# Acid-Soluble Phosphates in Monkey Brain as Affected by Certain Central Nervous System Stimulants and Depressants.* (20024)

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A number of investigators(1-7) have examined the effects of certain central nervous system stimulants and depressants on the acid-soluble phosphates of brain. In the majority of instances significant changes in inorganic phosphate, phosphocreatine, and adenosine triphosphate (ATP) have been reported to occur. However, there is little uniformity as to the direction these changes take, and in some cases the significance of the alterations might be questioned on the basis of technic or lack of sufficient data. In none of these studies was a concerted effort made to compare the effects of stimulation to those of depression of the central nervous system on the distribution of acid-soluble phosphates within it and in only one investigation(7) were experiments performed on animals higher in the phylogenetic scale than the dog. For these reasons the study described herein was undertaken in an attempt to determine whether or not direction of change of any acid-soluble phosphates in the brain could be correlated with an increase or decrease in activity of the central nervous system.

*Methods.* Thirty-one adult, male and female, rhesus monkeys were employed in these experiments. Under pentobarbital anesthesia a longitudinal, midline incision was made in the scalp of each animal and the major portion of the calvarium removed. The skin incision was closed loosely and 24 hours later, when the animal had recovered from the anesthetic, the incision was reopened and the brain exposed for subsequent freezing with liquid air. Nine animals received no drug prior to freezing of the brain. Four animals received *d*-tubocurarine hydrochloride (1-2 units/kg) intravenously. When necessary, respiration was maintained artificially until the brain was frozen. The remaining 18 monkeys were divided into 2 groups of 9 each, one group receiving, by the intravenous route, a central nervous system depressant [pentobarbital (35 mg/kg) or chloral hydrate (125 mg/kg)] and the other group receiving a central nervous system stimulant [pentylenetetrazol (20 mg/kg) or 5-ethyl-5-(1,3-dimethylbutyl) barbituric acid(8) (5 mg/kg)]. Immediately after the development of anesthesia or convulsions the cerebrum was frozen by pouring liquid air over the exposed brain. The entire cerebrum was then removed and analyzed for acid-soluble phosphates by the method described by Umbreit *et al.*(9).

*Results.* Since most of the conclusions in the literature relative to the effects of various stimulants or depressants on the distribution of acid-soluble phosphates in the central nervous system were based on comparisons with control animals which had received a curariform agent, it was of interest to determine the effects of curarization. It would appear, on the basis of the data in Table I, that administration of *d*-tubocurarine produces a rise in inorganic phosphate and a fall in phosphocreatine in the cerebrum. However, when analyzed statistically, only the difference in phosphocreatine content is significant. The mean value for ATP content in curarized animals is not significantly higher than that found in the non-curarized monkey. In animals anesthetized with pentobarbital or chloral hydrate the cerebral content of inorganic phosphate, phosphocreatine, or ATP was not significantly different from those values found in non-curarized controls. Likewise, convulsions, produced by pentylenetetrazol or the convulsant barbiturate, 5-ethyl-5-(1,3 dimethylbutyl) barbituric acid, caused no statistically significant alteration of inorganic phosphate or phosphocreatine content of cerebrum. The ATP content of cerebrum was not altered by pentylenetetrazol convulsions

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TABLE I. Effect of Various Drugs on True Inorganic Phosphate, Phosphocreatine and Adenosine Triphosphate Content of Monkey Cerebrum.

| Drug | No. of animals | μM phosphorus/100 g brain (mean ± S.E.) True inorganic phosphate | Phospho-creatine | Adenosine triphosphate |
|---|---|---|---|---|
| 0 | 9 | 451 ± 26 | 155 ± 7 | 54 ± 16 |
| *d*-Tubocurarine | 4 | 536 ± 37 | 98 ± 13 | 92 ± 24 |
| Pentobarbital | 5 | 466 ± 27 | 144 ± 11 | 30 ± 8 |
| Chloral hydrate | 4 | 495 ± 21 | 146 ± 15 | 41 ± 6 |
| Pentylenetetrazol | 4 | 515 ± 30 | 220 ± 31 | 72 ± 18 |
| 5-Ethyl-5-(1,3-dimethyl-butyl) barbituric acid | 5 | 483 ± 25 | 151 ± 16 | *48 ± 22 |

* Mean not statistically significant.

and it was impossible to determine the significance of the difference of cerebral ATP content between those animals receiving the convulsant barbiturate and the controls, since the mean value for the former was not statistically significant.

*Discussion.* The data presented in this paper are, in general, not in agreement with the results of similar experiments reported in the literature. This lack of conformity may be due, in some instances, to a difference in the species of experimental animals employed (2,4). In other cases, conclusions have been drawn from inadequately controlled experiments(1) or based on data from a limited number of experimental animals(3,5,6), the number of animals employed being too small to allow a statistical analysis of results for determination of the significance of any differences observed. A single study(7) of the effects of convulsions on the distribution of acid-soluble phosphates in the brain of the monkey has been reported. This study involved one animal convulsed by electric shock which caused a decrease in ATP and phosphocreatine and a rise in inorganic phosphate. The significance of such findings, based on observations on only one animal, are open to question.

*Summary.* The influence of *d*-tubocurarine, two central nervous system depressants (pentobarbital and chloral hydrate) and two central nervous system stimulants (pentylenetetrazol and 5-ethyl-5-(1,3 dimethylbutyl) barbituric acid) on the concentrations of inorganic phosphate, phosphocreatine, and ATP in the cerebrum of the rhesus monkey has been investigated. *d*-Tubocurarine was the only one of these compounds to produce any statistically significant effect. With this agent there was a significant decrease in phosphocreatine content without any alteration in inorganic phosphate or ATP.

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