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The anti-diuretic action of L-azaserine, as compared with ω-diazoacetophenone

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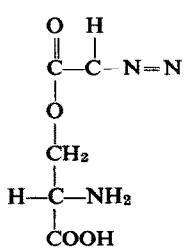
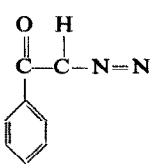
WHEN mice were injected i.p. with the anti-mitotic, *O*-diazoacetyl-L-serine, (azaserine),[1] it was observed that they drank less water than a control group of animals, maintained under the same conditions, and injected with an equivalent volume of saline.

The anti-neoplastic action of azaserine is well known,[2] and it has been used clinically against several types of tumours.[3, 4] Levenberg *et al.*,[5] showed that L-azaserine blocked *de-novo* purine biosynthesis, by irreversibly combining with the enzyme, α-*N* Formyl-glycinamide ribotide amidotransferase (EC 6.3.5.3), in the absence of L-glutamine. We can find no reports of the action of L-azaserine, or diazo compounds in general, on water balance in experimental animals. In an attempt to determine whether the effect on water balance was due to the active diazo group of L-azaserine, or to the molecule as a whole, we have compared the action of L-azaserine with that of another diazo compound, ω-diazoacetophenone[6] (Fig. 1).



L-azaserine



ω-diazoacetophenone

FIG. 1. A comparison of the structure of L-azaserine and ω-diazoacetophenone.

The diuretic activity of groups of twenty male, Hornes mice of body weight 27–32 g, was investigated by the method of Heller and Blackmore.[7] The animals were given three water loads, by stomach tube, 1·0 ml/20 g body weight, at hourly intervals. Immediately after the last water load, the test group of mice was given L-azaserine, 1·0 mg/kg, in a volume of normal saline of 0·2 ml/30 g body weight, by the i.p. route. Controls were injected with an equivalent volume of saline. The ω-diazoacetophenone was given at the same dose, in the same manner.

The urine output of the animals was recorded, after the last water load, at 10-min intervals, for 70 or 80 min.

The results are shown in Figs. 2 and 3, they suggest that at the dose and both L-azaserine, and ω-diazoacetophenone cause a fall in urine production.

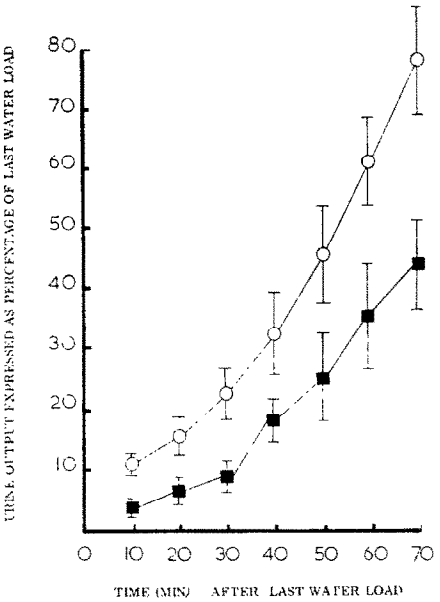


FIG. 2. The anti-diuretic effect of a single dose of L-azaserine, 1 mg/kg, given by the i.p. route, in mice. The urine output is expressed as a percentage of the final water load.
○—○ mean values control animals ■—■ mean values from L-azaserine-treated animals. Vertical bars indicate standard error of the mean.

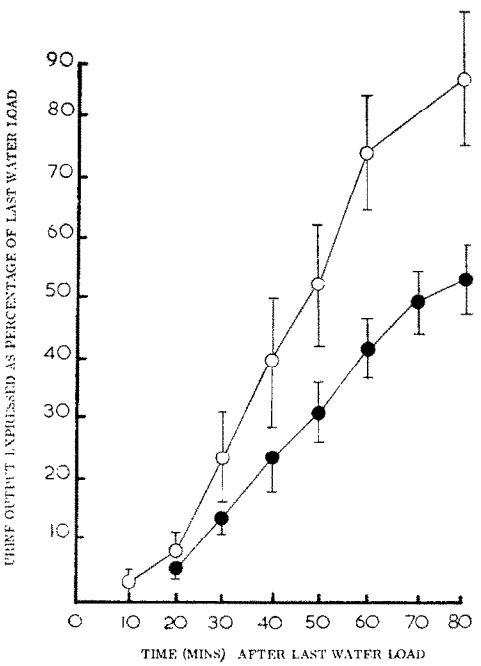


FIG. 3. The antidiuretic effect of a single dose of ω-diazoacetophenone, 1 mg/kg given by the i.p. route, in mice. The urine output is expressed as a percentage of the final water load.
○—○ control animals. ●—● ω-diazoacetophenone-treated animals. Vertical bars indicate standard error of the mean.

The common occurrence of the diazo group in these two compounds suggests that this may be the active group causing this effect. We have shown,* that in other respects, this unsubstituted ω-diazoacetophenone, and several other meta and para substituted ω-diazoacetophenones do not have the actions of L-azaserine, in respect of its action in competing with L-glutamine in purine synthesis, or in having an antimitotic action on cell systems that are affected by L-azaserine. We therefore suggest that this common effect is caused by a mechanism distinctly different from that which operates when L-azaserine acts as an antagonist to L-glutamine in purine biosynthesis.

Although we are unable to suggest a site of action for this effect, we suggest that it is due to the possession of the diazo group on the molecule.

* Unpublished results.

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Stathmokinetic action of pentobarbital on cultured human kidney cells

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THE USE of synchronized cell cultures facilitates the investigation of the mode of action of pharmacological agents on cells by differentiating the susceptible phases of the cycle at which the compound is effective. Thus in the examination of mitotic poisons compounds which block division by interfering with DNA synthetic processes can be easily distinguished from compounds showing a true G_2 blocking action.

Furthermore a compound which blocks the onset of prophase can be distinguished from a stathmokinetic agent, such as colcemid, blocking in metaphase. By the use of cultures of human kidney cells, synchronized by the double thymidine blocking technique, it has been found that pentobarbital