such differences have not yet been revealed by spectral studies. Alternatively, phenobarbital and PCN may differentially affect other components of the mixed-function oxidase system or its microenvironment.

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Selectivity of pentylenetetrazol on brain monoamine metabolism

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IT IS WELL established that drugs which lower monoamine concentrations in brain tissue lower seizure threshold, and drugs which increase these levels increase threshold.[1] These data have suggested that a relationship exists between brain monoamine metabolism and seizure activity. To investigate this, we have studied the effects of pentylenetetrazol alone and in conjunction with seizures on brain monoamine metabolism. We have estimated the effects of pentylenetetrazol on the metabolism of monoamines in feline brain tissue *in vivo* after doses which did little to change behaviour and after those which produced frank clonic convulsions. Because changes in monoamine metabolite concentrations in cerebrospinal fluid (CSF)[2–5] are thought to reflect changes in central monoamine-mediated activity, we have examined these metabolites in serial samples of cisternal cerebrospinal fluid of the cat.

Cats were caged individually in a room maintained at 23–24° with lights on from 7:00 a.m. to 7:00 p.m. They were observed, and rectal temperature was monitored from 9.00 a.m. to 6.00 p.m. during control and experimental periods. Cats were divided into four groups and cannulas were implanted[6] into the cisterna magna which permitted repeated sampling of CSF from the unanesthetized animal. We assayed[7,8] for the major brain metabolites of 5-hydroxytryptamine and dopamine, 5-hydroxyindolacetic acid (5-HIAA) and homovanillic acid (HVA), respectively, which exit from brain via CSF.[5] During a control period, 1·0 ml samples of CSF were withdrawn (four to five/day) at intervals not less than 2 hr. Experimental samples were withdrawn at the same times of day used in the control period and the percentage change from control absolute concentration was individually determined for each cat. Thus, each cat served as his own control. The mean and variation of the experimental samples for each group and for similar times of day

were calculated and compared to the variation of the control samples for that group of cats using the paired *t*-statistic.

An analysis of variance on the samples withdrawn during the control period showed that 5-HIAA and HVA did not change significantly from the values of 117·4 ± 14·1 μg/ml and 121·4 ± 12·8 μg/ml, respectively (eighty samples of CSF obtained from eleven cats; mean ± S. E., n = 11), after saline injection. Nor was the concentration of these metabolites affected by the frequency of sampling nor by the time of day.

Pentylenetetrazol was administered intraperitoneally in non-convulsant (10 mg/kg or 20 mg/kg), threshold (30 mg/kg) or convulsant (50 mg/kg) doses, and CSF was withdrawn 0·25, 2, 4, 6 and 24 hr after injection.

The lowest dose of pentylenetetrazol produced no changes in behavior, rectal temperature or significant alterations in metabolite concentration in CSF. The dose of 20 mg/kg produced agitation and panting, which lasted for 30–45 min; the rectal temperature dropped 1·0 to 1·5° in 45 min, but returned to control values within 2 hr. The top panel of Fig. 1 shows that this dose of pentylenetetrazol increased the 5-HIAA concentration but not that of HVA. The 5-HIAA concentration reached a maximum of 102·8 ± 47·3 per cent (mean of three cats ± S. E.) 4 hr after injection and remained above control values 24 hr later. Animals receiving 30 mg/kg of pentylenetetrazol demonstrated, within 2 min, a "pseudoconvulsion"[9] characterized by clonic motor movement and vocalization which subsided within 15 min. Signs of sympathetic stimulation (viscous salivation, mydriasis, panting and pilo-erection) were prominent for a 30 min period. A maximal decrease of 1·0 to 1·5° in rectal temperature occurred within 1 hr after injection and returned to control values within 4 hr. The middle panel of Fig. 1 shows that the same dose of pentylenetetrazol increased the 5-HIAA levels to a maximum of 44·1 ± 6·3% (mean of four cats ± S. E.) in 4 hr and that it remained elevated 24 hr later. A rise of 26·8 ± 17·1 per cent in HVA levels was also seen 2 hr after injection; however, this was transient and did not remain elevated 24 hr later as did 5-HIAA. Frank clonic convulsions involving all limbs, as well as the head and tail, occurred within 3 min in all cats receiving the highest dose of pentylenetetrazol. These seizures lasted several min, after which the cats exhibited depression, panting and a reduction in rectal temperature of 1·5 to 2·5° which returned to control values within 4 hr. The bottom panel of Fig. 1 shows that this dose resulted in elevated levels of 5-HIAA and HVA the following day.

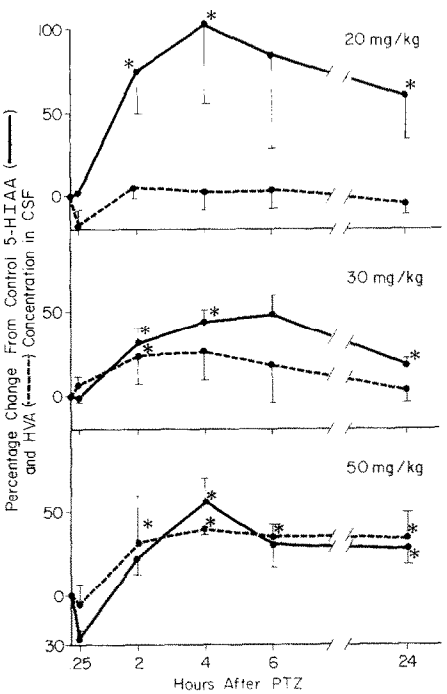

FIG. 1. Effect of three doses of pentylenetetrazol (PTZ) on 5-HIAA (——) and HVA (- - -) in cerebrospinal fluid (CSF) obtained from the cisterna magna of cats. Responses to 20, 30 and 50 mg/kg, i.p., are shown in the top, middle and bottom panels respectively. Each point represents the average percentage change for three to four cats ± S.E. Significant differences from control samples have been labeled with an asterisk (*) where P is at least less than 0·05.

These results show that pentylenetetrazol administration resulted in greater elevations of brain 5-hydroxytryptamine metabolism than that of dopamine. An analysis of variance of the changes in 5-HIAA levels showed that the responses to the various doses of pentylenetetrazol are not different. We believe these initial responses to be more a function of body temperature than pentylenetetrazol dosage, because previous work[10] showed that a reduction in body temperature increases 5-HIAA concentration, but not HVA levels, in fluid from the cisterna magna of cats. Present results are in agreement with the previous findings and suggest that initial changes in 5-HIAA levels may be attributed to the secondary effects of pentylenetetrazol on body temperature. Since dopamine metabolism was increased only after convulsions, the change may be secondary to convulsant activity. There was a rise of HVA of short duration after the dose of 30 mg/kg which may indicate that non-convulsant doses of pentylenetetrazol (somewhat greater than 30 mg/kg) could indeed promote dopamine metabolism.

Even though 70 per cent of an injected dose of pentylenetetrazol is excreted in 24 hr in rats and man,[11] it is not clear whether the elevation of 5-hydroxytryptamine metabolism for 24 hr is due to residual drug action or to persistent changes in neuronal activity. It is clear, however, that the increased 5-HIAA 24 hr after injection cannot be attributed to temperature alteration since increases after a decrease in body temperature persisted only 2–4 hr.[10] Changes in brain function enduring for at least 90 days have been reported after repeated injections of pentylenetetrazol in rats.[12]

Our results suggest that pentylenetetrazol in non-convulsant doses increases the metabolic activity of central 5-hydroxytryptamine systems for a period greater than 24 hr while not affecting dopamine systems. The fact that HVA is not affected at the lower doses does not rule out a selective action of pentylenetetrazol at a site other than brain (e.g. acid transport system). This seems unlikely, however, because 5-HIAA and HVA utilize the same acid transport system to exit from CSF,[13,14] and if pentylenetetrazol altered the efficiency of this system, one would expect an increase in both metabolites. Additional evidence supporting our conclusion is based on the observations that 5-HIAA in CSF originates from central rather than peripheral metabolism and that 5-HIAA in CSF parallel those in the cerebral parenchyma.[4,15–19] Convulsions after pentylenetetrazol injection cause a non-specific increase in the metabolism of monoaminergic systems indicated by the rise in both dopamine and 5-hydroxytryptamine metabolites in cerebrospinal fluid. It is possible that pentylenetetrazol can be used to selectively increase brain 5-hydroxytryptamine metabolism while not affecting dopamine metabolism.

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