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Pentobarbitone distribution in various regions of the rat brain in relation to the kinetics of its effect

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The radioactivity of rat brain was measured at various intervals (5, 10, 15, 20, 30, 40, and 70 min) after intraperitoneal administration of ^{14}C-labelled pentobarbitone (20 μc/kg) together with unlabelled pentobarbitone (62 mg/kg). The brain was carefully dissected, and pieces of nervous tissue were sampled. The regions studied were as follows: frontal, parietal and occipital cortex, fornix and nucleus caudatus, anterior and posterior thalamus, rostral and caudal hypothalamus, ventral mesencephalus, anterior and posterior colliculi, pons, cerebellar hemispheres and vermis, medulla oblongata and cervical spinal cord.

Close agreement was observed between the overall time-course of the distributions and that of its concentration on the receptor biophase, as determined from the times of the disappearance and reappearance of the righting reflex (Palumbi, Rossini & Segre, 1966; Giorgi, Palumbi, Rossini & Segre, 1966). The highest activity was reached after 20 min in the inferior posterior nucleus of the hypothalamus. This area does not appear to have an especially high blood flow, as evaluated with ^{131}I-labelled serum albumin (150 μc/kg, i.v.). The inferior posterior basal ganglia showed a much higher concentration than the other regions when incubated for 20 minutes at 37° C in oxygenated Krebs-phosphate medium containing non-labelled pentobarbitone at 62 mg/l. and labelled pentobarbitone with an activity of 20 μc/l.

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A metabolic explanation for differences between species of the anticonvulsant activity of diazepam

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A selective activity against metrazol-induced convulsions is a characteristic property of benzodiazepines, although species differences have been observed. The anticonvulsant activity of diazepam (5 mg/kg intravenously) in respect to metrazol (100 mg/kg, intraperitoneally) disappears in rats after 6 hr while it is present in mice for about 24 hr. Furthermore diazepam (5 mg/kg) antagonizes a higher dose of metrazol in mice (300 mg/kg) than in rats (150 mg/kg).

The brain concentrations of diazepam and its N-desmethyl metabolites were measured with a sensitive gas chromatographic method taking advantage of an electron capture detector. Table 1 shows that the rate of disappearance of diazepam from brain is similar in rats and in mice.

TABLE 1. *Anticonvulsant effect and levels of diazepam in brain after administration of diazepam (5 mg/kg intravenously)*

Rat				Mouse			
Time after diazepam	Diazepam (μg/g)	N-Des-methylated metabolites (μg/g)	Anti-metrazol effect*	Time after diazepam	Diazepam (μg/g)	N-Des-methylated metabolites (μg/g)	Anti-metrazol effect*
1 min	3·270 ±0·050	0·101 ±0·007	100	1 min	3·407 ±0·070	–	100
30 min	0·600 ±0·010	0·065 ±0·021	100	30 min	0·495 ±0·023	0·781 ±0·070	100
60 min	0·305 ±0·070	0·051 ±0·037	100	60 min	0·392 ±0·041	0·490 ±0·022	100
2 hr	0·020 ±0·004	–	20				
3 hr	–	–	0				
5 hr	–	–	0	5 hr	n.d	0·732 ±0·061	100
10 hr	–	–	0	10 hr	–	0·390 ±0·033	100
15 hr	–	–	0	15 hr	–	n.d.	100
20 hr	–	–	0	20 hr	–	n.d.	80
24 hr	–	–	0	24 hr	–	n.d.	60

* Percentage of animals protected from the convulsions induced by metrazol (100 mg/kg intraperitoneally).
n.d., Not detectable.

In contrast, while the N-desmethyl metabolites are present in mice brain for about 15 hr, only traces were found in the brain of rats and these were detected for only 2 hr. Studies on the toxicity and antimetrazol activity of diazepam and the metabolites N-desmethyldiazepam and oxazepam, indicate that the N-desmethyl metabolites of diazepam are less toxic than diazepam but they exert an anticonvulsant activity similar to the parent compound. It is therefore suggested that the different effect of diazepam in rats and mice may be related to a different rate of formation or brain accumulation of the N-desmethylated metabolites.

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Metabolism of prostaglandins by the rat isolated liver

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Prostaglandins are rapidly removed from the circulating blood (Ferreira & Vane, 1967), yet little is known either of the mechanism of uptake by the tissues, or of the subsequent metabolism (Änggard & Samuelsson, 1966). Following systemic injection of tritium labelled prostaglandin E_1 (PGE_1) to rats, rapid uptake of labelled