

extracellular H^+ during contraction of frog stomach smooth muscle and more recently Kulbertus(11) has observed this in carotid artery strips. Both of these authors have attempted to relate this change to metabolic events. The pattern of H^+ increase which we have monitored in association with vasoconstriction seems to be related to Na^+ exchange, however, and this suggests to us that ion exchange processes rather than metabolic events may be responsible.

Summary. PLV-2, a synthetic vasopressin, administered subcutaneously in the nephrectomized rat, produces a shift of water and, in greater degree, of Na out of the extracellular space and into cells as measured chemically in aorta and skeletal muscle. No shift of K can be measured. When arterial blood in the intact rat is monitored with glass electrodes following intravenous injection of PLV-2, the shift of Na in excess of water into cells is reflected by a rise in blood K^+ . Since these changes are associated with an increase in blood H^+ it is suggested that ion exchange processes may be involved.

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Synthesis of Deoxyribonucleic Acid in the Liver of Hypophysectomized Rats After Partial Hepatectomy.* (30499)

H. RABES, H. WRBA† AND H. BRANDLE (Introduced by Vernon Riley)
Institute of Pathology, University of Munich, Germany

The role of the pituitary in liver regeneration following partial hepatectomy is not clearly understood. Cater *et al*(1) were able to demonstrate a prolongation of DNA synthesis and mitotic activity in partially hepatectomized rats following somatotropin injections. The peak of mitotic activity shifts in time following hypophysectomy (Hemingway and Cater(2), Weinbren(3)). Mitotic activity and growth need not follow a directly proportional course in an organ having cells of different stages of ploidy; however, it

should be possible to more accurately define the effect of hypophysectomy on liver regeneration by determining the rate of synthesis or turnover of DNA.

Method. Sprague-Dawley rats weighing 180 g were hypophysectomized by the technique described by Reiss *et al*(4). Thirty days later, $\frac{2}{3}$ of the liver was removed from the animals. Non-hypophysectomized control rats of the same age were also partially hepatectomized at the same time. At varying intervals following hepatectomy, the rats received intraperitoneally 0.8 μ c thymidine-6-T(n) (Radiochemical Centre of Amersham, specific activity 1.9 C/mM) per g body weight. The animals were sacrificed 60 minutes later and the liver was removed and

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† Present address: Inst. for Exp. Path., German Cancer Research Center, Heidelberg, Germany.

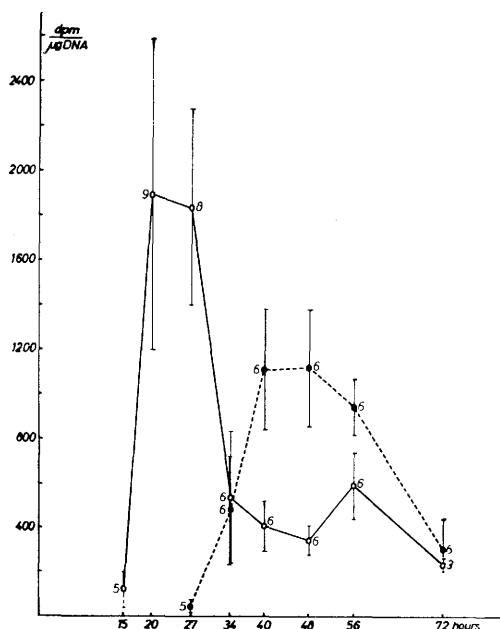


FIG. 1. DNA synthesis in regenerating liver of normal (solid line) and hypophysectomized rats (dotted line) at various intervals following partial hepatectomy.

Abcissa: Time of injection of thymidine-6-T(n) after surgery (0.8 μ C/g body wt, specific activity 1.9 C/mM). Liver taken out after 60 min and DNA extracted.

Ordinate: Disintegrations per min/ μ g of DNA. Mean values of number of animals indicated for each point on graph.

Vertical lines equal standard deviations.

deep-frozen. DNA was extracted from 0.5 g of liver of both hypophysectomized and normal rats by the method described by Schmidt and Thannhauser(5) and Hecht and Potter (6). The activity of aliquots of the extract was measured with a Packard liquid scintillation counter (model 3214), and the number of disintegrations per minute was corrected with an internal standard. The DNA content was determined by photometry with diphenylamine according to Dische(7) at 600 $m\mu$.

Results. Fig. 1 illustrates the specific activity of DNA (disintegrations per min/ μ g of DNA) in normal regenerating liver and agrees with the statements of other workers (Hecht and Potter(6)). DNA synthesis begins in the liver between 15 and 20 hours following surgery. A steep decline of synthetic activity follows, and a minimum is reached after 48 hours. However, 56 hours

after surgery the specific activity of liver DNA rises again to a value significantly higher than the activities determined between 48 and 72 hours following hepatectomy.

In the hypophysectomized rat the synthesis of DNA starts later, beginning as late as 27 to 34 hours after surgery, and reaches a peak between 40 and 48 hours. Regenerating liver of normal rats shows but little DNA synthesis at this time, having passed its peak many hours earlier. After 72 hours, the specific activity of DNA returns to a lower level. Thus, following hypophysectomy, DNA synthesis in the regenerating liver exhibits a delayed start, a more prolonged period is required to reach its peak, a longer period of maximal incorporation of DNA precursor, and a slower decline of DNA synthesis. However, no certain quantitative relationship may be derived from the different levels of specific activity seen in livers of normal and hypophysectomized rats following partial hepatectomy, since no direct comparison of specific activities of DNA in hypophysectomized and hepatectomized rats with those in merely hepatectomized rats is possible. There may, however, be considerable differences between the two groups in the velocity of resorption of labeled material, in the competition of other organs, in the flow of DNA metabolites, and in degradation and storage. The question of a quantitative difference in the synthesis peak is being studied with the aid of autoradiographic techniques.

Discussion. The conclusion of the presynthetic phase is a prerequisite for the beginning of DNA synthesis. It would seem that the proper timing of processes in the presynthetic phase may be linked to pituitary cooperation. The supply or activation of suitable enzymes is obviously essential for DNA synthesis in a fully differentiated adult organ. The beginning of DNA synthesis parallels the rise in activity of enzymes catalyzing the formation and polymerization of nucleotides(8). Irradiation in the early phase following partial hepatectomy prevents this enzymatic rise(9) and also the formation of nucleolic ribonucleic acid(10).

These two observations may have some

connection. Following hypophysectomy the RNA content of the liver decreases, but is restored again by somatotrophic pituitary hormone(11). Korner(12) noted an increase in an RNA fraction, possibly messenger RNA, in hypophysectomized animals following the administration of somatotrophic hormone. It might be possible that the pituitary promotes the synthesis of specific enzymes involved in DNA synthesis by affecting messenger RNA formation, which would accelerate the beginning of DNA synthesis in partially hepatectomized animals.

Summary. DNA synthesis in regenerating liver following partial hepatectomy of normal and hypophysectomized rats was measured following administration of thymidine-6-T(n). Such DNA synthesis in the hypophysectomized animals exhibits a delayed start and a prolonged period before its peak is reached, as compared with intact animals. However, there is a prolongation of maximal incorporation of DNA precursor, and a slower decline of DNA synthesis in hypophysectomized rats. The promotion of enzyme

activity involved in DNA synthesis may be linked to the pituitary effects upon messenger RNA formation.

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Interactive Effects of X-Irradiation and Barbiturates.* (30500)

V. NAIR, S. FINER AND D. SHAH

Neuropharmacology and Biochemistry Laboratories, Michael Reese Hospital Psychiatric Institute, and Department of Pharmacology, Chicago Medical School, Chicago, Ill.

Previous studies have shown that the anti-convulsant action of acetazolamide was enhanced with respect to the potency, onset and duration of action in head X-irradiated rats(1). It was also found that the enhanced pharmacological effects were temporally related to increased entry of drug into specific brain regions. The present investigation was undertaken to ascertain whether the pharmacological effects of other centrally acting drugs are enhanced or modified in head X-irradiated animals. This report describes our studies with the barbiturates, thiopental, pentobarbital and barbital. These 3 barbitu-

rates differ in their spectrum of action. Thiopental is an ultra short acting drug with a rapid onset of action. Pentobarbital has a short to intermediate duration of action. With barbital, the onset of action is slow and duration of action long. These 3 drugs are well suited to differentiate the radiation effects on the onset and duration of barbiturate hypnosis.

Materials and methods. A total of 140 male Sprague-Dawley rats weighing 200-250 g were employed in these studies. Food and water were given *ad libitum* except when otherwise indicated. Pentobarbital and thiopental were obtained from Abbott Laboratories and sodium barbital from Merck and Co.

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