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The Influence of Glucocorticoids on Plasma Cholinesterase (38219)

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An about 50% decrease of plasma butyrylcholinesterase (acylcholine acyl hydrolase; EC 3.1.1.8; BuChE) activity developed in 12 days in patients who received relatively large (50–100 mg) daily oral doses of prednisone. After tapering the dose of prednisone to 10–15 mg per day, BuChE activities gradually returned in 30–60 days toward their pretreatment values (Zarday, Z., and Foldes, F. F., unpublished data). These findings strongly suggested that the decrease of BuChE activity was caused by prednisone. To investigate the validity of this assumption the effects of glucocorticoids on BuChE and AChE were investigated in dogs.

Materials and Methods. A group of 4 mongrel dogs (2 males and 2 females) were injected subcutaneously, 2 mo apart, first with 10 mg/kg methylprednisolone and subsequently with 2 mg/kg dexamethasone per day for 12 consecutive days. After discontinuation of the injections the animals were observed until their BuChE activity became stabilized at or near control levels.

BuChE activity was determined with acetylcholine (ACh) and benzoylcholine (BeCh) and AChE activity with acetyl-β-methylcholine (MeCh) substrates using a 0-point potentiometric titration method (pH-Stat, Radiometer, Copenhagen). Heparinized blood samples were centrifuged at 1000g for 15 min. The plasma was removed, red cells were washed twice with 0.9% NaCl and then hemolyzed with equal volume of distilled water. The volume of the assay system was 2 ml. The final plasma and red cell dilutions were 1:10 and 1:20 respectively and the substrate concentrations were 2×10^{-2} with ACh and BeCh and 10^{-2} M with MeCh. For the determination of AChE activity 0.5 M NaCl was added to the system to obtain optimal rates. Determinations were carried out in duplicates at pH 7.4 and 37°. Correction was made for nonenzymatic hydrolysis. Enzyme activities were expressed as μmol substrate hydrolyzed by 1 ml plasma or red cell per hour. The results were tested for significance with Student's t test.

Results. The findings presented in Fig. 1 indicate that during the administration of both methylprednisolone and dexamethasone there was a significant fall in the hydrolysis rate of both substrates by BuChE. After discontinuation of the corticoid administration BuChE activity gradually returned towards pretreatment levels. There was no change in AChE activity during or after the administration of either drug.

Discussion. There are several possible explanations for the decreased BuChE activity encountered after the administration of glucocorticoids. These compounds may conceivably inhibit BuChE, stimulate the synthesis of a biological inhibitor, interfere with its synthesis in the liver or increase its rate of degradation.

In vitro glucocorticoids did not inhibit either BuChE or AChE; neither did the admixture of plasma samples from patients or dogs in whom BuChE activity has been depressed by glucocorticoids inhibit *in vitro* BuChE activity of normal human plasma.

Plasma BuChE is synthetized in the liver (1) and in man has a half life of about 9 days (2). Therefore, the finding that BuChE activity of patients decreased by about 50%

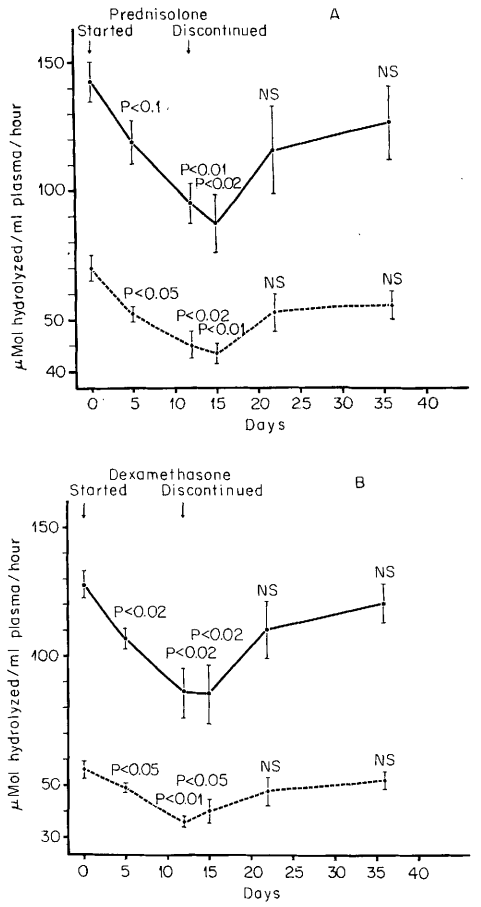

FIG. 1. Reversible depression of plasma butyrylcholinesterase (BuChE) activity by prednisolone (A) or dexamethasone (B). Means ± S.E. of plasma BuChE activities in 4 dogs who received daily subcutaneous injections of 10 mg/kg methylprednisolone or 2 mg/kg dexamethasone for 12 days. Solid line acetylcholine, broken line benzoylcholine substrate ($2 \times 10^{-2} M$).

after 12 days of prednisone administration could be interpreted as presumptive evidence of the almost complete inhibition of BuChE synthesis by this compound. Inhibition of the synthesis of nucleic acids and proteins by glucocorticoids in lymphoid tissues, both *in vivo* and *in vitro,* had been reported (3, 4). In the liver, however, instead of depression, glucocorticoids were found to cause a marked increase in the rate of synthesis of RNA (5, 6) and proteins (5–7), including certain enzymes, such as transaminases (8, 9).

The findings presented indicate that glucocorticoids, similarly to their effect on lymphoid tissues, are capable of depressing the activity of at least one enzyme, BuChE, synthetized in the liver. Although BuChE has no known physiological function, it has considerable pharmacological significance. It is the enzyme that hydrolyzes the widely used neuromuscular blocking agent, succinylcholine chloride (10, 11) and the ester-type local anesthetics, for example, procaine hydrochloride or tetracaine hydrochloride (13, 14). Significant decrease of BuChE activity may increase the intensity and duration of action of hydrolyzable muscle relaxants (15–17) and the systemic toxicity of ester-type local anesthetic agents (18).

It remains to be determined whether the depression of the synthesis of BuChE by glucocorticoids is a specific process, or the synthesis of other proteins and perhaps, also, other functions of the liver are also depressed by these compounds.

Summary. The daily subcutaneous injection of 10 mg/kg methyl-prednisolone or 2 mg/kg dexamethasone for 12 days to mongrel dogs caused a significant decrease of plasma butyrylcholinesterase (BuChE) activity. BuChE activity returned toward predrug values after discontinuation of glucocorticoids. There were no changes in erythrocyte AChE activity.

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1. Sawyer, C. H., and Everett, J. W., Amer. J. Physiol. **148**, 675 (1947).

2. Jenkins, T., Balinsky, D., and Patent, D. W., Science **156**, 1748 (1967).

3. Makman, M. H., Nakagawa, S., and White, A., Recent Prog. Horm. Res., **23**, 195 (1967).

4. Kornel, L., Acta Endocrinologica 74, Suppl. **178**, 1 (1973).

5. Feilgelson, M., Gross, P. R., and Feigelson, P., Biochim. Biophys. Acta (Amst) **55**, 495 (1962).

6. Yu, F. L., and Feilgelson, P. L., Program III Int. Congr. Hormonal Steroids, Excerpta med. (Amst) Int. Congr. Series No. **210**, 29 (1970).

7. Clark, I., J. Biol. Chem. **200**, 69 (1953).

8. Kenney, T. F., and Flora, R. M., J. Biol. Chem. **236**, 2699 (1961).

9. Raina, P. N., and Rosen, F., Biochem. Biophys. Acta (Amst) **165**, 470 (1968).

10. Glick, D., J. Biol. Chem. **137**, 357 (1941).

11. Whittaker, V. P., and Wijesundera, V., Biochem. J. **52**, 475 (1952).

12. Tsuji, F. I., Foldes, F. F., and Rhoades, D. H., Jr., Arch. Int. Pharmacodyn. Ther. **104**, 146 (1955).

13. Kalow, W., J. Pharmacol. Exp. Therap. **104**, 122 (1952).

14. Foldes, F. F., Davis, D. L., Shanor, S., and Van Hees, G., J. Amer. Chem. Soc. **77**, 5149 (1955).

15. Evans, F. T., Gray, P. W. S., Lehmann, H., and Silk, E., Lancet **1**, 1229 (1952).

16. Foldes, F. F., Swerdlow, M., Lipschitz, E., Van Hees, G. R., and Shanor, S., Anesthesiology **17**, 559 (1956).

17. Foldes, F. F., Foldes, V. M., Smith, J. C., and Zsigmond, E. K., Anesthesiology **24**, 208 (1963).

18. Foldes, F. F., Molloy, R., McNall, P. G., and Koukal, L. R., J. Amer. Med. Ass. **172**, 1493 (1960).

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