Analysis of the Convulsant Action of Pentylenetetrazol

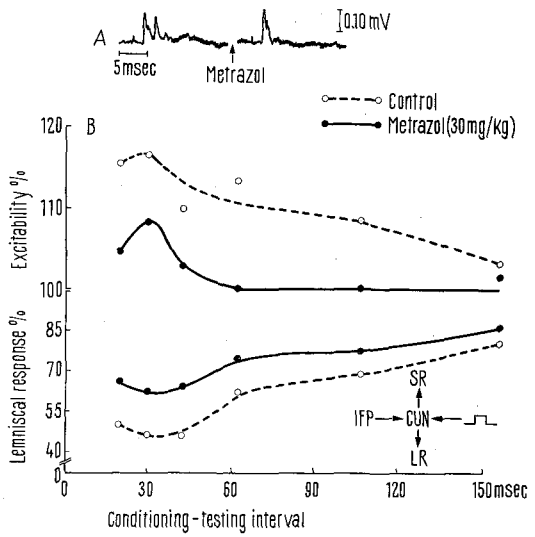
Strychnine has been shown to block post-synaptic inhibition[1], whereas picrotoxin has been found to act by reducing presynaptic inhibition in the spinal cord[2]. The results obtained with pentylenetetrazol (Metrazol, Cardiazol), however, were inconclusive[2-4]. The purpose of the present investigation was to reexamine the effects of small convulsant doses of pentylenetetrazol on presynaptic inhibition in the cuneate nucleus using direct as well as indirect testing procedures. The cuneate nucleus was chosen for study because of its accessibility and because inhibition of tactile input at that level has a strong presynaptic component. The methods of displaying presynaptic inhibition in this nucleus and the underlying synaptic mechanisms have been elucidated[5]. Furthermore, cuneate presynaptic inhibition has been shown to be sensitive to the convulsant drug picrotoxin[6] in the same way as spinal presynaptic inhibition is. Pentylenetetrazol was instilled locally or administered i.v. in doses close to those required to produce convulsions in the intact cat.

Adult cats were anesthetized with pentobarbital (i.p.) and later maintained under light anesthesia with small i.v. doses. Some cats were decerebrated at the intercollicular level under ether anesthesia, after which the ether was discontinued. All cats were mounted stereotaxically, immobilized with gallamine, and maintained under artificial respiration. Two types of experimental procedures were used to investigate presynaptic inhibition. First, gross potentials were recorded from the surface of the cuneate nucleus with a silver ball electrode after electrical stimulation of the ipsilateral or contralateral forepaw or of the contralateral sensorimotor cortex. Second, a glass microelectrode was inserted into the cuneate nucleus for direct stimulation, and the antidromic response recorded in the ipsilateral superficial radial nerve with a bipolar platinum electrode. The synaptically-conducted, orthodromic discharge was recorded by a monopolar electrode placed stereotaxically in the contralateral medial lemniscus. Conditioning stimulation was applied to the ipsilateral forepaw or to the contralateral peri-cruciate region of the cortex.

The onset of action of pentylenetetrazol, administered i.v. in doses of 20–80 mg/kg, was almost immediate and its duration was brief. The antidromic response, recorded in a cutaneous nerve after direct stimulation of the cuneate nucleus, normally consists of 2 spike complexes (Figure A). The second spike complex is thought to be the dorsal column reflex, reflecting stimulation of interneurons which are on the presynaptic inhibitory pathway[7]. This reflex is very sensitive to picrotoxin. It was also found to be depressed by convulsive doses of pentylenetetrazol. The effect of pentylenetetrazol on the ability of conditioning pulses to increase the amplitude of the first spike complex was studied in 6 experiments. In all the doses used it depressed the increase in excitability of the cuneate afferent terminals produced by the conditioning volleys at all conditioning-testing intervals (15–160 msec), as shown in Figure B. These effects could also be observed after local application of a 2% solution of pentylenetetrazol in physiological saline, in which case, however, the onset of action was somewhat delayed (10 min).

Inhibition of the synaptic discharge of the cuneothalamic neurons by conditioning volleys in cutaneous sources was also studied. In 5 out of 7 experiments pentylenetetrazol decreased this inhibition both after local instillation as well as after i.v. administration. In some experiments pentylenetetrazol resulted in a 20% depression of the test lemniscal response. Finally, the *P* waves recorded after cutaneous as well as contralateral cortical stimulation were reduced in size by pentylenetetrazol. *P* waves recorded in decerebrate unanesthetized cats after cutaneous stimulation were similarly depressed. The *P* wave is a reflection of underlying depolarization of cuneate terminals. In all the experimental procedures described, no correlation could be observed between the dose of the drug and the effect produced. The blood pressure effects of pentylenetetrazol were mild and independent of the neurophysiological changes.

It is thus apparent that pentylenetetrazol blocks afferent terminal depolarization and reduces presynaptic inhibition. This has been observed even in doses as low as 20 mg/kg. All its effects could be antagonized by pentobarbital. It is interesting to speculate why, unlike picrotoxin, pentylenetetrazol sometimes decreased the size of the post-synaptic discharge in the medial lemniscus and exerted a less pronounced, and more erratic, effect on presynaptic inhibition. This combined effect of excita-



The effects of pentylenetetrazol on cuneate transmission. (A) antidromic potentials recorded in the superficial radial nerve after direct stimulation of the cuneate nucleus, showing the reduction of the second spike complex (the dorsal column reflex) by metrazol (30 mg/kg). (B) Time course of the increase in excitability of the cuneate terminals and the depression of the lemniscal response after conditioning pulses in the ipsilateral forepaw pad (IFP). The cuneate nucleus (CUN) was stimulated directly with a glass microelectrode and the synaptically conducted lemniscal response (LR) as well as the antidromic potentials in the superficial radial nerve (SR) were recorded.

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tion and inhibition has also been reported in the spinal cord[3]. There is anatomical evidence[8] for the presence in the central nervous system of excitatory interneurons which synapse with presynaptic terminals as well as with the dendrites of the neurons on which these presynaptic terminals end. If pentylenetetrazol blocks both of these sites, its combined effects of facilitation and inhibition, as well as the lack of dose-response relationship, would be accounted for.

Résumé. Les effets du pentylènetetrazol sur la transmission de l'influx nerveux dans le noyau de Burdach furent étudiés. Il apparut que ce produit empêche l'augmentation de l'excitabilité des extrémités afférentes cunéaires et l'inhibition de la réaction lémnisque, ceci en conditionnant les décharges cutanées. Le pentylènetetrazol réduit aussi l'intensité de l'onde de surface positive. Le pentobarbital parut s'opposer à ces effets. En conclusion, le cardiazol bloque l'inhibition présynaptique.

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Vitamin A-Deficiency and Cartilage in Healing Skull Fractures of Rats

During the healing of skull vault defects in the rat fed adequately, cartilage is seen rarely[1] or none is reported[2,3], except in one experiment[4] involving 50 rats less than 7 days old of which 19 formed some cartilage. HOWELL and THOMPSON[5] have related an abnormal subperiosteal formation of cartilage in the lumbosacral vertebrae to a vitamin A-deficient state in chicks. This report concerns the incidence of cartilage development observed in repairing parietal bone defects in 32 albino rats made vitamin A-deficient[6] beginning at weaning and in 24 control litter-mates treated similarly but given orally in almond oil a supplement providing 50 IU of vitamin A palmitate per day. The bone lesions were made by scraping back the pericranium of one side, drilling through the skull and enlarging the hole by breaking off small bone pieces.

Operations were performed on animals between 12–18 weeks of age. At that time the vitamin A-deficient group alone showed most or all of the following symptoms: white fur, pale incisor teeth, inflamed eyelid margins, low weight and loss of appetite. Assays[7] performed at death on 10 deficient animals gave vitamin A concentrations between 0–9 μg/100 ml in the blood and 0–9 μg/g in the liver. All fractured skull vaults were prepared for histological examination.

Cartilage developed between the 9th and 28th postoperative day in 12 of the 21 vitamin A-deficient animals, but only in 1 of the 19 A-supplemented rats, surviving into that period. The cartilage occurred as

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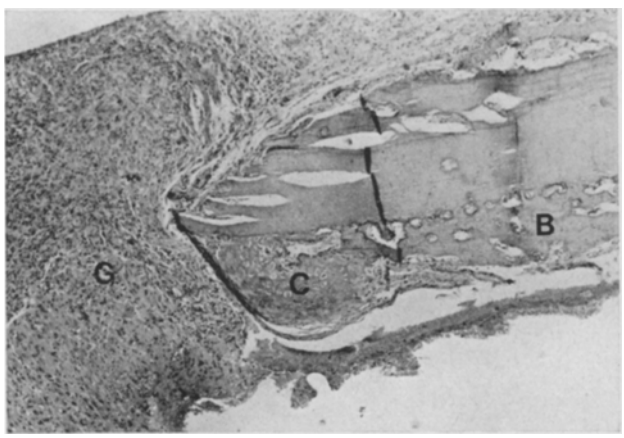

Fig. 1. The skull margin of a vitamin A-deficient rat surviving 21 days has a callus on its dural side comprising bone (B), and cartilage (C) near to the brain (G) herniating through the defect. Haematoxylin and eosin. × 80.

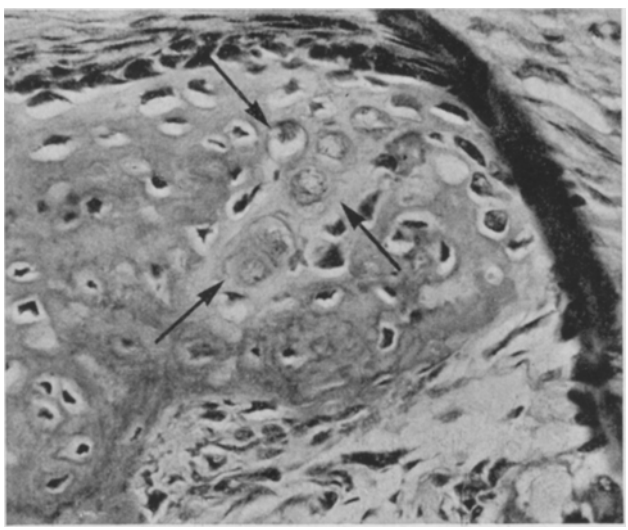

Fig. 2. The bony callus of a vitamin A-supplemented rat living 21 days post-operatively includes a small area of cartilage (arrowed). Haematoxylin and eosin. × 500.