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## Research Topic: On the Mode of Action of Barbiturates In Vivo

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#### **Abstract**

Aldridge and Parker (1960) using suspensions of liver mitochondria demonstrated with oxybarbiturates an inhibition of respiration without uncoupling oxidative phosphorylation. This was in contrast to the views expressed by Brody and Bain (1954) who suggested that the mode of action of the barbiturates on the C.N.S. was mediated by an uncoupling of oxidative phosphorylation.

Aldridge and Parker further showed that the use of succinate as substrate for the mitochondrial suspension abolished the inhibition of respiration caused by the oxybarbiturate and suggested therefore that the site of action of the oxybarbiturate was at some stage before the entry of succinate into the oxidative chain. Succinate is known to enter the oxidative site at a point after the pyridine nucleotide stage and hence the site of action of barbiturate was proposed to be at the oxidation of pyridine nucleotide.

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#### RESEARCH TOPIC

#### ON THE MODE OF ACTION OF BARBITURATES IN VIVO

Aldridge and Parker (1960) using suspensions of liver mitochondria demonstrated with oxybarbiturates an inhibition of respiration without uncoupling oxidative phosphorylation. This was in contrast to the views expressed by Brody and Bain (1954) who suggested that the mode of action of the barbiturates on the C.N.S. was mediated by an uncoupling of oxidative phos-

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glucose
|
pyruvate
|
KREB'S CYCLE
|
NADPH2
|
cytochrome b
| ← succinate
cytochrome c
|
cytochrome a
|
oxygen

Chance and Hollinger (1963), again using an isolated system of liver mitochondria, identified the precise site of action as being between pyridine nucleotide and cytochrome b.

In view of this work on isolated systems it was decided to test the validity of the proposed site of action of barbiturate in vivo by the effect of sleeping time caused by amylobarbiturate in rats with or without treatment with sodium succinate.

The succinate was administered in 1M cone. in small quantities  $(15 \mu L)$  into the right ventricle of the rat's brain using specially prepared needles. This obviated any effect caused by systemic metabolism of succinate or delayed passage across the "blood brain barrier".

The rats (140-160g) were fasted overnight before all experiments in an attempt to standardize conditions as much as possible.

#### SLEEPING TIMES

Results show that intraventricular injection of this small amount of succinate reduced the sleeping time of rats to about one-third of that of controls given either pruvate (1M) or NaCl. (2M). (Pyruvate was given as control because (a) it is also a metabolizable intermediate, and (b) should not affect sleeping time from normal with barbiturate anaesthesia since it enters the oxidative process before the proposed site of barbiturate block. The latter was shown to be true.)

The difference between mean sleeping time of control (pyruvate group) and succinate treated group of rats was statistically highly

significant.

#### **BLOOD LEVELS**

A standard spectrophotometric method for the estimation of blood barbiturate level was adapted to a micro method which gave reproducible results which obey Beer's law.

The results showed that blood barbiturate levels measured at the time of waking from anaesthesia in succinate treated rats were statistically significantly higher than in pyruvate treated controls. These results suggest that the effect of succinate was not mediated through an increase in barbiturate metabolism thereby leading to a decrease in blood level since succinate treated rats awoke with blood barbiturate level inconsistent with consciousness in control rats. As a further control, blood and brain levels were estimated for the same rats and a good correlation was shown to exist, showing that blood barbiturate levels accurately represent brain barbiturate levels.

#### DISCUSSION

The results confirm the in vitro findings of Chain and Hollinger (1963) on isolated liver mitchondria and extend their conclusions to cover brain in vivo.

The present results give a very good indication that the pharmacological action of the oxybarbiturates in the intact animals is identical to that indicated by the biochemical experiments in vitro. The fact that succinate has such a marked antagonistic action to the barbiturates in contrast to pyruvate indicates that metabolism of the former substrate by-passes the site of action of the oxybarbiturates.

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#### ACKNOWLEDGMENTS

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#### REFERENCES

ALDRIDGE & PARKER 1960. Biochem. J. 76, 47. BRODY & BAIN 1954. J. Pharm. Exp. Ther. 110, 148. CHAIN & HOLLINGER 1963. J. Biol. Chem. 278, 419.

#### DIAGNOSTIC PROBLEM

(from page 33)

#### Diagnosis:

Retroperitoneal bleeding from oesophageal varices produced by alcoholic cirrhosis.

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