J. Pharm. Pharmac., 1968, **20**, 364–367 Received December 27, 1967

The depletion and recovery of noradrenaline in the brain and some sympathetically innervated mammalian tissues after tetrabenazine

JAN HÄGGENDAL

The depleting effect of tetrabenazine on the monoamine levels appears generally to be less in peripheral tissues than in the central nervous system. The noradrenaline levels in brain and some sympathetically innervated tissues such as heart, submandibular glands, and skeletal muscle were examined in the rat after administration of the drug. The levels of 5-hydroxytryptamine, dopamine and noradrenaline were also estimated in the rabbit brain after tetrabenazine and compared with the levels in the rabbit heart. In both the brain and peripheral tissues the monoamine levels were strongly reduced 4 hr after tetrabenazine and increased thereafter, reaching normal levels after about 36 to 48 hr. The site of action of tetrabenazine is briefly discussed and compared to the site of action of reserpine.

CERTAIN benzoquinolizine derivatives like tetrabenazine cause sedation and reduce the levels of noradrenaline and 5-hydroxytryptamine (5-HT) in brain (Pletscher, Besendorf & Bächthold, 1958; Pletscher, Besendorf & Gey, 1959; Pletscher, Brossi & Gey, 1962; Quinn, Shore & Brodie, 1959). Tetrabenazine thus has several features in common with reserpine (Carlsson, 1965). When tetrabenazine is given before reserpine it partially affords protection against the long-lasting reserpine effects on the monoamine levels in brain, and in addition it antagonizes the effect of reserpine upon the gross behaviour. This indicates that the two drugs compete for the same site of action (Quinn & others, 1959; Carlsson & Lindqvist, 1966).

The effect of tetrabenazine on monoamine levels has been reported to be less pronounced in peripheral tissues than in the brain (Pletscher & others, 1962; Carlsson, 1965). Relatively high doses of tetrabenazine given to rabbits or guinea-pigs do not cause much reduction in the levels of 5-HT in blood platelets or small intestines (Quinn & others, 1959; Schwartz, Pletscher & others, 1960). On the heart, however, the results are inconsistent. In rabbits given 50 mg/kg intravenously, noradrenaline levels were found to be unchanged 4 and 24 hr later (Quinn & others, 1959). But in the guinea-pig 20 mg/kg intraperitoneally decreased the noradrenaline levels in heart and brain to about the same extent so that the levels between 1 and 4 hr after tetrabenazine administration were about half the normal (Schwartz & others, 1960).

With the histochemical fluorescence technique of Hillarp & others (see Corrodi & Jonsson, 1967) tetrabenazine has been shown to have a depleting effect in the peripheral tissues of the rat and mouse. The fluorescence of noradrenaline accumulated proximal to a ligation of the rat sciatic nerve disappears 4 to 8 hr after tetrabenazine, 100 mg/kg (Dahlström, 1966, 1967). It has also been observed that after tetrabenazine the noradrenaline fluorescence in the iris and vas deferens

From the Department of Pharmacology, University of Göteborg, Göteborg, Sweden.

of the rat disappears (Malmfors, and also Norbert & Hamberger, personal communication).

The purpose of the present investigation has been to compare quantitatively the effect of tetrabenazine on the noradrenaline levels in brain and some sympathetically innervated tissues such as heart, submandibular glands, and skeletal muscle in rat. The levels of 5-HT, noradrenaline and dopamine in rabbit brain were also compared with the noradrenaline levels in the heart after administration of tetrabenazine.

Experimental

MATERIAL AND METHODS

Experiments were made on male albino rats of the Sprague-Dawley strain, weighing about 250 g, and on albino rabbits of either sex, weighing about 2 kg. Tetrabenazine was given intraperitoneally (100 mg/kg) to the rats and intravenously (50 mg/kg in single or repeated injections) to the rabbits. The animals were killed at various intervals after the injections. The experiments were done at room temperature (21–23°). Noradrenaline was estimated fluorimetrically (Bertler, Carlsson & Rosengren, 1958; Häggendal, 1963). Dopamine was estimated according to Carlsson & Waldeck (1958) with the modifications of Carlsson & Lindqvist (1962). The 5-HT estimation (Bertler, 1961) was modified in that the perchloric acid residue was re-extracted once with 0·4N perchloric acid.

Results

The results of the noradrenaline estimation on different tissues from rat are shown in Fig. 1. The values are given as per cent of normal values. Four hr after the administration of the drug, values were very low; the

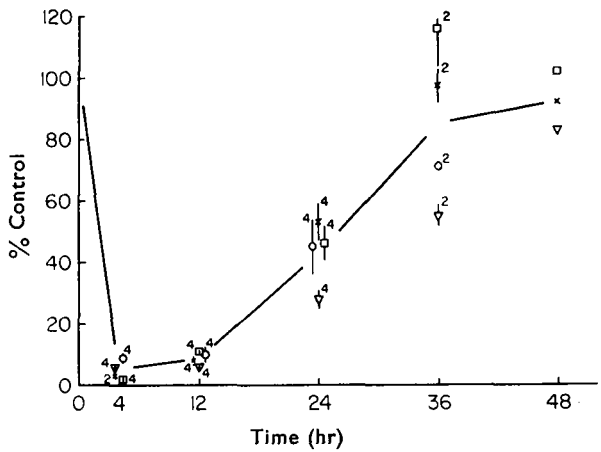

FIG. 1. The noradrenaline levels in per cent of normal values in rat brain (×), heart (▽), submandibular gland (□), and skeletal muscle (○) after tetrabenazine 100 mg/kg body weight, i.p. Means ± s.e. Small figures indicate number of observations.

mean being less than 10% of the normal levels in all the tissues. The levels increased similarly for the different tissues and were about normal 36 to 48 hr after the administration.

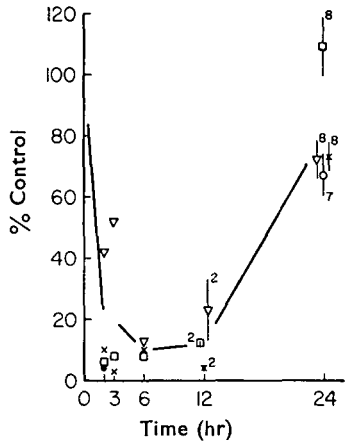

FIG. 2. The brain levels of noradrenaline (×), dopamine (□), and 5-hydroxytryptamine (○), and the heart levels of noradrenaline (▽) in per cent of normal values in rabbits after tetrabenazine 50 mg/kg body weight, i.v. in a single injection. 3 hr values: 50 + 50 mg/kg were given at an interval of 1½ hr and the animal was killed 3 hr after the first injection. 12 hr values: 50 mg/kg were given 4 times at an interval of 3 hr and the animals were killed 12 hr after the first injection. At 2 hr also the noradrenaline in skeletal muscle (●) was estimated. The points are single observations except at 12 and 24 hr where the values are means ± s.e. Small figures indicate number of observations.

The results from the estimation on rabbits are shown in Fig. 2. A similar pattern was found for the changes of the noradrenaline levels in the rabbits as in the rats. Dopamine and 5-HT in rabbit brain were changed in about the same way as noradrenaline. However, the dopamine level after 24 hr was higher than the noradrenaline level.

Discussion

The present results showed only small differences between the noradrenaline changes in brain and sympathetically innervated tissues after tetrabenazine. The doses used were high, being the same as those used by Quinn & others (1959) when they reported little or no noradrenaline depletion in peripheral tissues of rabbits. Differences in strain may be of importance for the explanation of the different results.

These results do not support the suggestion that tetrabenazine should have a relatively specific action on the central nervous system. That tetrabenazine has only a weak effect on the blood pressure compared with the effect of reserpine cannot be explained by suggesting that tetrabenazine has mainly a central nervous effect while reserpine acts centrally and peripherally.

Tetrabenazine, like reserpine, causes *in vitro* release of platelet 5-HT (Paasonen & Pletscher, 1959) and blockade of the specific storage mechanism of adrenal medullary granules (Carlsson, Hillarp & Waldeck, 1963). The two drugs probably have the same site of action (Carlsson & Lindqvist, 1966). After reserpine the noradrenaline stores in different tissues recover to normal values only after several weeks. The recovery after tetrabenazine, however, takes place within about 48 hr. Reserpine's action is thought to be irreversible so that normal levels depend upon the transport to the nerve terminals of fresh granules synthesized in the cell body of the neuron (Dahlström & Häggendal, 1966). The effect of tetrabenazine on amine storage granules appears, however, to be short-lasting and pronounced in both central and peripheral tissues.

Acknowledgements. I would like to express my gratitude to Prof. A. Carlsson and Miss M. Lindqvist for permission to include their results of monoamine estimations on rabbits after tetrabenazine treatment, and to Dr. A. Dahlström for help and discussions. For technical assistance I wish to thank Miss A. Wilén. For generous supply of tetrabenazine I am indebted to Roche-Produkter AB, Stockholm. The study was supported by the Swedish State Medical Research Council (grants B67-14X-166-03 and B68-14X-166-04).

References

Bertler, Å. (1961). *Acta physiol. scand.*, **51**, 75–83.
Bertler, Å., Carlsson, A. & Rosengren, E. (1958). *Ibid.*, **44**, 273–292.
Carlsson, A. (1965). *Handb. exp. Pharmak.*, **19**, 529–592.
Carlsson, A., Hillarp, N.-A. & Waldeck, B. (1963). *Acta physiol. scand.*, **59**, *Suppl.* 215.
Carlsson, A. & Lindqvist, M. (1962). *Ibid.*, **54**, 87–94.
Carlsson, A. & Lindqvist, M. (1966). *Acta pharmac. tox.*, **24**, 112–120.
Carlsson, A. & Waldeck, B. (1958). *Acta physiol. scand.*, **44**, 293–298.
Corrodi, H. & Jonsson, G. (1967). *J. Histochem. Cytochem.*, **15**, 65–78.
Dahlström, A. (1966). *M.D. Thesis*, Stockholm.
Dahlström, A. (1967). *Acta physiol. scand.*, **69**, 167–179.
Dahlström, A. & Häggendal, J. (1966). *J. Pharm. Pharmac.*, **18**, 750–752.
Häggendal, J. (1963). *Acta physiol. scand.*, **59**, 242–254.
Paasonen, M. K. & Pletscher, A. (1959). *Experientia*, **15**, 477.
Pletscher, A., Besendorf, H. & Bächthold, H. P. (1958). *Arch. exp. Path. Pharmak.*, **232**, 499–507.
Pletscher, A., Besendorf, H. & Gey, K. F. (1959). *Science, N.Y.*, **129**, 844.
Pletscher, A., Brossi, A. & Gey, K. F. (1962). *Int. Rev. Neurobiol.*, **4**, 275–306.
Quinn, G. P., Shore, P. A. & Brodie, B. B. (1959). *J. Pharmac. exp. Ther.*, **127**, 103–109.
Schwartz, D. E., Pletscher, A., Gey, K. F. & Rieder, J. (1960). *Helv. physiol. pharmac. Acta*, **18**, 10–16.