The relationship between fenfluramine and norfenfluramine blood levels and anorectic activity in the rat

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The central anorectic activity of fenfluramine is thought, in contrast to the amphetamines, to be mediated through the serotonergic neurones, although the exact locus of cerebral activity is unknown (Blundell & Lesham, 1974). There is increasing evidence to show that the de-ethylated metabolite of fenfluramine, norfenfluramine, possesses marked central (Broekkamp, Weemaes & van Rossum, 1975) and peripheral (Kirby, 1974) properties and could account for the total activity. This supposition was investigated by comparing in two experiments the combined anorectic activity of fenfluramine and norfenfluramine after fenfluramine administration and the anorectic activity of norfenfluramine alone when given at a dose which produces the same blood level as measured following fenfluramine administration.

Male, Black-Hooded rats (n = 6) were tested for food intake, using the procedure of Blundell, Campbell, Lesham & Tozer (1975) following intraperitoneal injection of ± fenfluramine HCl (10 mg kg^{-1}) or saline control (0.9 w/v NaCl). Thirty minutes after the injection, the food consumption of the animals was measured at 1, 4, 8 and 24 h after ingestion. Blood was taken from a second set of animals kept under identical conditions to the first by cardiac puncture for the measurement of fenfluramine and norfenfluramine. The peak reduction in food intake (75% over control) occurred at 1 h and remained at approximately the same intensity for approximately 24 hours. Fenfluramine blood levels peaked at 1 h (1.00 μg/ml) but rapidly declined with a half-life of 2.6 hours. Norfenfluramine levels were lower at 1 h (0.22 μg/ml) rising to a peak at 4 h (0.060 μg/ml) and then gradually declining with a half-life of 14 hours. The best fit of anorectic potency was given by the sum of the norfenfluramine and fenfluramine blood levels.

The second experiment was undertaken to investigate the contribution of norfenfluramine in the initial anorectic activity of fenfluramine. Four doses of norfenfluramine, 1, 2.0, 2.5 and 3.0 mg/kg were administered intraperitoneally to four groups of animals (n = 5). Blood samples were collected after one hour. A linear relationship was found between the dose and the 1 h blood level. The dose which produced a 1 h concentration of 0.22 μg/ml, equivalent to that which occurred after fenfluramine administration, was calculated to be between 1-2 mg/kg.

Under the same conditions as for the first experiment, it was shown that administration of norfenfluramine alone (2 mg/kg) produced a 28% reduction in food intake after one hour. This is statistically lower ($P < 0.01$) than that produced after fenfluramine administration, 75%, although both these injections gave rise to approximately the same norfenfluramine blood level.

From these results, it seems likely that fenfluramine itself plays a major role in the initial anorectic potency of the drug but the prolonged activity of fenfluramine in the rat is mediated by the active metabolite, norfenfluramine.

References

BLUNDELL, J.E. & LESHAM, M.B. (1974). Central action of anorexic agents: Effects of Amphetamine and Fenfluramine in rats with lateral hypothalamic lesions. *Europ. J. Pharmac.*, **28**, 81-88.

BLUNDELL, J.E., CAMPBELL, D.B., LESHAM, M.B. & TOZER, R. (1975). Comparison of the time course of the anorectic effect of fenfluramine and amphetamine with drug levels in blood. *J. Pharm. Pharmac.*, **27**, 187-192.

BROEKKAMP, C.L.E., WEEMAES, A.J.M. & VAN ROSSUM, J.M. (1975). Does fenfluramine act via norfenfluramine? *J. Pharm. Pharmac.*, **27**, 129-130.

KIRBY, M. (1974). Dose related effect of fenfluramine and norfenfluramine on glucose uptake into human isolated skeletal muscle. *Br. J. clin. Pharmac.*, **1**, 511-512.