Subsequent experiments were performed with various mixtures of the above keto acids with the amino acids found previously to be protective. It was established that an isomolar combination of arginine, glutamate, α-ketoglutarate, and oxalacetate gave considerably better protection against hydrazine toxicity than did the previously best combination, which contained arginine, glutamate, and alanine. The results of experiments performed at various levels of hydrazine are shown in Fig. 1. The LD_{50} values in mmoles hydrazine/kg estimated from the curves are as follows: saline controls, 2·65; arginine–glutamate–alanine, 3·58; arginine–glutamate–oxalacetate–α-ketoglutarate, 4·54.

These experiments suggest that two intimately related phases of metabolism may be directly or indirectly effected by hydrazine. The protective effects of arginine suggest that nitrogen metabolism may be disturbed in the intoxicated mice and that arginine may act by facilitating the conversion of ammonia to urea. The results with the keto acids indicate that the operation of the tricarboxylic acid cycle may be partially inhibited and that exogeneously administered oxalacetate and α-ketoglutarate may enhance the function of the cycle by increasing availability of limiting substrates. Since it is not possible to elucidate biochemical mechanisms at the cellular level only from toxicity studies in intact animals, biochemical investigations of the tissues of hydrazine-poisoned animals have been begun. Preliminary results show that the activity of the condensing enzyme (citrate synthesis) is unaffected in the livers of hydrazine-poisoned mice.

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Changes in pentobarbital distribution with time in neural and non-neural tissue of the cat brain*

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SEVERAL studies [1–5] have dealt with the penetration of barbiturates into the central nervous system and their regional distribution in the brain, but none has considered what types of cells the drugs go to. This paper will describe the concentration of phenobarbital in the medial geniculate bodies of cats after cortical lesions have caused neuron loss.[6,7]

METHODS

All cortical areas known as temporal, insular, AI, AII, and SII were removed unilaterally in cats,[6] and six weeks later they were given 39 mg pentobarbital/kg i.v. in 1–2 min. Their brains were exposed and then removed at various intervals after injection. Four cats were killed at 5 min, one at 10, four at 15, two at 20, and three at 30. The brains were chilled in ice-cold water, and the medial geniculates were stripped of their pia, removed, and weighed. Pentobarbital was measured by its u.v. extinction.[8] The tissue was homogenized with 15μg pentobarbital in 1 ml distilled H_2O as internal standard, the homogenizer was rinsed with 1 ml 1M NaH_2PO_4 and then 5 ml ethylene dichloride and the mixture put into a 25-ml separatory funnel. The phenobarbital was extracted into the ethylene dichloride and then into 1·5 ml 0·5 N NaOH. The funnels were shaken 10 min each time. The NaOH extract was

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centrifuged and the u.v. extinction read at 260 mμ. The difference in extinction values of the samples was compared to that of standard solutions, and tissue blanks were run. Results were calculated in micrograms pentobarbital per gram of tissue.

RESULTS

The graph in Fig. 1 shows the relative concentrations of pentobarbital in experimental medial geniculates. The experimental concentrations were first expressed as percentages of their respective

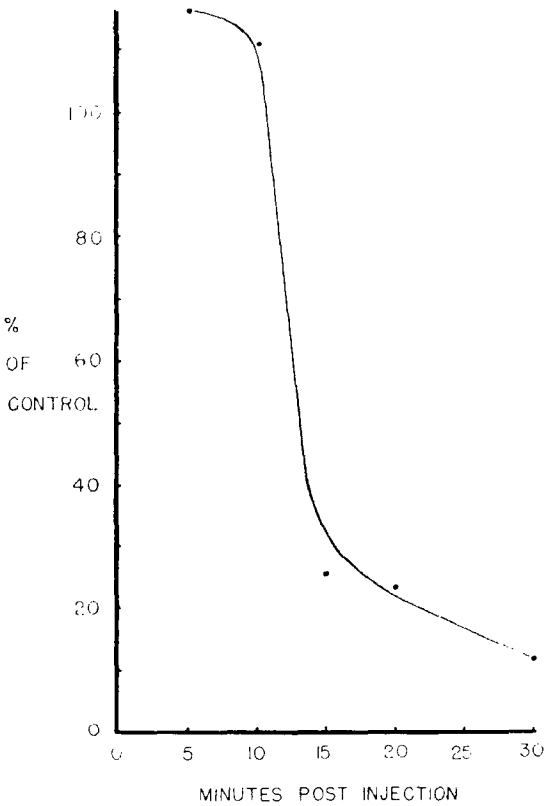

FIG. 1. Pentobarbital concentrations in experimental medial geniculates expressed as the averaged percentages of their respective controls. The standard deviation at 5 min is 26; at 15 min, 46; at 20 min, 24; at 30 min, 6.

controls, and these percentages were then averaged for each time interval. The control pentobarbital concentrations declined from 162 μg/g at 5 min to 90 μg at 30 min. Previous work [9] indicates that the whole-brain concentration of pentobarbital does not exceed twice that expected if uniform distribution in the entire body is assumed: the levels reported here are four times that expected concentration. Two factors may account for this. First, pentobarbital may be more concentrated in gray matter, and the results for whole-brain estimations involve dilution by white matter. The regional differences in barbital distribution in cat brain would support this.[5] Secondly, Barlow *et al.*[10] report that the lateral and medial geniculate bodies are highly vascular compared with other areas of the brain. This fact suggests that some of the pentobarbital measured here is in the blood. The slightly higher concentrations of pentobarbital in the experimental side in the first 10 min are not statistically significant but may also reflect higher vascularity of gliosed tissue. The rapid disappearance of drug on the experimental side may be due to declining blood concentration as well as loss from the glia. It is also possible that metabolites of pentobarbital are being measured by the u.v. extinction technique. The presence of these metabolites, however, does not alter the main interpretation.

DISCUSSION

After the appropriate cortical lesion most post-synaptic neurons of the medial geniculate degenerate and cause a 39% weight loss of the nucleus.[6,7] Koch *et al.*[11] have histologic evidence of this process in the cat lateral geniculate which they used to study ionic content of glia. It is probable that the degenerative processes in both geniculates are alike, so that their histological picture of the lateral would apply to the medial geniculates as well. The decrease in pentobarbital concentration in the degenerated tissue relative to the contralateral, control medial geniculate indicates that pentobarbital may normally be retained only in neurons. This is in contrast to certain hydroxamic acids which are apparently retained in equal concentration by both neurons and non-neural tissue (unpublished results).

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Rat stomach preparation *in vitro**

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THE INVERTED rat intestine, developed by D. H. Smyth and his colleagues in Sheffield,[1] has become a classical preparation for the study of active transport of body constituents. We wish to report on a new preparation—the inverted rat stomach—which is suitable for similar research and also for the study of gastric acid secretion.

Adult male rats weighing at least 200 mg and nade to fast for 24 hr, are killed and their stomachs removed together with 5 mm long pieces each of duodenum and oesophagus. The fundus (Fig. 1, above) is opened and the stomach is washed with cold saline through the pylorus. Then the duodenum and the oesophagus are united and simply closed from outside by a common ligature. Inversion of the stomach proceeds from below by pushing a glass rod from outside into the antrum until it reaches the opened fundus. Inversion is then completed. Now the whole stomach is closed by a ligature of the inversed fundus. Thus results an inverted closed stomach sac into which 3 ml of Ringer solution are injected through a fine 25–26 gauge canule. The operation takes about 2 minutes.

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