previously (Bergel 1961*a*, *b*). The adapted nerve firing rate has been related to the dimension changes of the sinus. An example of the response to perfusion of the sinus at the animal's own arterial pressure is shown in the figure.

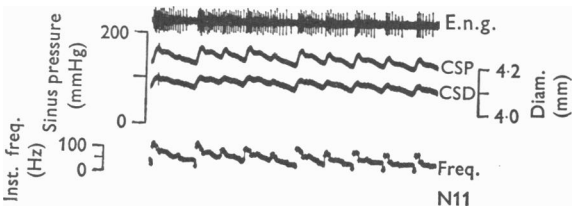

Fig. 1. Carotid sinus pouch perfused at the animal's own blood pressure. Records from the top down: electroneurogram (E.n.g.) from single carotid baroreceptor fibre; carotid sinus pressure, mmHg (CSP); carotid sinus dimension, mm (CSD) from ultrasound record; instantaneous firing frequency (Hz) of baroreceptor fibre. The close similarity of the lower three traces is apparent.

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A simple teaching film illustrating intestinal movements

BY BARBARA G. COLES and R. V. COXON. *University Laboratory of Physiology, Parks Road, Oxford.*

COMMUNICATIONS

Correlation between ultrastructure and histochemistry of mammalian intrafusal muscle fibres

BY R. W. BANKS, D. BARKER, D. W. HARKER and M. J. STACEY. *Zoology Department, Durham University, Durham*

We have devised a technique that allows for adjacent sections of the same muscle spindle to be prepared for either histochemical or ultrastructural study. Muscle is frozen in iso-pentane cooled to $-160°$ C and serial transverse sections cut in batches at about 15 μm alternating with much thicker ones at about 60 μm. Various histochemical techniques are then applied to the thin sections, while the thick sections are processed for

the observation of ultrastructure in both transverse and longitudinal section. We have sectioned cat and rabbit peroneus longus, peroneus digiti quinti and tenuissimus muscles, and the same peroneal and soleus

TABLE 1. Correlation of ultrastructure and histochemistry in cat, rabbit and rat intrafusal muscle fibres at two levels in the spindle: A, that adjacent to the area of equatorial nucleation; B, that part of the juxta-equatorial region lying nearest to the equator. Bag fibres designated 'bag_1' and 'bag_2' on the basis of their ATPase reactions following Ovalle & Smith (1972). Staining reactions: +, low; + +, medium; + + +, high. Condition of M line: 0, absent; M, present, dM, two faint parallel lines.

	Level	Fibre	Diameter	alk ATPase	P'ase	Glycogen	M line
Cat	A	Bag_1	Medium	+	+	+/+ +	0/dM
		Bag_2	Large	+ +	+ +	+ +	0/dM
		Chain	Small	+ + +	+ + +	+ + +	M
	B	Bag_1	Medium	+	+	+	0/dM
		Bag_2	Large	+ +	+ +	+ +	M
		Chain	Medium	+ + +	+ + +	+ + +	M
Rabbit	A	Bag_1	Medium/large	+	+	+ +	0/dM
		Bag_2	Large	+ +	+ +	+ +	0/dM
		Chain	Small	+ +	+ +	+ +	M
	B	Bag_1	Medium/large	+	+/+ +	+ +	0/dM
		Bag_2	Large	+ + +	+ +	+	M
		Chain	Medium	+ + +	+ + +	+ +	M
Rat	A	Bag_1	Medium	+	+	+	0/dM
		Bag_2	Large	+ +	+ +	+	0/dM
		Chain	Small	+ +	+ + +	+ +	M
	B	Bag_1	Medium	+	+/+ +	+ +	0/dM
		Bag_2	Large	+ +	+ +/+ + +	+ +	M
		Chain	Medium	+ + +	+ + +	+ +/+ + +	M

muscles of the rat, studying one spindle from each muscle. Histochemical profiles of intrafusal muscle fibres were determined with respect to actomyosin ATPase after alkali pre-incubation (alk ATPase; Guth & Samaha, 1971), phosphorylase (P'ase; Eränkö & Palkama, 1961), and glycogen (PAS method). Ultrastructural observations have so far been restricted to noting the M-line conditions.

The results (Table 1) show that there may be variations in histochemical profile along the length of all types of intrafusal muscle fibre, and that the bag_2 fibres also show regional differences in ultrastructure.

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The spontaneous activity of cortical neurones in sleep and wakefulness

By B. Delisle Burns and A. C. Webb. *National Institute for Medical Research, Mill Hill, London NW7 1AA*

Interval distributions derived from the spontaneous activity of single cortical neurones in the unrestrained cat can be described by log-normal curves (Burns & Webb, 1975). This description has proved satisfactory for those cells in visual, parietal and auditory cortex which fire faster than 2·5/sec. Thus, for these neurones, two parameters – a model interval and a geometric standard deviation (GSD) – are sufficient to define the whole temporal pattern of discharge. The same two parameters may be used to describe the first part of the interval distribution of cells firing less frequently. We have tried to find out whether the values of these parameters vary systematically with gross changes in the animal's state of alertness.

The spontaneous activity of single cortical neurones was recorded from unrestrained cats (Burns, Stean & Webb, 1974) when the animals were awake and when they were sleeping. A cat was said to be asleep when he lay with his head supported, eyes shut and pinnae unresponsive to laboratory noises. REM sleep was identified by jerky movements of the eyes and limbs. We have examined 70 trains of action potentials from 44 neurones in visual, parietal and auditory cortex, and the results justify the following conclusions:

We have confirmed the finding of other workers (Evarts, 1964; Noda & Adey, 1970) that sleep is invariably accompanied by a shortening of the modal interval. On average, the modal interval shortens by a factor of four when an animal falls into a quiet sleep. This coincides with an increase of nearly 75% in the size of the GSD. When an animal fell into REM sleep, these two parameters assumed mean values which were midway between those found in the waking animal and those appropriate to quiet sleep.

We were also able to assess the animal's state of arousal by examining a train of only 200 action potentials derived from a single neurone in any of the three areas studied. Our results suggest that interval distributions with modal intervals which are shorter than 19 msec are characteristic of neural activity recorded from a sleeping animal. This rule offers a 91% chance of successfully classifying a single interval distribution. A composite measure, the geometric coefficient of variation [log(GSD)/log(mode)], can also serve as an efficient 'test' of arousal. If one assumes that geometric coefficients of variation larger than 0·32 are diagnostic of records taken from animals which are asleep, one's chance of making an accurate classification is 87%. We were, however, unable to make any similar distinction between quiet and REM sleep.

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Possible central cholinergic mechanism for the production of catechol convulsions

BY A. ANGEL and D. G. DEWHURST.* *Department of Physiology, University of Sheffield S10 2TN*

Of the convulsant polyhydroxylic phenols, catechol has been shown to be the most potent (Angel & Rogers, 1972). The convulsions occur after administration of catechol, either spontaneously, or in response to tactile or auditory stimuli, and characteristically consist of severe tremor and brief clonic jerking of the body musculature. The convulsions are entirely central in origin (Angel & Lemon, 1973), so studies relating to the pharmacological mechanism of action of catechol were directed towards central neurotransmission.

The effects of various drugs on spontaneous convulsions were evaluated either by measuring total integrated activity (Angel, 1970) of anaesthetized mice following catechol administration, before and after drug treatment, or by looking for changes in the median convulsant dose, CD_{50}, of drug-treated as compared to control groups of mice (Weil, 1952).

Drugs which modify catecholaminergic transmission (reserpine, pargyline, iproniazid, pyrogallol, 6-hydroxydopamine, D-L propranolol, phenoxybenzamine, phentolamine, L-DOPA, and apomorphine) were found to be ineffective in changing the convulsive response, with the exception of pyrogallol, which was found to significantly potentiate the effects of catechol. Similarly drugs modifying 5-hydroxytryptamine transmission (para-chlorophenylalanine, L-tryptophan, methysergide) and cerebral γ-aminobutyric acid concentrations (GABA, amino-oxyacetic acid), had no consistent effect on the convulsions.

On the other hand, drugs affecting cholinergic transmission were active in modifying the response to catechol. Atropine and hyoscine significantly reduced the intensity of the convulsions, while eserine and neostigmine potentiated both the intensity and duration of the convulsions. Mecamylamine, pempidine and hexamethonium were found to be less effective than the muscarinic-receptor blocking drugs, while atropine methyl nitrate, a peripheral muscarinic blocker, had no effect on the convulsions.

* M.R.C. Scholar.

The results indicate that the catecholamines, 5-hydroxytryptamine, and γ-aminobutyric acid have no significant role in the production of the convulsions. Pyrogallol potentiates the effects of catechol by competitively inhibiting catechol breakdown by the enzyme catechol-*O*-methyl transferase. It appears that catechol has a central cholinergic mechanism of action, acting predominantly at muscarinic sites, possibly by increasing the amount of transmitter released per nerve impulse, as at the neuromuscular junction (Mogey & Young, 1949; Otsuka & Nonomura, 1963; Blaber & Gallagher, 1971).

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Control of collateral sprouting in mechanosensory nerves of salamander skin

BY E. COOPER, J. DIAMOND, LYNN MACINTYRE and C. TURNER. *M.R.C. Group in Developmental Neurobiology, Department of Neurosciences, McMaster University, Hamilton, Canada*

Our evidence from salamanders indicates that nerve section results in collateral sprouting of adjacent nerves not because of 'products of degeneration', or loss of function, but because fast axoplasmic transport is interrupted in the cut nerve (Aguilar, Bisby, Cooper & Diamond, 1973). Colchicine block of transport caused an identical sprouting of adjacent untreated nerves, although the treated nerve behaved normally, and its mechanosensory skin endings, we now know, are quantitatively unchanged in both number and function.

After partial denervation of the salamander hind limb, sprouting of the remaining nerves quantitatively makes up the loss of functional endings in the skin. There is, however, an invisible frontier between their territories which the 15th and 17th nerves will grow up to, but which they will not cross even if all the nerves beyond it are degenerating. The effect is not due to a mechanical barrier in the skin or to a limited capacity of those nerves to sprout. It seems that the local stimulus which evokes collateral sprouting, which we suggest is produced by the target-tissue, has a selectivity of action. Surprisingly, skin rotation experiments suggest that the origin of this selectivity may not be in the skin itself.

After amputation the hind limb regenerates fully; the skin is then quite

indiscriminately innervated by the original three spinal nerves. If it is present, the mechanism underlying selectivity is ineffective in these conditions. Even in the normal limb a *regenerating* nerve can to some extent ignore this regional specificity; guided into denervated foreign skin by way of a degenerating nerve trunk, it makes normally functioning sensory endings there, but it does not sprout beyond the limits of the presumed mechanical guidance. Apparently, regenerating and intact nerves have different 'drives' with regard to sprouting. Additional evidence for this comes from seasonal studies. In winter, cut nerves will regenerate to produce functional endings exactly as they do in summer; however, intact nerves often seem totally unable to sprout in response to section or colchicine treatment of adjacent nerves. Perhaps the peripheral stimulus is absent.

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A role for a descending sympatho-inhibitory pathway in the ventral part of the spinal cord

BY J. H. COOTE* and A. SATO. *Metropolitan Institute of Gerontology, 35–2 Sakaecho, Itabashiku, Tokyo 173, Japan*

The somatic afferent evoked reflex discharge into cardiac and renal sympathetic nerves usually involves a long pathway ascending to, and descending from, the brain stem (Sell, Erdelyi & Schaefer, 1958; Coote & Downman, 1966). A shorter spinal pathway can be demonstrated, but not readily when the central nervous system is intact. This led Coote & Downman (1966) to conclude that the spinal reflex pathways were normally inhibited by a bulbospinal inhibitory system, which is tonically active. In recent years several inhibitory pathways on to sympathetic neurones have been identified (Illert & Seller, 1969; Illert & Gabriel, 1972; Coote & Macleod, 1974) but the functional role of some of them has not been ascertained. The present experiments were designed to examine the possibility that one of these descending inhibitory systems is responsible for blocking the segmental pathway of the somato-cardiac reflex. In six cats anaesthetized with chloralose, the only example of a somato-cardiac reflex response elicited by single or double shock, to an intercostal nerve of an intensity 1·4–300 times the afferent fibre threshold, was acompact potential occurring after a mean latency of 56·0 msec, S.D. $\pm$ 8·0 msec (n = 68). The effect on this cardiac reflex of small transverse cuts in the spinal cord at the level of C4 was examined. In all six animals an early somato-cardiac reflex

* Present address: Department of Physiology, The Medical School, Birmingham.

appeared following a section made diagonally across the spinal cord from the contralateral dorsal horn to include the ventral part of the lateral funiculus and/or the lateral part of the anterior funiculus. A hemi-section of the contralateral spinal cord or a section of dorsal columns performed some hours previously had been without effect. The mean latency of these early reflex responses was 23 msec S.D. $\pm$ 5 msec. The latency of the early response was little changed following a complete section of the spinal cord, but the long latency response was abolished.

Histological examination showed that the effective lesion was in the region of the spinal cord which contains a known sympatho-inhibitory pathway which originates in the ventromedial reticular formation (Coote & Macleod, 1974, and unpublished observations), within the so-called medullary depressor region, as mapped by Alexander (1946).

It seems therefore that this is a major inhibitory system determining whether an afferent volley eliciting a response in cardiac nerves is routed over a long pathway to the brain stem or over a short spinal pathway. Such a system may play a vital role in fashioning a widespread and patterned autonomic response.

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Hind limb vasodilatation evoked by stimulation of the motor cortex

BY S. M. HILTON, K. M. SPYER and R. J. TIMMS. *Department of Physiology, The Medical School, Birmingham, B15 2TJ*

It has often been proposed that the motor cortex might initiate, via the pyramidal tract, the increased limb blood flow which occurs with exercise. Several investigators have reported that stimulation within the motor or pre-motor cortex can elicit vasodilatation in the limbs, mediated by inhibition of sympathetic vasoconstrictor tone exerted via the pyramidal tract (e.g. Zwirn & Corriol, 1962), or by sympathetic cholinergic dilator fibres (Eliasson, Lindgren & Uvnäs, 1952). We have reinvestigated these questions, using carefully controlled electrical stimulation of the motor cortex.

In cats, lightly anaesthetized with a continuous infusion of 'Althesin' (Glaxo, alphaxalone-alphadolone), the 'hind limb area' of the motor

cortex was stimulated via a monopolar electrode with rectangular pulses (50–100 Hz; 1–2 msec duration). Blood flow to each hind limb, with the paw ligated, was recorded using electromagnetic flowmeters. Arterial blood pressure and heart rate were also recorded and hind limb vascular conductance computed on-line. An e.m.g. was taken from one hind limb and a fronto-occipital e.e.g. was monitored to assess the level of anaesthesia.

Stimulation with currents of 400–900 μA evoked muscle contractions in the contralateral hind limb and an increase in conductance, usually with a slight fall in blood pressure and some tachycardia. The conductance increase was never elicited by stimulus intensities below the motor threshold, and its size was related to the strength of contraction. Radio-frequency lesions of the medullary pyramid did not reduce the vasodilator response except when the contraction was reduced; subsequently increasing stimulus intensity then restored both contraction and flow responses.

The hind limb vasodilatation was not elicited during neuro-muscular block by gallamine triethiodide (3–4 mg/kg I.V.), though a fall in blood pressure and tachycardia sometimes persisted. The dilatation was resistant to atropine (0·4–0·8 mg/kg I.V.) and guanethidine (3 mg/kg I.V.), but was abolished by cordotomy at L4–L5.

The hind limb vasodilatation evoked by cortical stimulation was therefore secondary to muscle contractions. The present work strongly suggests that the motor cortex does not exert a direct influence over the sympathetic vasomotor activity to the limb muscles. Such influences as were suggested in earlier reports may be explained as a consequence of weak contractions that were not noticed, or by effects of epileptiform discharges or current spread to afferent fibres in the meninges.

This investigation was supported by a grant from the Medical Research Council.

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Micro-electrophoretic study of cat dorsal horn neurones activated by noxious stimuli

BY MIRJANA RANDIĆ and H. H. YU. *Department of Biochemistry and Pharmacology, Tufts University School of Medicine, Boston, Massachusetts, U.S.A.*

Neurones principally or exclusively excited by an input in nociceptor afferent fibres have been reported to exist in the dorsal horn marginal layer, Rexed's lamina I, by Christensen & Perl (1970). By using a micro-electrophoretic method we have studied the chemical sensitivity of the isolated

cat dorsal horn neurones activated by noxious stimuli (at the level of Rexed's laminae I and II) to putative central neurotransmitter substances (acetylcholine, L-glutamic acid, 5-hydroxytryptamine) and pain-producing polypeptide, bradykinin.

The experiments were performed on sixteen adults cats initially anesthetized by ether or Halothane. The brain was anaemically destroyed by bilateral occlusion of the common carotid and vertebral arteries. The spinal cord was transected at the first cervical level. Thereafter, the animal was artificially respired and immobilized by gallamine triethiodide or by a constant infusion of succinylcholine chloride. A coccygeal dorsal root was freed and placed on a bipolar stimulating electrode distally and a bipolar recording electrode centrally, leaving both peripheral and central connections intact. This electrode arrangement served for electrical stimulation and recording of compound action potentials of different kinds of myelinated and unmyelinated afferent fibres. The activity of the dorsal horn neurones located in the sacral and coccygeal segments of the spinal cord was recorded extracellularly through the central barrel of a multibarrelled glass micropipette filled with a solution of fast green (FCF, Matheson, Coleman and Bell) saturated in 3 M sodium chloride. The site of recording was marked by iontophoresis of a dye. Conventional micro-iontophoretic technique was used to study the effects of the following substances: acetylcholine chloride (1 M, pH 4·0, Schwarz/Mann); bradykinin triacetate dihydrate (10 mM in distilled water or 165 mM-NaCl, Calbiochem.); L-glutamic acid (1 M, pH 8·0, Calbiochem); 5-hydroxytryptamine creatinine sulphate (0·1 M, pH 4·3, Regis).

High-intensity mechanical stimuli were delivered to the skin of the tail (e.g. pressure from sharply pointed objects; squeezing a skin-fold between two rigid surfaces).

We have found that a majority of the cat dorsal horn neurones activated by noxious stimuli were excited by L-glutamate (20–80 nA) and some by acetylcholine (40–80 nA). Bradykinin, applied either micro-electrophoretically (50–200 nA) or intra-arterially (5–10 μm), excited nociceptive units after a variable, but relatively long latent period (30–90 sec). Excitation of polymodal nociceptors was also observed. 5-Hydroxytryptamine depressed the firing of almost all units activated by noxious stimuli, located in lamina I.

These results suggest a possible chemical transmitter or modulator role for L-glutamic acid, acetylcholine and 5-hydroxytryptamine at the level of spinal neurones that could be excited exclusively or predominantly by noxious stimuli.

This work was supported by PHS grant NS 11174–01 and NSF grant GB 37864.

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Functional coupling between nerve terminals in teeth

BY B. MATTHEWS. *Department of Physiology (Oral Biology), The Medical School, University Walk, Bristol BS8 1TD*

Action potentials can be recorded from the crown of a cat's lower canine tooth when chemical stimuli are applied to dentine and when single pulpal fibres in the inferior dental nerve are stimulated electrically. Recordings can also be made from isolated nerve fibres during chemical or electrical stimulation of the tooth (Horiuchi & Matthews, 1974; Matthews, 1975). Some of the observations made with this preparation prompted the suggestion that action potentials might be propagated from one nerve to another at their terminals and that several nerves might be coupled together to form a complex sensory unit in which stimulation of one fibre caused a near synchronous discharge in all of them. The experiments described were carried out to test this possibility.

Single fibres dissected from the inferior dental nerve were stimulated electrically and simultaneous recordings were made from another inferior dental nerve strand, which included several pulpal nerves, and from the canine tooth. Eight units have been isolated which, on stimulation, produced a complex, all-or-none potential in the record from the tooth and an action potential propagated away from the tooth in a fibre in the multiunit strand. The conduction velocities of the units were between 16 and 30 $msec^{-1}$.

One of these units also responded to the application of 2·5 mole/l. NaCl to the exposed dentine. This solution causes pain from human dentine (Anderson & Matthews, 1967) and is known to evoke a response from nerves in cat's teeth (Horiuchi & Matthews, 1974). With the one unit that showed evidence of coupling and also responded to this stimulus, each action potential recorded from the isolated fibre was associated with a complex action potential in the record from the tooth and an action potential propagated along the coupled fibre in the multiunit strand.

This work was supported by a grant from the Medical Research Council.

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Backward placing in intact kittens and adult cats

By V. E. Amassian. *Department of Physiology, SUNY Downstate Medical Center, New York, U.S.A.*

When initiated by contact with the dorsal, radial or ulnar aspect of the forelimb, contact placing (CP) has an initial lifting–withdrawal phase that is produced by activation of flexors (Amassian, Ross, Wertenbaker & Weiner, 1972). Backward placing is readily elicited by gentle contact of either the ventral apect of the wrist or the back of the heel of an unsupported limb with the side or the edge of a solid. Unlike forward, medial or

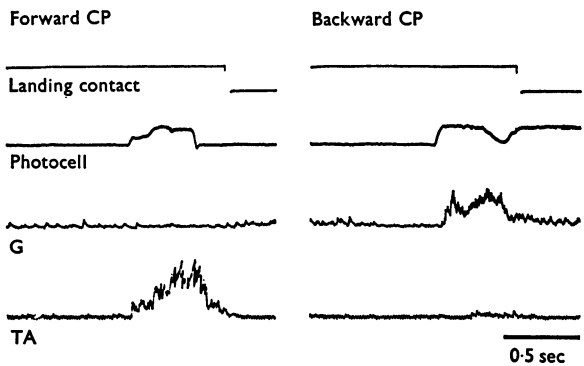

Fig. 1. Forward and backward placing in an intact 47-day-old kitten. Contact of the hind paw with the front of the apparatus interrupts light beams incident on a column of photocells. The altered output of the photocells is restored by lifting–withdrawal of the paw. Subsequently, if the paw lands on the solid, a circuit is completed through the kitten, the small current being driven by dissimilar electrode potentials. The electromyograms were each recorded with bipolar pins inserted percutaneously into the gastrocnemius (G) and tibialis anterior (TA) muscles; they were integrated with a decay time constant of 10 msec. The overall gain for TA is approximately five times that for G. At left, the dorsum of the digits contacts the apparatus. At right, contact of the back of the heel leads to backward placing, but the light beams are occluded by the protruding foot. All records played back from tape through an ink-writing oscillograph.

lateral CP, the paw is usually only partially placed on top of the solid, the digits protruding beyond the edge. Backward CP was elicited in adult cats and in kittens tested as early as 6–10 days old. In the intact kitten, the tibialis anterior is a prime mover in the initial phase of forward (dorsal) CP of the hind limb (Fig. 1. left), as was previously shown for the responses recorded in chronic spinal kittens by Forssberg, Grillner & Sjöström (1974). However, in backward CP, gastrocnemius is a prime mover and tibialis anterior is initially either silent or is only weakly activated with the ankle extensors (Fig. 1, right).

Flexors are prime movers in stepping (Grillner, 1973), which is prominent in spinal kittens. In such preparations, the difficulty in eliciting placing to tactile stimulation of the lateral aspect of the hind paw encountered by Forssberg *et al.* (1974), suggests the possibility that the response they readily obtained to dorsal stimulation started as a triggered step. Testing for backward CP provides an additional criterion which may be useful in distinguishing the full tactile placing reaction from other motor responses seen after lesions of the higher motor control systems.

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Synthesis of microtubule protein in rat visual cortex during early post-natal life in relation to eye-opening

BY J. R. CRONLY-DILLON and G. W. PERRY. *Department of Ophthalmic Optics, University of Manchester Institute of Science and Technology, Manchester M13 9PL*

In several species the functional organization of the visual cortex can be disrupted by visual deprivation during a certain 'critical period' in early development (Hubel & Wiesel, 1970). Recent evidence implicating microtubules in axonal transport suggests the possibility that the turnover of brain tubulin may be critical in determining growth during early development of the visual cortex. We have therefore measured the rate of tubulin synthesis during early life, paying particular attention to the period immediately preceding and following eye-opening.

Rats were reared under normal conditions of illumination and then killed at various times after birth, whereupon a plug of tissue was removed from the visual cortex in each hemisphere, care being taken to remove the white matter. The remaining plug of visual cortex grey matter was used for the estimation of tubulin. Both the concentration of tubulin and its rate of synthesis were studied using a double labelling technique. Tritiated colchicine was used to assay tubulin and radioactive [^{14}C]L-leucine injected intraventricularly 2 hr prior to death, to study rate of synthesis at different times post-natally.

Both concentration and rate of synthesis of tubulin initially show a gradual increase from birth. Then, at eye-opening, there is a very marked rise both in concentration and rate of tubulin synthesis which reaches a maximum at about 3–4 weeks. The rate then declines to a steady level at the sixth week which is maintained thereafter into adult life (see Fig. 1).

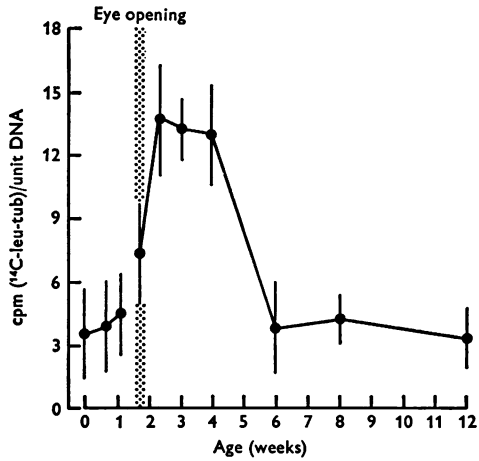

Fig. 1. Rate of tubulin synthesis. All results normalized with respect to the amount of DNA per unit wet weight visual cortex.

We are tempted to suggest here that the peak in tubulin synthesis which extends from eye-opening until about the sixth week after birth may indicate that the visual cortex at that time, is 'primed for growth and ready for learning'; and as such, this pattern in tubulin synthesis may be correlated with the critical period of susceptibility to visual deprivation. However, this has yet to be demonstrated physiologically.

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Comparison of effects of ammonia and CS aerosol upon exercise ventilation and cardiac frequency in healthy men

BY T. J. COLE, J. E. COTES, G. R. JOHNSON, H. DE V. MARTIN, J. W. REED and M. J. SAUNDERS. *M.R.C. Pneumoconiosis Unit, Llandough Hospital, Penarth, Glamorgan CF6 1XW, and Chemical Defence Establishment, Porton Down, Wiltshire*

Exposure to CS aerosol (0-chlorobenzylidene malononitrile) appears to reduce the exercise ventilation and increase the cardiac frequency (Cotes, Evans, Johnson, Martin & Reed, 1972). To help elucidate the mechanism

the response to a dosage of 0·4–4·4 mg m^{-3} has been compared with that to ammonia in the dosage 50–340 mg m^{-3} (70–480 ppm). The 17 subjects and the methods (including a progressive submaximal exercise test, Cotes, 1972) were similar to those used previously.

Measurements were made on three control days and during exposure to CS and ammonia in two concentrations. The conditions were similar on all occasions, except that during exposure, due to the ventilation of the chamber being turned off, the ambient temperature was on average 24·0° C compared with 20·4° C on the control days.

Ventilation and cardiac frequency were interpolated to an oxygen uptake of 45 mmol min^{-1} and tidal volume to a respiratory frequency of 20 min^{-1} ($\dot{V}_{E_{45}}$, $f_{C_{45}}$ and $V_{T_{20}}$ respectively).

$f_{C_{45}}$ was increased by exposure to CS by on average 6·0 min^{-1} ($P < 0·05$) from 101·3 to 107·3 min^{-1}; the increase was apparently related to dose. A similar increase was observed with ammonia.

$\dot{V}_{E_{45}}$ was depressed during exposure to both gases on average by 1·5 l. min^{-1} ($P < 0·01$) from 25·1 to 23·6 l. min^{-1}. The change reflected a diminution in the exercise tidal volume, the average $V_{T_{20}}$ diminishing from 1·34 to 1·14 l. ($P < 0·01$). The reduction for CS was independent of dose but for ammonia it was dose-related above a concentration of about 108 mg m^{-3} (150 ppm). The respiratory frequency was increased slightly by exposure to CS. With ammonia it was reduced by exposure to low concentrations and increased during exposure to higher ones.

These results confirm the earlier findings. They suggest that in the dosage used, the cardiorespiratory response to CS is small in relation to the associated intense discomfort and not much different from that to ammonia in doses which cause only minimal symptoms. The increase in cardiac frequency during exposure is that to be expected from the associated rise in ambient temperature (Miller & Martin, 1975). The reduction in ventilation volume may be due to the aerosols stimulating receptors in the respiratory tract (e.g. Boushey, Richardson, Widdicombe & Wise, 1974) and the changes in respiratory frequency to the operation of compensatory mechanisms.

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Assessment of closure of lung units based on the pressure–volume curve

By Jane Davis. *Physiological Flow Studies Unit, Imperial College, London, S.W. 7,* D. H. Glaister, *Royal Air Force Institute of Aviation Medicine, Farnborough, Hampshire,* and R. C. Schroter, *Physiological Flow Studies Unit, Imperial College, London, S.W. 7*

The deflation limb of the vital capacity pressure–volume curve in upright seated subjects and in excised lungs is sigmoid in shape. We have shown earlier (Glaister, Milic-Emili, Schroter & Sudlow, 1972) that the upper portion of the curve may be closely represented by an exponential function. The inflexion point, occurring at a distending transpulmonary pressure of approximately 3 cmH_2O, is associated with the onset of closure of lung units. This closure is either functional in form or real closure of small terminal airways.

We have studied the pressure volume curve at transpulmonary pressures below the inflexion point and separated the effects of progressive closure of units from the elastic properties of individual lung units. If closure of air spaces occurred simultaneously at residual volume then the pressure–volume curve would be exponential throughout its length. The ratio of the slopes of the actual and hypothetical pressure–volume curves at a given low transpulmonary pressure thus indicates the proportion of units ventilating at that pressure.

Deflation pressure–volume curves of excised dog and primate lungs and of seated normal subjects have been assessed in this way. It was found that approximately 70% of lung units closed when the transpulmonary pressure was reduced to 3 cmH_2O below the inflexion point, the pressure at which closure began. This indicates that the majority of lung units close around zero transpulmonary pressure. The rate of closure became much less as the pressure was further reduced and even at residual volume (-5 to -10 cmH_2O) approximately 10% of the units were still not closed. Units which have closed will resist any further reduction in size and will thus provide a degree of support for patent units making them stiffer and thus preventing their closure.

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Influence of smooth muscle tone on intrapulmonary airway calibre

By T. P. Clay, J. M. B. Hughes and Hazel A. Jones. *Departments of Medicine and Radiology, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS*

In the lung, airway expansion is linked to parenchymal expansion by virtue of tissue attachments (Mead, Takashima & Leith, 1970). At constant lung volume the compliance of peribronchial tissues might be sufficiently low to limit severely bronchodilation or constriction, especially at high lung volumes. Nevertheless, in excised lungs at constant volume a 20% narrowing of bronchial diameter occurred when intraluminal pressure was lowered by 15 cmH_2O relative to pleural pressure (Hughes, Jones, Wilson, Grant & Pride, 1974). In the present study the competing effects of (*a*) mechanical interdependence and (*b*) changes of smooth muscle tone, upon intrapulmonary airway calibre have been studied.

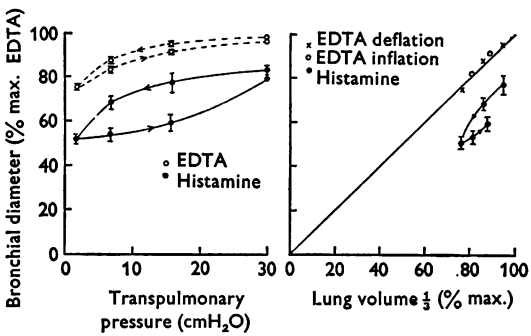

Fig. 1. Mean bronchial diameter as percent maximum after EDTA treatment plotted against (*a*) transpulmonary pressure and (*b*) cube root of lung volume (as percentage maximum) after treatment with histamine and EDTA solutions. Vertical bars indicate S.E. mean for all airways measured (n = 52, diameter range 0·9–6·4 mm). Line of identity between diameter and volume $\frac{1}{3}$ passes through EDTA points. Note almost parallel shifts produced by changes in smooth muscle tone.

Ten lower lobes from freshly excised dog lungs were degassed and filled with solutions of isotonic saline, histamine (5 μg/ml.) or isoprenaline (10 μg/ml.), and after twenty minutes emptied. Tantalum dust was insufflated into the airways and stereoscopic X-ray pairs taken to measure bronchial dimensions at several distending pressures during deflation and inflation. Lung volume changes were determined and absolute volume obtained from the weight and water displacement. The procedure was repeated after degassing and filling the lung with 4 mM-EDTA solution.

Fig. 1 shows airway diameter plotted against (*a*) lung distending pressure and (*b*) a linear function of volume, under conditions of high (histamine) and low (EDTA) airway tone. On inflation, changes of diameter occur at the same pressure and volume (up to 35 %) between EDTA and histamine, and these changes persist up to full inflation. Smaller airways (< 2 mm i.d.) showed the larger differences. Isoprenaline had a similar effect to EDTA.

We conclude that for the same lung volume the stiffness of peribronchial tissue attachments is not sufficient to prevent 30–35 % changes of intrapulmonary airway calibre when smooth muscle tone is varied.

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An evaluation of rebreathing techniques used in the measurement of cardiac output

BY E. ZEIDIFARD. *Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, London W12 0HS*

The non-invasive carbon dioxide and nitrous oxide rebreathing methods have often been used to determine cardiac output during exercise. The CO_2 rebreathing method estimates oxygenated mixed venous P_{CO_2} ($P\bar{v}_{CO_2}$) from a 10 to 12 sec rebreathing manoeuvre, and this is then inserted into the Fick equation for deriving cardiac output. In the N_2O rebreathing method, the cardiac output is determined directly from the rate of absorption of N_2O by pulmonary blood during a 10 to 12 sec rebreathing period.

A number of alternative techniques for performing these studies have been proposed, but little systematic evaluation of them appears to have been performed. Two alternative methods for measuring $P\bar{v}_{CO_2}$ during rebreathing are an exponential analysis of rising P_{CO_2} starting with a low gas concentration (Defares method) and linear extrapolations from near plateau levels (Denison method). In the N_2O method various alternative calculations have been used with varying degrees of correction for experimental errors.

In a series of studies, the various methods for measuring $P\bar{v}_{CO_2}$ and cardiac output during exercise were initially compared. Plateau estimates of $P\bar{v}_{CO_2}$ and cardiac output were found to be more reproducible than corresponding exponential estimates. Furthermore, for a range of rebreathing mixtures, a linear (Denison) as opposed to an exponential (Defares) extrapolation of $P\bar{v}_{CO_2}$ also improved the reproducibility of the

estimates. Investigation of various N_2O rebreathing methods indicated that the reproducibility of cardiac output was improved when the exponential-like uptake of N_2O by pulmonary blood was corrected for changes in the total rebreathing volume, and for a quantity of N_2O dissolved in lung tissue.

A comparison of the plateau CO_2 with the modified N_2O rebreathing method indicated that the absolute value of cardiac output, and their reproducibility, were similar in both methods. The two methods also compared favourably with direct Fick and dye dilution estimates of cardiac output.

The separate effects of alternate-breath oscillations of P_{A,CO_2} during hypoxia on inspiration and expiration

By D. J. C. Cunningham and S. A. Ward.* *The University Laboratory of Physiology, Oxford*

We have examined the phase relations of the breath-by-breath reflex responses of inspiration and expiration provoked by alternate inspirates of high and low P_{CO_2} during hypoxia (Marsh, Lyen, McPherson, Pearson & Cunningham, 1973; Cunningham & Ward, 1975; cf. Wolff, 1975). Thirty runs were performed at rest and 28 in mild exercise (H.R. ~ 120 min^{-1}), each run comprising 40–150 breaths from which 13 respiratory output variables were obtained (inspiratory and expiratory times, volumes, flows and accelerations).

A priori, flow and the time for which it occurs may be regarded as the primary variables of inspiration and expiration. The patterns of alternating response were therefore characterized in terms of mean inspiratory and expiratory flows ($\bar{v}_I$ and $\bar{v}_E$) and expiratory time (T_E). Inspiratory time was excluded from the analysis because of its stability in the face of the P_{A,CO_2} oscillation.

A variety of patterns was observed, one tending to predominate over the others in a given experiment both at rest and during exercise.

(1) A synergistic alternation of inspiratory and expiratory variables, in which an inspiratory stimulation ($\bar{v}_I$ increased) and an expiratory stimulation (either $\bar{v}_E$ increased or T_E decreased, or both) occurred in the same breath, and a depression of both in the next breath, *et seq.*

(2) An antagonistic alternation of inspiration and expiration, in which an inspiratory stimulation and an expiratory depression occurred in the same breath, and the converse in the next breath, *et seq.* This tended to stabilize ventilation.

* States of Guernsey Graduate Research Scholar.

(3) An alternation of inspiration alone.

(4) An alternation of expiration alone.

$V_{T,I}$ usually alternated more prominently than $V_{T,E}$; the breath-by-breath difference between them, which is ΔFRC, also alternated, indeed more consistently than any other variable. Thus the passive relaxation volume of the lung is accessible to the alternating signal.

These results are interpreted in terms of the dynamic properties of the carotid chemoreflex arc. In the cat either a stimulation of inspiration or a depression of expiration (increased T_E) may be produced by afferent chemoreceptor volleys, depending upon the time of arrival of the volley at the brainstem during the current respiratory cycle (Black & Torrance, 1967; Eldridge, 1972). Pattern 2 (antagonistic) could result if the alternating input to the brainstem arrived in phase with the respiratory cycle, and pattern 1 if the signal were out of phase by half a respiratory cycle.

It appears, therefore, that no single respiratory variable (e.g. ventilation) is the sole target for a changing drive under the conditions of our experiments. The ability to influence inspiration and expiration independently argues against an immutable linkage between them. Furthermore, the observation that FRC alternates is scarcely consistent with the return of lung volume to FRC being important for the initiation of inspiration.

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Effect of airway anaesthesia on the ventilatory response to CO_2 in man

BY BRENDA CROSS, A. GUZ and S. K. JAIN. *Department of Medicine, Charing Cross Hospital Medical School, London W. 6*

An aerosol of 5% bupivacaine hydrochloride was used to anaesthetize the airways of nine normal subjects. The method of administration, physical characteristics and effects on respiratory reflexes of the aerosol have been described previously (Archer *et al.* 1975; Jain, 1975). The cough reflex is abolished; the apnoeic response to lung inflation is severely reduced as is the reflex broncho-constriction produced by airway surface irritation with citric acid. There were no consistent changes in resting frequency, tidal volume or end-tidal P_{CO_2}(P_{ET,CO_2}).

Subjects rebreathed from a bag containing 6 l. 7 % CO_2/O_2 before and after bupivacaine inhalation. For each subject, linear slopes for minute ventilation $(\dot{V})/P_{ET,\,CO_2}$ and frequency $(f)/P_{ET,\,CO_2}$ were drawn visually from points of rise of $\dot{V}$ and f respectively, to the points of their peak responses. After bupivacaine, mean slopes of $\Delta\dot{V}/\Delta P_{ET,\,CO_2}$ and $\Delta f/P_{ET,\,CO_2}$ were greater and shifted to the left (Fig. 1). Bupivacaine increased the severity of the dyspnoea associated with rebreathing. The ventilatory response to inhalation of a single concentration of 5 % CO_2/O_2 was also enhanced. Control experiments using aerosols of saline or phosphate buffer (pH 5·4, like bupivacaine), or I.V. infusions of bupivacaine to produce comparable blood levels, produced no significant changes.

Airway anaesthesia in man thus appears to enhance the ventilatory sensitivity to CO_2.

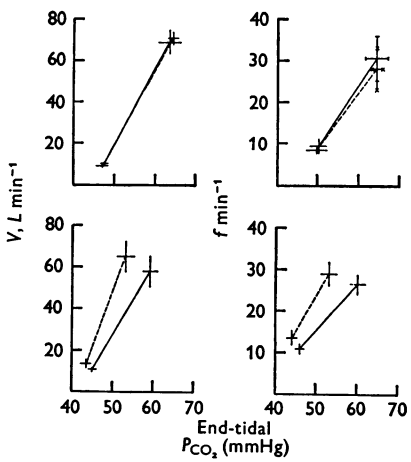

Fig. 1. $\dot{V}/CO_2$ and f/CO_2 response curves obtained before (——) and after (– – –) inhalation of aerosols of saline or phosphate buffer (upper graphs, n = 5), and inhalation of bupivacaine aerosol (lower graphs, n = 9). Lower and upper points of the slopes represent the means ± S.E. at the points of rise and peaks of the responses.

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The sympathetic contribution to increase in heart rate evoked by cutaneous nerve stimulation in the dog

By Yoko Kumagai,* J. Norman and J. G. Whitwam. *Department of Anaesthetics, Royal Postgraduate Medical School, Hammersmith Hospital, DuCane Road, London W12 0HS*

In dogs an increase in heart rate evoked by stimulation of a cutaneous nerve can be mediated by a cholinergic vagal pathway (Norman & Whitwam, 1974) and the magnitude of the response is related to the blood pressure before stimulation of the peripheral nerve (Norman & Whitwam, 1973*a*). However, stimulation of cutaneous nerves also evokes activity in sympathetic nerves in dogs (Fussey, Kidd & Whitwam, 1969; Norman & Whitwam, 1973*b*) and the experiments reported here were concerned with the role of the sympathetic nervous system in reflexly evoked increases in heart rate.

Dogs in which anaesthesia was induced with methohexitone and maintained with chloralose were artificially ventilated and paralysed with suxamethonium. The vagus nerves were exposed in the neck and a cutaneous branch of the radial nerve was desheathed, cut and mounted on stimulating electrodes in a mineral oil pool. Arterial blood pressure, the e.c.g., heart rate and a respiratory wave form were recorded. Trains of stimuli (intensity 40–60 V, duration 0·5 msec, frequency 20 Hz and train duration 10 sec), triggered by an *R* wave occurring in expiration, were applied to the radial nerve and the evoked changes in heart rate and blood pressure were measured.

Before and after vagotomy radial nerve stimulation evoked comparable increases in heart rate (averages 33 and 36 beats/min respectively) but the maximum heart rate was delayed from an average of 4·7 to 7·0 sec after vagotomy. Also after vagotomy the relation between resting blood pressure and heart rate showed a smaller change in heart rate in response to a change in blood pressure than in sympathectomized dogs (Norman & Whitwam, 1973*a*). The changes in the evoked increase in heart rate as blood pressure was altered were also smaller.

In dogs in which the vagus nerves were divided and the post-ganglionic nerves blocked with bretylium tosylate (10 mg kg^{-1}), stimulation of the radial nerve evoked no change in heart rate, but a small rise in blood pressure was seen which could be abolished either by adrenalectomy or by hexamethonium bromide (5 mg kg^{-1}).

It was concluded that stimulation of a cutaneous nerve can evoke increases in heart rate which are mediated by increased sympathetic activity

* British Oxygen Company Research Fellow.

whose magnitude is dependent on the blood pressure but that the adrenal medulla makes no significant contribution to these responses. The sympathetic component of heart rate changes is less sensitive to variations in blood pressure and to cutaneous nerve stimulation than the vagal component.

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Entrainment of the human RR interval by thermal stimuli

BY R. I. KITNEY. *Department of Physiology, Basic Medical Sciences Group, Chelsea College, Manresa Road, London SW3 6LX*

In a previous communication to the Society (Kitney, 1974), I discussed the entrainment of heart rate by the thermoregulatory system; the subject of this communication is the identification of the nature of this thermal entrainment (of the RR interval wave form). Experiments were undertaken in which periodic square wave thermal stimuli (18° and 46°, 7 (0·142 Hz)–10 (0·1 Hz) sec period) were applied to the left hand of 5 subjects while their e.c.g.s were recorded; the duration of each experiment was (15 min). The normal result as previously described was that the power spectrum of the derived RR interval wave form exhibited a large component at the thermal stimulus frequency. However, other results showed spectra with large frequency components around, but not actually at, the stimulus frequency. In RR interval spectra there are often large components corresponding to respiration, blood pressure control and thermoregulatory control (Sayers, 1971), but they obey the principle of super position, being additive. The analysis of the present experimental results led to the hypothesis that the spectra resulted from interference of a multiplicative rather than an additive nature. Separation of signal and noise under such circumstances can only be achieved using homomorphic filters (Oppenheim, Schafer & Stockham, 1968).

Following such filtering two conditions were revealed: the first showed spectra with a large component precisely at the stimulus frequency; in the second the filtered RR interval wave forms showed regions where an oscillation at the stimulus frequency was clearly visible, indicating that the wave form was moving in and out of entrainment (relative entrainment). This phenomenon was studied further using a Van de Pol oscillator

(Kitney, 1975), which is a mathematical equation which generates oscillations at a frequency defined by a parameter of the equation and corresponding to the fundamental heart rate.

A forcing function, equivalent to the thermal stimulus, was then introduced into the equation and the effect of changing its frequency observed. The results were as follows: a stimulus 7 sec period produced stable entrainment, a stimulus with a period of > 10 sec had no effect, and stimuli around 8 sec period caused relative entrainment. The synthetic data showed that the conditions of stable and relative entrainment were purely a function of the difference in frequency between the fundamental heart rate and the thermal stimulus. Such entrainment is unaffected by any respiratory or blood pressure components in the RR interval wave form, although it is often obscured by random multiplicative noise.

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Changed vascular sensitivity to noradrenaline in rats trained by physical exercise

BY INGEGERD ÖSTMAN*. *Department of Physiology I, Karolinska Institutet, Stockholm, Sweden*

Regular physical exercise over an extended period leads to various adaptive changes in the cardiovascular system, e.g. cardiac hypertrophy, bradycardia, an increased concentration of noradrenaline in the heart and a decreased turnover rate of noradrenaline stores in cardiac sympathetic nerves (Östman, Sjöstrand & Swedin, 1972). In addition, both during rest and in exercise, trained rats excrete less noradrenaline in the urine than do control rats under the same conditions (Östman & Sjöstrand, 1975). The latter observations imply that the sympathetic nervous system operates at an overall lower level of activity in trained rats than it does in normal laboratory rats. The possibility that this adaptive change in the sympathetic nervous system is secondary to an increased sensitivity of innervated tissues to the action of noradrenaline has been studied.

* Present address: Department of Medicine, Radcliffe Infirmary, Woodstock Road, Oxford.

The isolated hind-body of the rat was perfused with a modified Krebs solution containing colloid as described by Folkow, Hallbäck, Lundgren & Weiss (1970) and the perfusion pressure was measured continuously during the infusion of stepwise increasing concentrations of noradrenaline. Experiments were done on control male Sprague–Dawley rats and on rats of the same age that had been trained for 17 weeks by swimming for up to 2·5 hr each day (Östman *et al.* 1972). The respective curves of log–dose of noradrenaline *versus* steady-state perfusion pressure differed in two respects: that for the trained rats showed a parallel shift to the left and rose to a greater maximum pressure when compared with that for the control rats. The concentrations of noradrenaline that gave 50% of the maximum pressure responses were $0{\cdot}66 \pm 0{\cdot}05$ μM for trained rats ($n = 8$) and $0{\cdot}96 \pm 0{\cdot}04$ μM for control rats ($n = 7$), being significantly different with $P < 0{\cdot}001$ in Student's test. The maximum pressure responses were 225 ± 3 mmHg for trained rats and 202 ± 3 mmHg for control rats ($P < 0{\cdot}001$).

These observations reveal further adaptive changes in the cardiovascular system of trained rats: firstly, the blood vessels have a greater sensitivity to the vasoconstrictor action of noradrenaline; secondly, the vascular smooth muscle is able to develop and maintain a higher tension than it can in untrained rats.

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Enhanced pressor response to noradrenaline in human subjects with chronic sympathetic decentralization

By N. J. Christensen, H. L. Frankel, C. J. Mathias and J. M. K. Spalding. *2nd Clinic of Internal Medicine, Kommunehospitalet, Århus, Denmark; National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury; and Department of Neurology, Oxford Hospitals, Oxford*

The enhanced pressor response to infused noradrenaline in patients with dysautonomias has been used to provide evidence of a peripheral sympathetic lesion (Barnett & Wagner, 1958; Hohl, Frame & Schatz, 1965). This response, however, may not necessarily indicate post-ganglionic denervation, for there is some evidence suggesting that it may also occur in subjects

with chronic sympathetic decentralization. To investigate this further, we studied the effect of graded intravenous infusions of noradrenaline (Levophed, Winthrop Laboratories) in 5 tetraplegic subjects with physiologically complete cervical spinal cord transections, and in 10 control subjects (4 paraplegics with lesions below L1, and 6 normals). Blood pressure in the tetraplegics and paraplegics was measured by intra-arterial catheter, in the normals by sphygmomanometer. The electrocardiograph (e.c.g.) was continuously monitored. Heart rate was derived from the blood pressure signal or from the e.c.g. Student's t test was used for statistical analysis.

In the tetraplegics the blood pressure response to noradrenaline was significantly greater ($P < 0{\cdot}005$) than in the controls over a range of infusion rates up to 9·2 μg/min. At 2·3 μg/min the average increase in mean blood pressure was $45{\cdot}3 \pm 2{\cdot}3\%$ ($\pm$S.E. of mean) in the tetraplegics, and $6{\cdot}8 \pm 1{\cdot}4\%$ in the controls. At 9·2 μg/min it was $77{\cdot}4 \pm 10{\cdot}2\%$ in the tetraplegics and $19{\cdot}5 \pm 1{\cdot}8\%$ in the controls.

Animal studies suggest that after post-ganglionic denervation, noradrenaline hypersensitivity is due to decreased uptake of noradrenaline (Trendelenburg, 1972). We therefore measured plasma noradrenaline (using a double-isotope technique (Christensen, 1973)) before and during an infusion of noradrenaline (0·100 μg/kg.min). Mean resting levels of plasma noradrenaline in tetraplegics were $0{\cdot}08 \pm 0{\cdot}014$ ng/ml. ($n = 7$) and in the controls $0{\cdot}24 \pm 0{\cdot}027$ ng/ml. ($n = 14$), significantly different ($P < 0{\cdot}0005$). After 5 min of infusion, mean levels of plasma noradrenaline were $1{\cdot}81 \pm 0{\cdot}204$ ng/ml. in the tetraplegics, and $1{\cdot}38 \pm 0{\cdot}157$ ng/ml. in the controls, not significantly different from each other ($P < 0{\cdot}10$).

The evidence demonstrates that subjects with chronic sympathetic decentralization have an enhanced pressor response to noradrenaline infusions. This may be due to an increase in receptor response or to the absence of some vascular reflexes which normally tend to restrain the rise in blood pressure. Such reflexes include those baroreceptor reflexes in which the efferent pathway is in the sympathetic nervous system.

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Retinotopic organization in visual cortex and superior colliculus of the golden hamster

BY C. BLAKEMORE and TIAO, YUN-CHENG.* *Physiological Laboratory, University of Cambridge, Cambridge CB2 3EG*

We have recorded activity from unit clusters and single units in the visual cortex (twenty-two animals) and superior colliculus (four animals) of hamsters, anaesthetized with I.V. infusion of urethane and paralysed with Flaxedil.

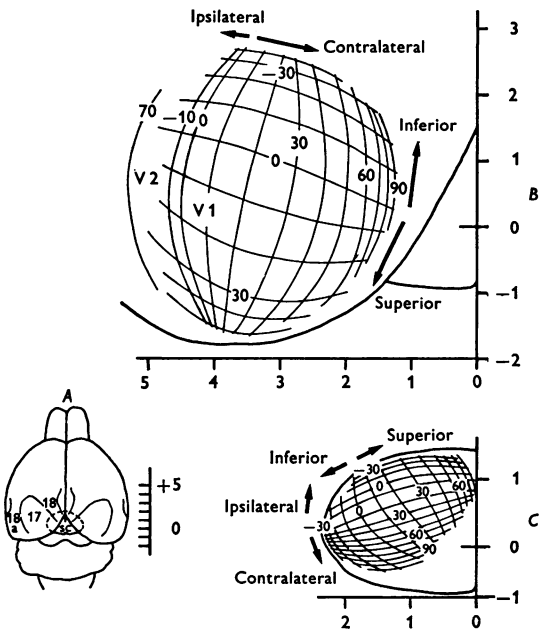

Fig. 1. *A*, surface of hamster brain, showing superior colliculus (SC) and Schneider's (1969) architectonic divisions of posterior cortex. *B*, left visual cortex, showing representation of cartographic, axis-vertical coordinates of a hemisphere centred on the eyes (inferior and ipsilateral directions negative). *C*, projection of left superior colliculus on to horizontal stereotaxic plane showing retinotopic organization. All dimensions in millimetres. Stereotaxic zero is the middle of the lambda suture.

In the cortex (Fig. 1*B*) there are two main visually responsive areas, V 1 (corresponding to cytoarchitectural 17) and, more laterally, V 2 (area 18a), with a retinotopic reversal at the border. The projection to V 1 is largely binocular and extends from 10° ipsilateral to 90° contralateral,

* British Council Research Visitor on leave from Institute of Biophysics, Academia Sinica, Peking, The People's Republic of China.

from 40° down to 60° up. A larger area of visual field, virtually the entire contralateral retina, is mapped on to the tectum (Fig. 1*C*), but only a small region around the area centralis representation has binocular input.

The differences in the area of field represented and the magnification in cortex and colliculus may partly account for the contrasting effects of lesions in the two areas (Schneider, 1969).

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Visual signals in the cat

BY B. G. CLELAND, W. R. LEVICK and W. A. H. RUSHTON. *John Curtin School, Canberra, Australia, A.C.T. 2601*

A green flash of strength ϕ, falling upon a red steady background of strength θ, elicits from rods a signal S that is transmitted to the connector ganglion, and generates N extra spikes. We have counted N after various flashes, and deduced the size of the ganglion input S.

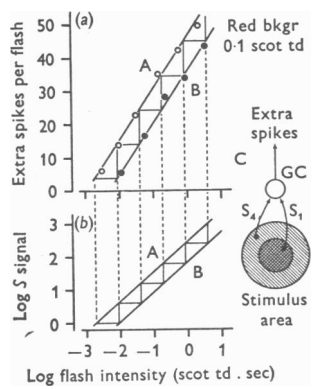

Fig. 1

Flashes fell entirely upon the centre of the ganglion's receptive field, illuminating a circle of diameter either 0·46° (white circles, Fig. 1) or 0·23° (black circles). Since white circles lie 0·6 (= log 4) to the left of black, quadrupling the area and quartering the flash intensity leaves N unchanged (Ricco's Law). To deduce S (lower staircase) we assume (*a*) equal N values imply equal S values, (*b*) with fixed retinal illumination, S_4 (from 0·46°) = $4S_1$ (from 0·23°). In lower staircase all 'risers' are 0·6 high (assumption *b*); 'treads' are as wide as 'treads' above, namely 0·6 (Ricco,

assumption *a*). Hence stair gradient is 1·0, $S \propto \phi$, and N is linear with log S.

Repeating with different θ-values confirms

$$10^{aN} = bS = \frac{\phi}{\phi+\sigma}\,\frac{\theta_D}{\theta_D+\theta}$$

(Alpern, Rushton & Torii, 1970),

The formula holds over a thousandfold range.

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Response of cat visual cortical cells to kinetic contours and static noise

BY P. HAMMOND and D. M. MACKAY. *Research Department of Communication, University of Keele, Staffordshire*

With the moving black/white bars and straight edges commonly used as stimuli for visual cortical units it is difficult to distinguish sensitivity to orientation from sensitivity to direction of motion, since the effective component of stimulus movement is always perpendicular to edge orientation. Using movable patterns of static visual noise, however, one can test for sensitivity to motion without presenting an oriented luminance contour. At the boundary between two areas of noise in relative motion one can also generate a 'kinetic contour' whose orientation and location can be changed independently of the direction of noise motion.

We have already found qualitatively (Hammond & MacKay, 1975) that such moving noise fields, or noise bars moving in the optimal direction against stationary backgrounds of noise of identical texture, excite complex cells in area 17 of the lightly anaesthetized, paralysed cat when simple cells in the same orientation column show no response. (We classified these cells by such criteria as field size; presence or absence of discrete 'on' and 'off' areas; sensitivity to bar length; preferred velocity; directional bias; sharpness of orientational tuning; spontaneous firing rate and pattern of discharge to movement; and recording depth.) We now report a quantitative study of cell responses in visual cortex, showing that although most simple cells are indifferent to noise fields drifting in their preferred direction, or to noise bars moving on stationary noise fields, many complex cells show directionally biased responses to such stimuli which in some cases are stronger than those to optimally oriented light or dark bars of comparable dimensions moving against the same noise backgrounds. All of 48 complex cells, compared with only one out of 44 simple cells, showed some responsiveness to moving noise.

The few simple-type and complex-type hypercomplex cells so far encountered resemble their simple or complex counterparts in these respects.

These findings appear to raise difficulties for current concepts of 'hierarchic feature extraction' by simple and complex cells.

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The application of thermography to the detection of energy metabolism of the brain in the new-born infant

BY K. W. CROSS, J. K. STOTHERS, RUTH M. WARNER and R. W. WOODROUGH. *Department of Physiology, The London Hospital Medical College, Turner Street, London E1 2AD, and Department of Medical Electronics, St Bartholomew's Hospital, West Smithfield, London, E.C. 1*

We have recently reported that the aural temperature of the new-born infant when measured by the zero gradient aural thermometer (Keatinge & Sloan, 1973) is, in the neutral environment, considerably higher than that of the oesophagus (Cross & Stratton, 1974). Cross, Stothers & Stratton (1975) have also reported that after the infant has been fed this differential temperature becomes even greater, and concluded that this was more likely to be because brain blood flow decreased than that a further increase of brain energy metabolism occurred.

We have now started a different approach towards estimating heat output from the brain by examining thermographically the vertex of the infant while it is in an incubator at a neutral environment (Aga Thermovision 680 Medical). The posterior portion of the anterior fontanelle shows itself to be considerably warmer than the surrounding skull-covered areas of the brain. Once again, after feeding there is a sharp rise of temperature (particularly in the posterior part of the vertex), and in a baby thought to be brain-damaged there was unilateral difference of temperature. The damaged part of the brain appearing to be less thermally responsive than the normal hemisphere. Our impression is that this method of examining the baby's brain, provided that the very strictest environmental conditions are maintained, provides a new and exciting insight into brain heat production and may have very considerable applications, not only in considering infant physiology, but also for the early detection of brain abnormalities. We feel that we are even nearer than we were with the aural thermometer in obtaining an index of brain heat output.

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Afferent sympathetic nerve fibres with aortic endings

BY M. PAGANI. *Cardiovascular Research Institute, University of Milan, and C.N.R., Milano*

Using anaesthetized and vagotomized spinal cats we have recently shown that stretching the wall of the thoracic aorta induces reflex changes in the activity of single efferent sympathetic fibres in the left third thoracic ramus communicans (T 3) which is known to contribute to the innervation of the heart (Pagani, Schwartz, Banks, Lombardi & Malliani, 1974).

In this preparation the same stimulus was found to induce reflex increases in heart rate, myocardial contractility and arterial blood pressure, thus suggesting the existence of positive feed-back mechanisms in the neural control of the circulation (Lioy, Malliani, Pagani, Recordati & Schwartz, 1974).

The present paper summarizes an electrophysiological investigation into the properties of afferent sympathetic fibres which are likely to mediate these reflexes.

Experiments were performed on anaesthetized, paralysed cats under artificial ventilation. Details of the methods used for recording single unit activity (T3–T6) and haemodynamic variables have been described previously (Pagani *et al.* 1974).

We recorded the activity of 21 single units, the endings of which were found to be localized in the aortic wall. 18 fibres were spontaneously active at a mean systolic blood pressure of 134 ± 5 (S.E.) mmHg, giving not more than a single impulse per cardiac cycle. Conduction velocities suggested that the fibres involved were mainly small myelinated (A delta) ones and that the unmyelinated (C) fibres were few.

The activity in the fibres was markedly increased by raising aortic blood pressure, either by occluding the descending aorta with a snare or injecting pressor drugs intravenously. Maximal activity was attained while arterial pressure was rising and was related to the extent and rate of such a rise. During this maximal excitation the units could give more than a single impulse per cardiac cycle. Induced hypotension caused a decrease or suppression of the impulse activity.

Five units were studied at the end of the experiment, after the animal had been killed. A saline-filled latex balloon was introduced into the aorta

through the opened left ventricle in order to apply graded increases in pressure to the aortic segment where the endings were located. The endings responded to the various increases in pressure (ranging from 0–50 to 0–300 mmHg) with a burst of activity. For any given pessure step, after a short latent period the firing rate reached a maximum frequency, which rapidly declined toward much lower values (adaptation). In the range of pressures studied, the relationship between pressure and the peak frequency was approximately linear, the threshold being between 75 and 100 mmHg. The role of these mechanoreceptors in sustaining a high sympathetic efferent activity through spinal excitatory mechanisms seems worth studying under various physiological and pathological conditions (e.g. strenuous exercise, arterial hypertension and hyperdynamic heart).

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Human blood platelet aggregation induced by dopamine, 5-hydroxytryptamine and analogues

BY D. J. BOULLIN, A. R. GREEN and R. P. J. GRIMES. *M.R.C. Unit and University Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford OX2 6HE*

5-Hydroxytryptamine (5-HT) induced platelet aggregation has been known for some years (Mitchell & Sharp, 1964) and is associated with the transport of the amine into platelets (Baumgartner & Born, 1969). As dopamine is similarly transported (Boullin & O'Brien, 1970), we have compared the effects of dopamine, 5-HT and some analogues on platelet aggregation.

Platelet-rich plasma (PRP) was prepared and aggregation studied as described previously (Boullin, Grahame-Smith, Grimes & Woods, 1975). 20–50 μM dopamine induced aggregation in 15 out of 18 subjects of either sex aged 17–35. The responses were similar to those normally seen with 5-HT, being transient and reversible. In some instances dopamine produced irreversible responses as recently described for 5-HT (Besterman & Gillett, 1974; Boullin *et al.* 1975). Dopamine responses were more difficult to evoke than 5-HT, being most frequently observed 0·5–1 hr after blood collection; occasionally subjects responded only to 5-HT.

When 20–50 μM dopamine and 5-HT were applied successively to the same sample of PRP at 5 min intervals, each drug evoked aggregation,

irrespective of the order of application. Also each of a series of applications of dopamine produced aggregation. In contrast, in the case of 5-HT, only the first of a series of doses produced aggregation.

Dopamine aggregation was specifically blocked by 10 μM Haloperidol or Spiperone, without affecting 5-HT responses, while the effects of 5-HT were blocked by lysergic acid diethylamide or methysergide (10 μM).

Of three dopamine analogues tested, only α-methyl *N*,*N*-dimethyl dopamine produced transient reversible aggregation; *N*,*N*-dimethyl dopamine produced irreversible aggregation while α-methyl dopamine did not aggregate but blocked dopamine responses.

Several 5-HT analogues also produced aggregation, with the following order of potency (5-HT = 100): 5-methoxytryptamine (80); 5,6-dihydroxytryptamine (56); 5-methoxydimethyl tryptamine (34). Like 5-HT, all these substances produced aggregation only on the first application to PRP.

As with the parent compounds, aggregation by dopamine and 5-HT analogues was only blocked by specific antagonists.

The data indicate that dopamine and 5-HT induce aggregation possibly by stimulation of separate receptors.

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The effect of cooling nucleus interpositus of the cerebellum in rhesus monkeys on the tracking of a visual target

BY J. F. STEIN and J. WATTAM-BELL*. *Department of Physiology, South Parks Road, Oxford*

The cerebellum contributes to the precision of voluntary movements by adjusting the magnitude and timing of muscular contraction. Interference with the cerebellar output nuclei therefore would be expected to lead to disorders of movement. Brooks, Kozlovskaya, Atkin, Horvath & Uno (1973) found that cooling the dentate nucleus did have this effect. However, cooling the interpositus nucleus did not. This is strange since n. interpositus receives from the paravermal regions of the cerebellar cortex where the spino-cerebellar tracts bringing feed-back from the limbs terminate,

* M.R.C. Scholar.

and it, in turn, projects indirectly to the spinal cord via the red nucleus, and to the motor cortex via the ventrolateral nucleus of the thalamus. Neurones here change their frequency of discharge in relation to voluntary movements (Thach, 1968; Pauls, Soye & Stein, 1974).

In the course of studies on cerebellar neurones we have been training monkeys to perform a visual tracking task. The monkeys move a joystick to follow a target which can be moved anywhere on an oscilloscope screen (Pauls *et al.* 1974). The animals can thus be led to make any movements we choose and their errors in so doing recorded and analysed. It seemed worth while to re-examine the effects of cooling n. interpositus during this versatile task.

We used a liquid-cooled probe whose tip could be cooled whilst the stem was kept automatically at 37° C by a servocontrolled heating coil. The probes were implanted stereotaxically under general anaesthesia and their locations confirmed histologically afterwards. A continuous plot of average positional error was obtained before, during and after cooling by rectifying and integrating the instantaneous difference between the positions of the target and of the monkey's hand (Pt–Pm).

During cooling of n. interpositus this error almost doubled. As cooling tests proceeded the animals learnt to compensate for their disability during cooling to some extent, but their errors were still substantial after 2 months of testing. As the method we have employed to quantify the error mixes the effects of misjudging amplitude and timing, we are computing the changes in gain and phase at different frequencies of sinusoidal movement, which occur during cooling.

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The visual acuity of the cat

BY K. B. J. FRANKLIN, S. G. JACOBSON and W. I. MCDONALD. *The Institute of Neurology, Queen Square, London, W.C.1*

Mechanisms for processing of odour concentration in salamander olfactory bulb neurones

By J. S. Kauer and G. M. Shepherd. *Department of Physiology, Yale University School of Medicine, New Haven, Conn. 06510, U.S.A.*

It has been shown previously (Døving, 1964) that olfactory bulb units change their response characteristics in relation to different concentrations of odorous stimuli. We have analysed this relationship further in salamanders using monitored step pulses of odour (Kauer & Shepherd, 1975). Response thresholds were generally at low levels, usually in the range of

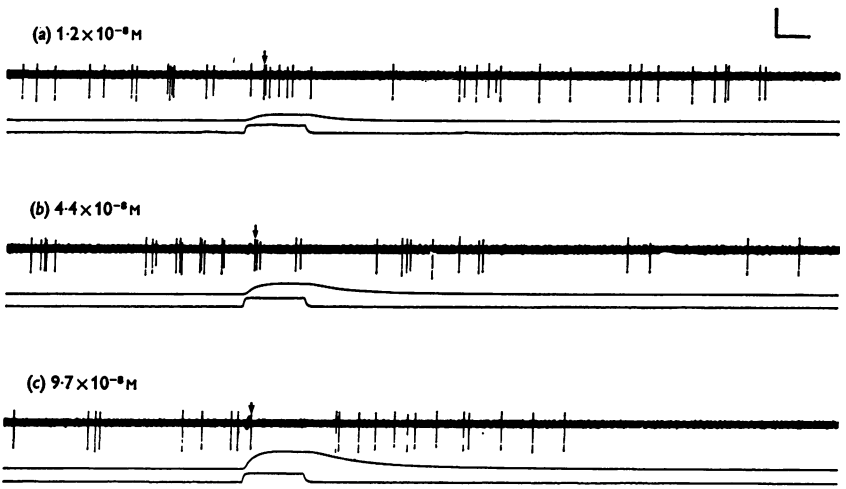

Fig. 1. Responses of olfactory bulb unit in salamander *Ambystoma tigrinum* to odour stimulation of the nose. Top trace, extracellular spike recording; vertical bar 1 mV. Middle trace, electro-olfactogram recorded from surface of exposed ventral olfactory epithelium. Bottom trace, monitor of time course of odour stimulation, by method of Kauer & Shepherd (1975). Time scale, 2 sec. Camphor odour, at molar concentrations indicated in (*a*)–(*c*). Arrows indicate onset of the impulse response time-locked to onset of the stimulus, as verified by repeated trials. Note also small-amplitude field potential in impulse recording traces in (*b*) and (*c*), occurring just after onset of stimulus and before first impulse response.

10^{-4} to 10^{-9} molar for different odours. Some responses consisted of an initial suppression of spontaneous activity; these showed little change with different odour concentrations. Other responses consisted of an initial excitatory discharge (Kauer, 1974). At or near threshold, the response took the form of a relatively prolonged spike train. With increasing concentration, the later spikes became suppressed, and the early response increased in frequency and shortened in duration. At the highest con-

centrations the initial discharge consisted of only one or two spikes. These patterns are illustrated in Fig. 1.

The results of this study suggest that concentration information is processed by an interplay of excitatory and inhibitory pathways feeding into or located within the olfactory bulb. The intrinsic bulbar pathways are organized into two main layers – glomerular and external plexiform – differentially accessible to activation by olfactory nerve and olfactory tract stimulation. Preliminary experiments suggest that unitary and summed potentials evoked through these fibres can be selectively suppressed during different phases of naturally evoked activity. This may provide evidence regarding the synaptic organization underlying the processing of information about odour concentration.

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Visual and taste neurones in the lateral hypothalamus and substantia innominata: modulation of responsiveness by hunger

BY M. J. BURTON, F. MORA and E. T. ROLLS. *Department of Experimental Psychology, Oxford University, South Parks Road, Oxford OX1 3UD*

Some neurones in the monkey lateral hypothalamus and substantia innominata respond only to the sight and/or taste of food (see Rolls, 1975). The responses to the sight of food appear to be visual in that the units do not respond in relation to motor movements, or during grasping the food and feeding in the dark, or in other control tests, so that the responses do not appear to be motor or due to salivation, or to anticipation of food. The greatest response of the visual neurones is to the sight of the animal's most preferred food. As these units are in the lateral hypothalamus and substantia innominata, which are involved in the control of food intake, we varied the hunger of the animals to determine whether this affected the firing rates of the units. At the start of the experiments the animals were hungry in that they had not eaten for 12 hr, and were willing to reach for food, for example for 20% glucose or saturated sucrose solution. Satiety was induced by feeding the animals 2 ml. of trial solution, until the animal became satiated and refused the solution. It was found that the mean spontaneous firing rate was unaffected by changes of hunger. But the sight and/or taste of food produced the largest response of the units (as measured by a change of rate from the mean spontaneous firing rate) if the animal was hungry, and ceased to produce a response if the animal was satiated.

These results were found in two squirrel monkeys and one rhesus monkey, in 6 units which responded to the sight of food, in 3 units which responded to both the sight and taste of food, and in 1 unit which responded to the taste of food. In control experiments on units recorded in the globus pallidus which fired in relation to swallowing, no effect of alterations of hunger on the response of the units to swallowing was found. It is suggested that the units in the lateral hypothalamus and the substantia innominata which only respond to the sight and/or taste of food if the animal is hungry are involved in the regulation of food intake by altering the response of the animal to the sight and taste of food.

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The role of the locus coeruleus in the acquisition of a conditioned avoidance response

BY T. J. CROW and S. WENDLANDT. *Division of Physiology and Pharmacology, National Institute for Medical Research, Mill Hill, N.W.7; Division of Psychiatry, Clinical Research Centre, Watford Road, Harrow, Middlesex, HA1 3UJ*

Tests of the hypothesis (Crow, 1968; Kety, 1972) that the adrenergic innervation of the cerebral cortex is necessary for establishing the neural changes involved in learning have given conflicting results (Anlezark, Crow & Greenway, 1973; Amaral & Foss, 1975). Stein, Belluzi & Wise (1975) report that animals injected S.C. with the dopamine-β-hydroxylase inhibitor diethyldithiocarbamate (DDC) show evidence of immediate acquisition of a passive avoidance response but fail to show long-term retention. In these experiments we have attempted to demonstrate that this specific deficit of learning capacity may be a consequence of impaired transmission in the coerulocortical adrenergic system. Seventy-nine female Sprague-Dawley rats (initial weight 150 g) were divided into an untreated control group, a group injected bilaterally with 6-OH-dopamine (16 μg in 4 μl. over 4 min) just anterior to the locus coeruleus, a group with burr holes, and a group injected S.C. with DDC 300 mg/kg between the first and second trials of the training procedure. The time taken for each animal to step off a platform onto the electrifiable grid floor of the test chamber was recorded in each of 5 test sessions. The first two trials were separated by 1 hr. On the third trial (1 min after the second) rats were shocked as they stepped down, and on the fourth (1 min later) and fifth (3 days later) trials the effect of this experience on the animals' subsequent step-down time was tested.

Both the 6-hydroxy-dopamine-lesioned and DDC-treated rats showed normal acquisition of the avoidance response as assessed by their performance on trial 4. By comparison with the two control groups, however, both these groups showed a failure of retention after a 3-day interval on trial 5. From trial 4 to trial 5 there was no significant change in the time spent on the platform in the two control groups (untreated controls, $5{\cdot}2 \pm 10{\cdot}2$ sec; burr-hole group, $-0{\cdot}9 \pm 16{\cdot}2$ sec) but a significant decrease in both the DDC-treated ($60{\cdot}8 \pm 17$ sec), and 6-hydroxy-dopamine-lesioned ($58{\cdot}5 \pm 10{\cdot}4$ sec) groups. Both values were significantly different from controls at the 1% level.

These findings suggest that the impaired long-term retention of conditioned avoidance behaviours seen after administration of a dopamine-β-hydroxylase inhibitor (Stein *et al.* 1975) may be due to interference with the function of the system of noradrenaline-containing neurones arising from the locus coeruleus.

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The importance of intracerebral decarboxylation of L-DOPA in the suppression of prolactin secretion

By S. Franks, N. F. Lawton and N. J. Marshall. *The Institute of Neurology, Queen Square, London W.C.1, and the Institutes of Nuclear Medicine and Clinical Science, Middlesex Hospital Medical School, London, W.1*

In normal subjects L-DOPA reduces serum prolactin concentration and the normal prolactin response to thyrotrophin releasing hormone (TRH) (Frantz and Suh, 1974). This effect of L-DOPA can be attributed to dopamine (Donoso, Bishop, Fawcett, Krulich & McCann, 1971). To test whether the site of L-DOPA decarboxylation might be intra- or extracerebral we have compared the suppressive effect on TRH-induced prolactin release of L-DOPA given with and without the inhibitor of extracerebral DOPA-decarboxylase, 1-alpha-methyldopahydrazine (Carbidopa).

Each of five normal subjects was given TRH 200 μg intravenously on three occasions. Only TRH was given in experiment 1. In experiment 2 oral L-DOPA 62·5 mg was given 90 min before TRH, and in experiment 3 the same dose of L-DOPA was combined with Carbidopa 6·25 mg. Venous

blood was collected for serum prolactin and thyroid stimulating hormone (TSH) assay prior to TRH and at 20, 30 and 60 min thereafter. Radioimmunoassay of serum prolactin was performed by the method of Sinha, Selby, Lewis & Vanderlaan (1973) and of TSH by a modification of the method of Odell, Wilbur & Paul (1965).

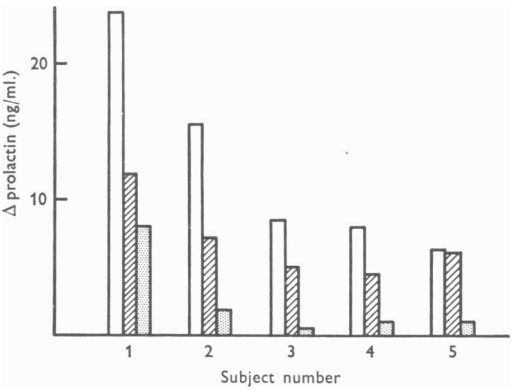

Fig. 1. The effect of L-DOPA 62·5 mg and of L-DOPA 62·5 mg with Carbidopa 6·25 mg on TRH-induced prolactin release in five subjects. Prolactin is the increment above the basal value 20 min after TRH injection. The increment after TRH alone is shown by the open columns, after pretreatment with L-DOPA by the hatched columns, and after L-DOPA with Carbidopa by the stippled columns.

The mean fall in basal prolactin after L-DOPA alone was 1·2 ng/ml. (range 0·5–2·4 ng/ml.) and after L-DOPA with Carbidopa 1·0 ng/ml. (range 0·1–2·2 ng/ml.). Fig. 1 shows that in 4 subjects the increase in prolactin concentration after TRH was reduced by L-DOPA alone and further reduced by L-DOPA with Carbidopa. In subject 5 L-DOPA was only effective combined with Carbidopa. There was no consistent effect on TSH release.

Consistent potentiation by an extracerebral DOPA-decarboxylase inhibitor of the L-DOPA effect on TRH-induced prolactin release indicates the importance of intracerebral DOPA-decarboxylase in the mechanism of this response.

Materials for radioimmunoassay were a gift from the National Institute of Arthritis, Metabolism and Digestive Diseases.

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Is prolactin a fluid and electrolyte regulating hormone in man?

BY E. N. COLE,* D. EVERED,† D. F. HORROBIN,† M. S. MANKU,† J. P. MTABAJI,† B. A. NASSAR.† * *Tenovus Institute, Welsh National School of Medicine, Cardiff.* † *University of Newcastle upon Tyne Medical School.*

Prolactin causes renal sodium, potassium and water retention when injected or infused into cats, rats, sheep and humans (Lockett, 1965; Horrobin, Lloyd, Lipton, Burstyn, Durkin & Muiruri, 1971; Burstyn, Horrobin & Manku, 1972; Horrobin, 1973). In rats a low sodium diet increases prolactin secretion (Relkin, 1973) and in man plasma prolactin levels are influenced by plasma osmolality in the same way as is anti-diuretic hormone (ADH). These findings indicate that prolactin could play a part in human fluid and electrolyte metabolism but gives no indication that it does.

A woman of 41 presented with extremely severe premenstrual syndrome which was associated with monthly weight gain and loss of 5–8 kg. The story was confirmed by admission to a metabolic ward during the luteal phase of one menstrual cycle when marked premenstrual thirst and reduction in renal sodium, water and potassium excretion were noted. Since conventional diuretics had proved ineffective treatment with lithium carbonate (Sletton & Gershon, 1966) was attempted. Initially there was a considerable improvement but after about 6 months the therapeutic effect wore off and fluid and electrolyte retention became almost as severe as before. The treatment was then changed to the prolactin suppressing drug, bromocriptine, one 2·5 mg tablet each evening during the last 3 weeks of each menstrual cycle. The patient has now been on this therapy for almost a year and seems to be completely relieved of all signs and symptoms.

In the untreated state mean follicular phase plasma prolactin level was $5{\cdot}25 \pm 0{\cdot}85$ (S.E. of mean) ng/ml. while in the luteal phase it was $10{\cdot}52 \pm 0{\cdot}88$ ng/ml. During lithium therapy luteal phase levels rose to $21{\cdot}75 \pm 1{\cdot}43$ ng/ml. We have preliminary evidence that lithium inhibits prolactin actions on rat kidneys and arterioles in a competitive fashion. While on bromocriptine luteal plasma prolactin levels were $6{\cdot}94 \pm 0{\cdot}86$ ng/ml. Although bromocriptine is a dopamine agonist and might be expected to have renal effects in its own right we suggest that this patient may be the first example of a prolactin-induced fluid and electrolyte disorder.

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Osmoreception and thirst in the dog

BY D. J. RAMSAY, BARBARA J. ROLLS and R. J. WOOD. *University Laboratory of Physiology and Department of Experimental Psychology, University of Oxford*

Hypothalamic osmoreceptors may be involved in the control of drinking in the dog (Andersson, 1972) as in the rat (Blass & Epstein, 1971). In this study, a 24 hr period of water deprivation in 8 dogs raised plasma osmolality from $297{\cdot}5 \pm 0{\cdot}9$ to $309{\cdot}6 \pm 0{\cdot}9$ m-osmole/kg.H_2O ($P < 0{\cdot}001$). The effect of removing the central osmotic stimulus on deprivation induced drinking was investigated.

Eight dogs prepared with unilateral carotid loops were deprived of water for 24 hr. They were infused through the carotid loop with distilled water for 5 min at 0·6 ml./kg.min, a rate designed to reduce the osmolality in the cerebral circulation to pre-deprivation levels. The intake of water during a further 5 min of infusion was measured. Water intakes were variable and were not significantly less than those following control infusions of 0·15 M-NaCl. The ineffectiveness of this procedure may reflect a non-uniform distribution of the infusate in the cerebral circulation. To test this, second carotid loops were prepared on all dogs and the experiment repeated, infusing the same dose bilaterally. This reduced the jugular blood osmolality to pre-deprivation levels without measurably affecting systemic blood, and produced a marked and significant reduction in water intake (Fig. 1*a*). Infusion of water to the deprived dogs at different rates shows the effect is dose related ($R = 0{\cdot}56$, $N = 24$, $P < 0{\cdot}01$).

Further evidence for the importance of osmolality in thirst was obtained by infusing 0·3 M, 0·45 M and 0·6 M-NaCl solutions at a rate of 0·6 ml./kg.min for 10 min into the eight dogs via both carotid loops when fluid replete. A graded stimulation of drinking was obtained with increasing the osmolality of the saline ($R = 0{\cdot}59$, $N = 32$, $P = < 0{\cdot}001$) (Fig. 1*b*).

The suggestion that central osmoreceptors may play an important role in the mediation of thirst receives support from these results.

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