

INCREASE IN SEROTONIN (5-HYDROXYTRYPTAMINE) SENSITIVITY  
OF SEGMENTS OF THE COLON OF RATS WITH AVITAMINOSIS K  
CAUSED BY LIGATION OF THE BILE DUCT

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Vitamin K not only possesses antihemorrhagic properties, but it also influences the permeability of the blood vessels [2, 3, 5, 11], increases the elasticity of the frog's intestine, and strengthens the peristalsis of the dog's intestine [8, 9]. Avitaminosis K, produced by ligation of the bile duct or by administration of dicoumarin, considerably weakens the reaction of segments of the small intestine of rats to adrenalin. The administration of vikasol (a vitamin K preparation) to such animals restores the reactivity of the intestine to adrenalin [15]. The ability of vitamin K, its derivatives, and the corresponding antivitamin to modify the tone and peristaltic activity of the gastro-intestinal tract has been used successfully in the treatment of spastic and atonic states [8, 12, 13]. However, the mechanisms by means of which vitamin K, its analogues, and its antivitamin exert their influence on smooth muscle have been inadequately studied, and this prevents the more rational and extensive use of these substances in clinical practice. One such mechanism may be the maintenance of a certain level of reactivity of the smooth muscle to the action of biologically active substances (acetylcholine, adrenalin, histamine, serotonin, and so on). It has been shown, for example, that vikasol potentiates the motor effect of acetylcholine on isolated segments of the intestine; this effect does not take place if the sulfhydryl groups of the preparations studied are first blocked with cadmium chloride [3]. Among the biologically active substances stimulating the motor function of the intestine, serotonin has a special role [16, 18-21].

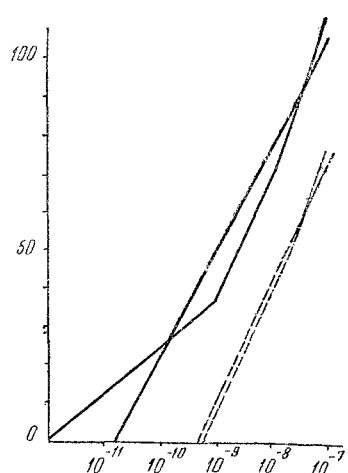
In the present investigation the sensitivity of isolated segments of the colon of rats was determined in avitaminosis K caused by ligation of the bile duct.

#### METHOD

Experiments were carried out on 24 albino rats weighing 110-160 g. In 9 animals avitaminosis K was produced by ligation of the bile duct [7]. The development of avitaminosis K was judged from the prothrombin time, determined by Quick's method, and the blood clotting time (by Mas y Magro's method). The experimental rats were sacrificed 26-30 days after ligation of the bile duct. Both the experimental and the control animals were killed by exsanguination (division of the carotid arteries). The sensitivity of the proximal segments of the colon, 2.5 cm in length, to serotonin was investigated by the method of Dalglish, Toh, and Work [17]. The creatinine-sulfate of serotonin was used in the experiments. The length of the short arm of the Engelmann's lever was 3 cm, and that of the long arm 27 cm.

#### RESULTS

In the course of the investigation the threshold concentration of serotonin and the intensity of tonic contraction of segments of the colon in relation to different doses of serotonin were determined. The threshold dose was taken to be the least concentration of serotonin causing the lever to rise by not less than 20 mm. A tenfold increase in this dose caused a twofold, or slightly greater, increase in the contraction. The threshold concentration of serotonin in the nine rats with avitaminosis K was  $0.00018 \pm 0.00011$   $\mu\text{g/ml}$ , compared with  $0.007 \pm 0.0011$   $\mu\text{g/ml}$  (i.e., approximately 20 times greater) in the 15 control rats ( $P < 0.001$ ).



Contractions of segments of the colon from rats with avitaminosis K under the influence of different doses of serotonin. Along the axis of ordinates—amplitude of contraction (in mm upward movement of lever). Other explanations are given in the text.

Attempts were made to obtain segments of colon of equal length, so that the intensity of their contraction could be compared (from the upward movement of the free arm of the lever) in relation to the dose of serotonin.

A graph plotted from the mean values of the maximal contractions of the colon in the 9 experimental (continuous line) and 15 control (broken line) animals under the influence of different concentrations of serotonin (from  $10^{-11}$  to  $10^{-7}$ ) is shown in the figure. The indices (straight lines) were compared by the method of least squares [4]. It is clear from the figure that the segments of colon of the rats with avitaminosis K were more sensitive to low concentrations of serotonin and reacted more intensively to successively increasing doses of this substance. The indices of intensity of contraction of the segments of colon under the influence of different doses of serotonin in the control animals lie below those for the animals with avitaminosis K and are almost parallel to them. The intensity of contraction of the segments of colon, in relation to the dose of serotonin in both groups of animals, is expressed by lines which are practically straight, especially in the range of serotonin concentrations from  $10^{-9}$  to  $10^{-7}$ .

This linear relationship between the amplitude of the contraction and the concentration of serotonin makes this a particularly suitable model for the quantitative estimation of this substance. Consequently, ligation of the bile duct in rats, performed 26-30 days before the determination, leads to a considerable increase in the sensitivity of segments of the colon to serotonin. Probably a fundamental role in this phenomenon is played by the development of avitaminosis K, and not by the deficient secretion of bile. This

may be concluded from earlier investigations, which showed that the administration of vikasol to dogs or rats following ligation of the bile duct completely compensates for the disturbance of tone of the smooth muscle of the gastro-intestinal tract and of certain other organs [3]. Administration of dicoumarin to animals causes disturbances of the intestinal tone similar to those arising as a result of ligation of the bile duct. It is not yet clear why avitaminosis K should produce a decrease in the reactivity of the gastro-intestinal tract to adrenalin, and at the same time it should increase the sensitivity of some of its parts to serotonin.

The method used above is often adopted for the quantitative estimation of serotonin as being the simplest and most convenient. However, segments of the colon of rats are comparatively less sensitive to serotonin than strips of stomach or of virgin uterus [10, 14]. Ligation of the bile duct in rats 26-30 days before the investigation increases the sensitivity of segments of the colon to serotonin, and it may be used in practice when the necessity for determining very small quantities of serotonin arises.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.