their original "hormonal activities". Some of these compounds, e.g., pregnanolone (a metabolite of progesterone) or the ring A-reduced form of deoxycorticosterone were in some tests up to ten times more active than barbiturates. In the liver, these metabolites are however also esterified, become less lipid soluble and lose hypnotic activity. Interest in the physiology of the hypnotic properties of steroids was revived when it was found that they can be produced and secreted into the blood stream at sites from where they can reach the brain without having to pass first through the liver. For example, the ovary of the rat can produce several ring A-reduced steroids in quantities similar to or even larger than those of progesterone (Holzbauer, 1969, 1971a; Holzbauer & Mason, 1970; Ichikawa, Morioka & Sawada, 1971). Their rate of production and secretion varies during the oestrous cycle and it has been suggested that phase dependent changes in mood or behaviour during the sexual cycle can be caused by these reduced steroids (Holzbauer, 1971b). In addition it may be possible that they depress the activity of those hypothalamic neurons which stimulate the release of the luteinizing hormone releasing factor and may thus play a major role in a feed back system. Observations on their secretion during pregnancy and other factors which influence their production rate will be discussed.

References

HOLZBAUER, M. (1969). Pregnenolone and metabolites of progesterone in the ovary. *J. Physiol.*, **204**, 8-10P.

HOLZBAUER, M. (1971a). Ovarian secretion of steroids with central depressant actions. *J. Physiol.*, **215**, 16P.

HOLZBAUER, M. (1971b). *In vivo* production of steroids with central depressant actions by the ovary of the rat. *Br. J. Pharmac.*, **43**, 560-569.

HOLZBAUER, M. & MASON, P. (1970). Increase in the ovarian content of progesterone metabolites during late proestrus in the rat. *J. Physiol.*, **210**, 128-130P.

ICHIKAWA, S., MORIOKA, H. & SAWADA, T. (1971). Identification of the neutral steroids in the ovarian venous plasma of LH-stimulated rats. *Endocrinology*, **88**, 372-383.

γ-Aminobutyric acid metabolism and the anticonvulsant action of ethanolamine-o-sulphate and di-n-propylacetate

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We have evaluated the anticonvulsant effects of ethanolamine-o-sulphate (EOS) and di-n-propyl acetate (DPA) in two test systems, audiogenic seizures in genetically susceptible mice (DBA/2, 21-25 days old) and picrotoxin-induced seizures in chicks (5-6 days old, Rhode Island Red) and correlated changes in behaviour and seizure response to changes in brain γ-aminobutyric acid (GABA) concentration and the activity of enzymes involved in GABA catabolism.

In mice EOS was administered intracerebroventricularly 24 h before test. At 7.5 mg/kg 50% of the animals and at 15 mg/kg 80% showed mild to moderate ataxia and were completely protected against the convulsant effect of auditory stimulation. The remainder showed no behavioural effects, and were not protected or showed partial protection against audiogenic stimulation. GABA transaminase (GABA-t) activity was inhibited 54% and 68% and cerebral GABA concentration increased 4 and 10 fold, after 7.5 and 15 mg/kg respectively. Succinic semialdehyde dehydrogenase (SSADH) activity was not altered.

In chicks, EOS (300 or 600 mg/kg given i.p. 48 h earlier) inhibited GABA-t activity by 54-59% and doubled brain GABA concentration but only raised the ED_{50} for picrotoxin seizures by 30-40% (not significant).

In mice, DPA was administered i.p. 45 min before test. Seizure responses were unaffected at 200 mg/kg, severely reduced at 400 mg/kg and completely absent at 600 mg/kg. Slight behavioural effects were seen only after 600 mg/kg. GABA concentration and GABA-t activity were unchanged after 200 or 400 mg/kg. GABA concentration was increased by 57% and GABA-t activity inhibited by 33% after 600 mg/kg. SSADH activity was unchanged.

In chicks, DPA (400 or 800 mg/kg i.p., 0.5-1 h before test) produced a 33% or 100% increase respectively in the ED_{50} for picrotoxin seizures. Brain GABA concentration was increased 16-30%, but GABA-t was inhibited only by 4-6%.

DPA is claimed to be a competitive inhibitor of GABA-t *in vitro* (Simler, Ciesielski, Maitre, Randrianarisoa & Mandel, 1973). Our results with mouse brain homogenates show that DPA is a poor

in vitro inhibitor of GABA-t, but a potent competitive inhibitor of SSADH activity, confirming the findings of Harvey, Bradford & Davison (1975).

In these mouse and chick test systems it is difficult to relate the anticonvulsant properties of the two compounds to changes in the metabolism of GABA. The quantitatively smaller changes seen after DPA compared to EOS might be at physiologically more important sites. However there is clearly no correlation between anticonvulsant action and the accumulation of GABA in the brain.

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References

HARVEY, P.K.P., BRADFORD, H.F. & DAVISON, A.N. (1975). The inhibitory effect of sodium n-dipropylacetate on the degradative enzymes of the GABA shunt. *Febs Letts,* **52**, 251-254.

SIMLER, S., CIESIELSKI, L., MAITRE, M. RANDRIANARISOA, H. & MANDEL, P. (1973). Effect of sodium n-dipropylacetate on audiogenic siezures and brain γ-aminobutyric acid level. *Biochem Pharmacol.,* **22**, 1701-1708.