*, **19**, 52–55.