Effect of short- and long-term administration of some anticonvulsant drugs on the folate content of rat brain

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Because folate deficiency is not infrequently seen in the serum and cerebrospinal fluid of epileptic patients treated with diphenylhydantoin, phenobarbitone or primidone and because the antiepileptic effects of these drugs can be partially reversed by folic acid, Reynolds, Chanarin, Milner & Matthews (1966) suggested that the therapeutic action of some anticonvulsant agents might be related to an effect on folate metabolism.

Wistar albino rats were made physically dependent on barbitone sodium by adding the drug to their drinking water in progressively increasing amounts, following the method of Crossland & Leonard (1963). After five weeks, the daily intake of barbitone averaged 400 mg/kg. Withdrawal of the drug at this stage was followed, some 12 to 18 h later, by the appearance of hypersensitivity to auditory stimuli, the animals suffering epileptiform seizures in response to the sound of a bell.

The folate content of the brains of untreated rats ranged from 675 to 700 ng/g but by the end of the five-weeks period of barbitone administration it had fallen to some 550 ng/g. After withdrawal of drug, the brain rapidly accumulated folate again, the concentration reaching more than 900 ng/g by the time that seizure susceptibility was at its height. All these changes in folate concentration were statistically significant at the 1% level.

Rats given phenobarbitone (up to 200 mg/kg) in their drinking water for six weeks also showed hyperexcitability when the drug was withdrawn. The concentration of folate in their brains reached a peak (comparable in size to that seen in rats withdrawn from sodium barbitone) at the time when seizure susceptibility was at its height. There was, however, no significant reduction in the concentration of folate in whole brain during the period of drug administration. Subsequent experiments revealed that this lack of effect in whole brain arose because a depression in the folate content of the cerebral hemispheres was countered by a corresponding increase in that of the cerebellum. Carbamazepine and diphenylhydantoin had essentially the same effects as phenobarbitone.

Single i.p. doses of the anticonvulsant drugs had no effect on the folate content of brain and changes in the folate content of serum were not detected at any time.

References

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Antiepileptic drugs and monoamine metabolism in the brain

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Single intraperitoneal doses of phenobarbitone (100 mg/kg), diphenylhydantoin (75 mg/kg), carbamazepine (50 mg/kg) and sodium bromide (1 g/kg) had no effect on the dopamine and noradrenaline contents of rat brain measured 30 min and 1 h after injection. Twice-daily doses of the same drugs, given for four weeks, also failed to influence the amount of dopamine or noradrenaline in the brain. However, when they were given simultaneously with α-methyl-*p*-tyrosine (250 mg/kg), phenobarbitone and sodium bromide significantly reduced the extent to which brain dopamine was depleted by the aminoacid alone. The other anticonvulsant drugs were ineffective in this respect and none was able to influence the extent to which α-methyl-*p*-tyrosine depleted the brain's noradrenaline content. The amount of dopamine and noradrenaline in the brains of animals withdrawn from phenobarbitone treatment was significantly less than that in the brain of habituated and control animals. Habituation to phenobarbitone decreased and withdrawal increased the depletion of dopamine brought about by α-methyl-*p*-tyrosine.

Single doses of the anticonvulsant drugs did not affect the 5-hydroxytryptamine content of brain and only diphenylhydantoin brought about a significant increase in the amount of 5-hydroxyindoleacetic acid in brain. Phenobarbitone significantly reduced the rate at which the concentration of 5-hydroxytryptamine rose in the brains of rats given pargyline (100 mg/kg) while carbamazepine and diphenylhydantoin reduced the extent to which the 5-hydroxyindoleacetic acid was depleted by pargyline.