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The depleting effect of vincamin on the cerebral serotonin level

(*Received* 20 *October* 1961; *accepted* 6 *November* 1961)

VINCAMIN is a cristalline alkaloid isolated from the plant *Vinca minor L.* with an unknown structural form. According to investigations hitherto carried out it has an indol skeleton. The compound has a considerable central hypotensive effect.[1] As pointed out in our previous paper, the noradrenalin content of the rat cerebrum and of other tissues is reduced by vincamin pretreatment.[2]

To elucidate further the mechanism of action, the influence of the compound on the cerebral serotonin content was investigated.

Our experiments were carried out on Wistar rats weighing 200–250 g. After intraperitoneal administration of vincamin the test animals were decapitated at different times. After removing the cerebellum, half the cerebral tissue was used for each determination. After homogenization in acetone the cerebral tissue was shaken for half an hour, and afterwards centrifuged; the acetone phase was evaporated in N_2 flow in vacuum at 35 °C. The dissolved lipids were removed by washing with petrol ether. The serotonin content of the extract was determined on a rat fundus band preparation according to Vane.[3] The disturbing effect of the noradrenalin was eliminated by enzymic degradation carried out with poliphenoloxidase.[4] The results obtained in our experiments are shown in the following table expressed in terms of mμg/g wet tissue.

TABLE 1. EFFECT OF VINCAMIN ON SEROTONIN CONTENT OF RAT CEREBRUM

Time, hr	Serotonin mμg/g	Mean	Percent of the control	*P*
0	230, 403, 333, 230, 223, 227, 341, 215, 275 326, 226, 238, 345, 298, 326, 313, 385	286 ± 50	100	
2	262, 285, 290, 233	268 ± 19	94	> 0·5
3	246, 220, 295, 161	231 ± 47	81	>0·2
4	167, 120, 211, 185, 122, 251, 124, 145	166 ± 45	58	≪0·01
6	196, 217, 157, 155	181 ± 27	63	≪0·01
16	254, 213, 318, 283	267 ± 38	94	> 0·5

The time recorded is the interval between intraperitoneal administration of 50 mg/kg vincamin and removal of the brain.

In the table only the effect of 50 mg/kg vincamin is given. For smaller doses no significant effect could be detected.

As may be seen from the table, after vincamin administration a slight decrease in the serotonin level could be observed, a significant difference as compared with the control value appeared only after 4–6 hr. In the 16th hr after administration of vincamin the cerebral serotonin level was normal again. The reducing effect is a considerable one but as compared to that caused by reserpin only of a minor degree, since complete depletion of the serotonin level is caused by a 5 mg/kg dose of the latter within 2 hr. Greater depletion cannot be caused by vincamin, as higher doses have a toxic effect and kill the animals.

As the compound reduces the cerebral serotonin level, vincamin as well as reserpin and other alkaloids with similar structure is a new material found to effect the metabolism of serotonin. Our investigations showed however that this effect of vincamin is different from that of reserpin, being of a lesser degree and developing more slowly. The diminishing effect of vincamin on noradrenalin level is more intensive sooner, and more durable. The effects of vincamin on the noradrenalin and serotonin level are probably due to different modes of action.

Further investigations have to be carried out in order to elucidate the role the depletion of the serotonin level plays in the pharmacological and therapeutical effect of the compound.

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Passage of caffeine into human gonadal and fetal tissue

(*Received* 4 *December* 1961; *accepted* 6 *December* 1961)

CAFFEINE is known to be mutagenic to bacteria,[1] fungi,[2] and Drosophila.[3] No report of mutagenic activity in mammals has yet appeared. However, the basic similarity of the mechanisms for replication of the genetic material in all forms of life poses the possibility that caffeine may be mutagenic in man. Because of the widespread consumption of caffeinated beverages a major part of the human race is chronically exposed to this compound. Mutagenic effects of a drug could be of genetic significance at any time before or during a person's reproductive years. In fetal life, exposure might be especially hazardous at about 6–8 weeks, during the period of segregation and proliferation of the germ cells. Several aspects of this problem have been discussed elsewhere.[4]

A first step in assessing the potential genetic hazard of exposure to a mutagen is to ascertain whether or not the compound in question gains access to germinal tissue. Axelrod and Reichenthal[5] have already shown in the dog that caffeine distributes freely into intracellular water of all tissues examined. It was thought desirable, however, to look into the matter directly in humans, and specifically in ovary, testis, and fetus, none of which had been included in their investigation. Moreover, there were some grounds for supposing that during early gestation the placenta might not permit the drug to pass freely.[6] The experiments described here, although necessarily conducted with a small number of subjects, show quite clearly that caffeine equilibrates freely between plasma and tissue water in the case of human ovary and testis, and also between maternal plasma and the human 7–8 week fetus.

MATERIALS AND METHODS

Tissues. Human gonads were obtained as surgical specimens. Testes were from patients undergoing bilateral orchidectomy for cancer of the prostate. Ovaries were from patients having bilateral oophorectomy for cancer of the breast. All gonads appeared to be normal. Fetuses were from therapeutic abortions performed for psychiatric indications during the 7th–8th gestational week. One specimen was obtained as fragments from curettage, the other intact by hysterectomy.

Caffeine administration. In the case of the ovaries, a control ovary and a 10-ml sample of oxalated blood were first obtained. Then 1 g of caffeine sodium benzoate (574 mg caffeine) was given by intravenous infusion over a period of 5 min. After a further 15–20 min for equilibration, the second ovary was removed and another blood sample drawn. The tissue and plasma controls proved to be unnecessary inasmuch as they contained no apparent caffeine. Zero-blanks were also found with one control testis and with control samples of fetal liver. Therefore, in the experiments with testes and on e