Analgetic Property of Vitamin K. (22128)

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(Introduced by A. J. Goldforb.)

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Vitamin K stimulates the liver in order to produce prothrombin. Insufficient amounts of vit. K produce insufficient amounts of prothrombin. From this arises one of the conditions for haemorrhagic diathesis. Vit. K is administered to prevent haemorrhagic diathesis following hypoprothrombinemia, after surgical intervention or, prophylactically, prior to operations.

The other properties of vit. K and Synkavit (diphosphoracid-ester of 2-methyl-, 4-naphtohydrochinon) which is pharmacologically identical with vit. K, have not yet been registered. Vit. K possesses, however, a strong analgetic property which has been observed in patients(1) and experimentally proved in animals(2).

We investigated the analgetic property of vit. K on mice according to the Wolfe-MacDonald method(3), which deals with the registration of thermoalgesia, as follows:

A glass vessel with double walls between which there is water at a constant temperature of 122°F (50°C) serves for testing the susceptibility of an animal to temperature. If the mouse is put into such a vessel, it will lick its paws after a certain time to mitigate the pain caused by the temperature at the bottom of the vessel. The time elapsing from the moment when the animal is put into the vessel to the moment of licking its paws is measured by chronometer. This period indicates the susceptibility of the animal to pain caused by warmth.

The normal reaction of licking in a series of mice, an average of 9.9 sec. served as control time. The mice were then given vit. K. We took measurements 4 times *i.e.* 30 sec., 1½ hr, 2½ hr, and 3½ hr following administration of vit. K. The results are shown in Fig. 1.

Vitamin K has a decidedly thermoanalgetic property, since the reaction to pain occurs much later than in the control mice. Whereas the reaction took place after 9.9 sec. in the control mice, the reaction in mice which were administered 2 mg/kg of weight of vit. K occurred after 17 sec. and in mice which were given 4 mg/kg of weight of vit. K after 16.3 sec. Increase of the amount of vit. K does not promote the thermoanalgetic effect but lessens it slightly.

To evaluate these results we investigated the thermoanalgetic effect of morphine by the same method. A series of mice were injected with 3 mg/kg of weight of morphine intraperitoneally and another series with 6 mg/kg of weight. The results are given in Fig. 2.

The results of the thermoanalgetic effect of vit. K in doses of 2 mg/kg of weight and 4 mg/kg of weight have been recorded. The thermoanalgetic effect of vit. K is even stronger than that of morphine. Although the maximal effect of morphine occurs immediately after administration the maximum with vit. K occurs toward the end of the experiment. The reason is the rapidity of resorption. Watery solution of

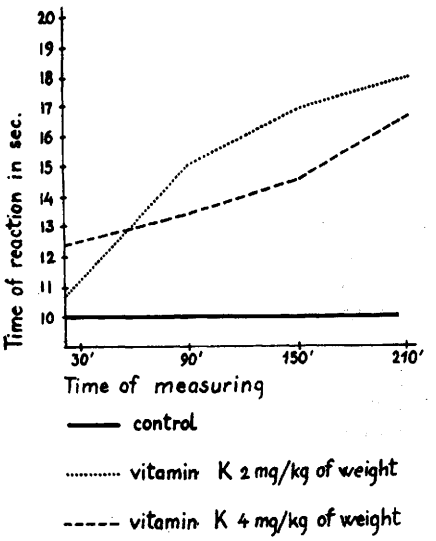

FIG. 1. Effect of Vit. K by normal mouse.

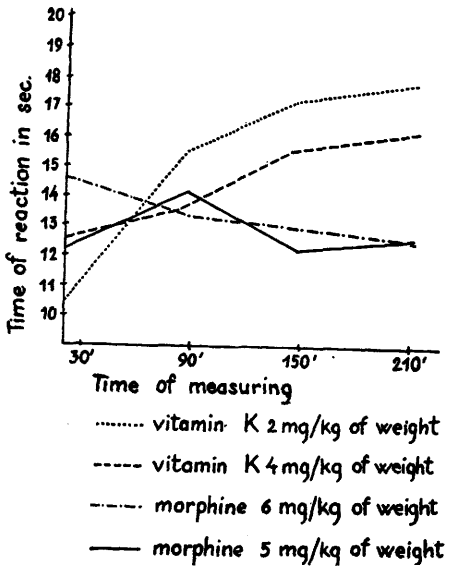

FIG. 2. Effect of Vit. K and morphine.

morphine administered intraperitoneally is readily resorbed while the oil solution of vit. K administered orally is resorbed much slower.

It is known that some substances may elicit the analgetic effect in such a way as to elicit directly or indirectly the mobilisation of cortisone from the root of the suprarenal gland through the hypophysis(4,5). Hench(6) has proved that cortisone has a highly analgetic effect and Jakob(7) has shown that morphine owes its analgetic property to the fact that it may mobilize cortisone. We therefore investigated whether vit. K can mobilize cortisone or some other hormone of the suprarenal gland. We have carried out the above described experiments on suprarenalectomised mice. The results are shown in Fig. 3.

The thermoanalgetic property of vit. K must not be ascribed to its ability to mobilize considerable amounts of cortisone in the organism since the suprarenalectomised mice showed the same reaction as normal mice. From these results we can conclude that the thermoanalgetic property of vit. K may be based on its depressive action either on the cortical or subcortical centres for pain.

To confirm our supposition that vit. K acts on certain areas of the central nervous system in an inhibiting way, we have investigated the registration of mobility according to Kosak's method(8) on a series of mice which were administered vit. K. Kosak's method seemed most satisfactory to us since it secures free movements and registers even the slightest movements. The principle of the method is the following:

The mouse is put into a vesel that is floating on water like a labile boat. All movements are transferred to the vessel and from the vessel recorded on a kymograph. From the frequency of the movements and the size of the registered curves we may deduce objective conclusions on the excitement or immobility of the animal. The results of these experiments are shown in Figs. 4 and 5. Fig. 4 shows the kymographic curve of the mouse which got 4 mg/kg of weight of vit. K and Fig. 5 shows the kymographic curve of a suprarenalectomised mouse given 4 mg/kg of weight of vit. K. From both figures the pronounced sedative and calming effect of vit. K is shown.

We also investigated whether vit. K had an antagonistic property against shock provoked with pentazol and whether it had any influence on the electroepileptic shock.

In a control series the mice were administered 75 mg/kg of weight of pentazol intraperitoneally. All mice displayed typical pronounced convulsions. In a second control series the mice were given 100 mg/kg of weight of pentazol. All mice died shortly after.

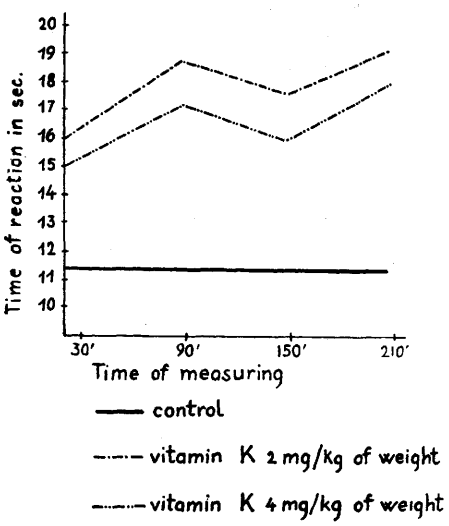

FIG. 3. Effect of Vit. K by suprarenalectomised mouse.

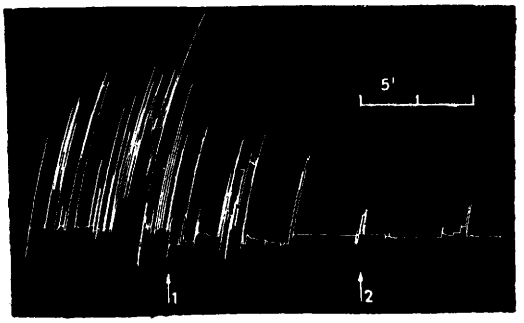

FIG. 4.

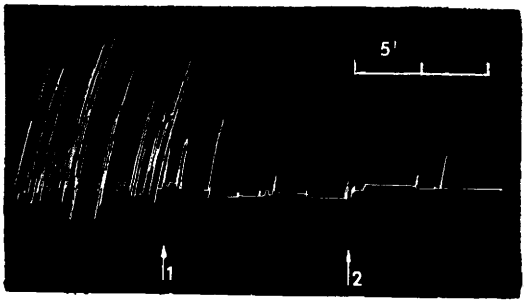

FIG. 5.

Owing to these control results a series of mice were given first 4 mg/kg of weight of vit. K and later 75 mg/kg of weight of pentazol. A second series of mice were first given 4 mg/kg of weight of vit. K and then 100 mg/kg of weight of pentazol. Vit. K had no effect either on the convulsions or on the lethality.

Finally we investigated whether vit. K had any influence on electroshock. The experiments showed that vit. K had no influence either on the intensity or on the duration of the electroshock. We have therefore concluded that vit. K has no depressive action on the motoric sphere of the brain or on the subcortical tonic centers.

We tested the analgetic property of vit. K in 115 patients with inoperative carcinomas or sarcomas with multiple metastases. All of them were given daily morphine and barbiturates against intense pain prior to initial administration of vit. K. We stopped administering morphine and barbiturates and gave daily injections of 20-30 mg of vit. K. Full analgesia was produced in 95 patients *i.e.* in 75%. In the remaining 20 patients the analgetic effect was either slighter or there was none at all.

Conclusion. 1. Vit. K has shown a considerable thermoanalgetic effect that is also evident in suprarenalectomised animals. This effect is stronger than the thermoanalgetic effect of morphine. 2. Vit. K has shown a strong sedative effect not being due to the mobilisation of the hormones of the suprarenal glands. 3. Vit. K has no depressive property on the cortical or subcortical motor-centers. 4. In patients with inoperative carcinomas and sarcomas with metastases and severe pains, vit. K showed such a pronounced analgetic property that we could cease administration of morphine and barbiturates. The complete analgetic effect was obtained in 73% of cases.

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