STUDIES IN DENERVATION

D.—THE MECHANISM OF AXONAL VASODILATATION

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(RECEIVED 14TH OCTOBER, 1943)

IN a recent paper Lewis (1939-42) has reviewed the evidence concerning the nature of the fibres concerned in axonal vasodilatation and has affirmed his belief that while they belong to the posterior root system they are not afferent fibres. Support for this contention might be obtained from the following case, though here a different interpretation is made. The opportunity is also taken to present an alternative to the explanation of Lewis for certain of the phenomena associated with the flare.

Case Report.—Subject F.J. suffered an incised wound, involving the ulnar nerve, above the right elbow. A primary suture of the nerve was performed and the wound healed by first intention. Examination two weeks later showed a typical loss of sensation and of sweating in the ulnar area. Figs. 1 and 2 record a similar state of

In the hope of showing conclusively that this nearly normal blood flow was present in the absence of axonal vasodilator reflexes the response to extreme cold was tested. As shown in Fig. 4, Exp. 3, this resulted in a

FIG. 1.—Sensory chart of subject F.J. 3 months after injury. Continuous line indicates margin of loss to 1 gm. hair; broken line—margin of loss to 15 gm. pin prick; hatched area—loss to a pressure of 15 gm. on a circular area of 10 sq. mm.

FIG. 2.—Photographs of sweat response to body heating of subject F.J. Left hand sweated evenly. (Chinizarin technique.)

FIG. 3.—Plethysmographic record ($\times \frac{1}{2}$) of subject F.J. Time in 1-sec. and 10-sec. intervals. Downstroke in respiratory tracing is inspiration. Volume of L.F.5 increases upwards, that of R.F.5 increases downwards. At signal which was 2-3 sec. late several pinpricks were given to the subject's leg.

affairs three months later. There was a fairly profound muscular paralysis at first, but at the end of a month there was sufficient power to act against gravity in all the muscles supplied by the ulnar nerve except the 4th dorsal interosseous. Percutaneous stimulation of the ulnar nerve at the wrist and of the median nerve at the elbow at an operation for resuture four months after injury showed that this persistence of voluntary power was due to a communication from the median nerve to the ulnar nerve in the forearm. Observations on the response to electrical stimulation of the hypothenar muscles indicating incomplete denervation are reported in paper I. Plethysmographic records (Fig. 3) showed the presence of neurogenic vasoconstrictions in the right fifth digit in response to pin prick but these were abnormal in that they lagged 5-6 seconds behind those in the normal finger as described by Wilkins and Kolb (1941) in cases of peripheral neuritis. Numerous thermometric records were obtained which also showed that there was an extraordinary persistence of reflex vasomotor activity in the fifth digit (Fig. 4, Exp. 1) combined with no great sensitivity to the vasoconstricting action of local cooling (Fig. 4, Exp. 2). This confirmed the patient's statement that the finger was neither abnormally warm nor cold.

phasic vasodilatation in the fifth digit which, though less marked than in the normal, was unmistakable. That this phasic response was not due to the periodic blocking of vasoconstrictor fibres, as has been mentioned as a possibility by Hertzman and Roth (1942), is shown by the high temperature of the index finger of the opposite hand indicating a complete inhibition of vasoconstrictor impulses induced by the immersion of the feet in hot water. Attempts to demonstrate a flare on any of the digits were not convincing. Unfortunately the method described by Grant and Bland (1929) was not known at the time, but

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there is little doubt that the flare and the vasodilator response to cold are essentially similar phenomena.

Discussion

This case, therefore, was of no help in supporting the thesis of paper B that a normal circulation may be present in the absence of axonal vasodilator reflexes. It did, however, provide rather convincing evidence that vasodilator axonal reflexes are not dependent on the presence of fibres which mediate a sensation. It should be stressed again that the loss of sensation in the fifth digit in this case was absolute, even the stimulus of immersion in ice water and subsequent warming was unappreciated, while on one occasion he had unwittingly burned the finger. Neither prolonged intensive faradism

those associated with axonal vasodilatation is that neither need give rise to a conscious sensation there are no grounds for pursuing the theme further. It is legitimate, however, to use the opportunity to discuss the mechanism of axonal vasodilatation and the reasons of Lewis for believing it to be dependent on efferent fibres.

It should be noted in passing that the type of unusual distribution of the median nerve present in this case is fully discussed by Hovelacque (1927) who also provides a complete bibliography bearing on this point.

OUTLINE OF LEWIS' THEORY.—The various aspects of the total concept of Lewis rest on assumptions of varying degrees of certainty. Thus his concept

FIG. 4.—Temperature charts of subject F.J. Lines representing the different digits are identified on the charts. Lower line of blocks if filled indicates that the legs were in water at 18° C.; if empty in water at 44° C. Upper line of filled blocks indicates immersion of the hands in water at 18° C. In Exp. 3, right hand was in a rubber glove and at 5 min. was immersed to the proximal phalanges in ice water.

nor galvanism elicited any sensation. He was, moreover, intelligent, co-operative, not hysterical, and sweat tests on numerous occasions showed an area of anhidrosis corresponding to the area of sensory loss. These findings might suggest that axonal vasodilatation is dependent on efferent fibres, but it is possible that it might be dependent on afferent fibres which do not mediate a conscious sensation.

Afferent fibres from the specialized receptors in the vascular system are conspicuous examples of afferents lacking an ability to produce a conscious sensation and of some pertinence to the present situation are the findings of Duthie and Mackay (1940). These authors report that after section of the spinothalamic tracts afferent nervous pathways are still present mediating reflex vasodilation, though temperature sensation is lost. The importance of these findings, if confirmed, is great, though it is true that they do not necessarily indicate that these two functions are subserved by different fibres in the periphery. However, it may be recalled that Carmichael *et al.* (1937) have demonstrated, in the posterior roots supplying the leg, the presence of afferent fibres particularly associated with vasomotor regulation, which they suggested might arise from receptors associated with the blood vessels. As the only link between these fibres and

may be summarized in the following two sentences, the first of which contains the doubtful assumptions while the second contains the deductions which appear to have achieved the status of truths.

(1) Lewis considers axonal vasodilatation to be dependent on efferent cholinergic fibres which may stimulate the cells of the skin to liberate H-substance.

(2) The nerve fibres subserving axonal vasodilatation have their trophic centre in the posterior root ganglia, and in the skin they are distributed in the form of a plexus which is readily stimulated by tissue injury, through the release of a substance or group of substances called H-substance.

Obviously only the doubtful points are of interest here, and they will be discussed in turn.

EFFERENT FIBRES IN POSTERIOR ROOTS.—The view that the posterior roots contain efferent fibres having effects on the peripheral vessels rests on observations in man and animals. It may be noted that there is overwhelming histological evidence that there are no fibres in the posterior roots with their trophic centres in the spinal cord (Westbrook and Tower, 1940). This point, however, is not in dispute and, in spite of the ontogenetical improbability, only physiological evidence can determine if any of these fibres subserve an efferent function.

The animal experiments have recently been reviewed by Dole and Morison (1940) who have filled a remarkable gap in our knowledge. Their evidence shows that in the dog the vascular responses that persist after sympathectomy persist also after complete denervation and are therefore not due to vasomotor fibres in the posterior roots as had been previously suggested. Such results, which are negative in the sense that no reflex efferent function was found for the posterior roots, do not entirely exclude such a function. They do, however, cast grave doubt on all the evidence supporting this belief. Brown and Maycock (1940) reported at about the same time the occurrence of a depression in blood pressure in totally sympathectomized animals in response to trauma in the region of the spinal cord. They concluded that this indicated an accessory vasomotor pathway and this could be interpreted in favour of a posterior root outflow, but the results of Dole and Morison suggest that some other mechanism is operating. In support of such a view is the fact that Brown and Maycock did not conclusively show that their results were reflexly produced and it is known that in the human under high spinal anaesthesia surgical trauma in the desensitized area produces a fall in blood pressure (Papper *et al.*, 1943). Whether or not these two phenomena are related it is impossible to say, but it is obviously important to elucidate their mechanism for both practical and theoretical reasons.

The finding of Barron and Matthews (1935) and of Toennies (1939) of an efferent discharge over posterior root fibres should not be used as an argument that these subserve true efferent functions. That they are sensory fibres is suggested by the finding of Toennies that the efferent posterior root impulses depress the excitability of tactile receptors and this is the known result of a back-fired volley in sensory fibres (Matthews, 1933; Gasser, 1939). Furthermore, they do not appear to be accessible to reflex activation as Barron and Matthews found that the potentials were restricted to branches of the fibres originally stimulated. It is true that Barron (1940) has found it necessary to modify this conclusion, but in doing so he has emphasized our ignorance of the mechanism of the phenomenon and appears even to suggest that it may be an artefact.

Section of the posterior roots has been demonstrated in animals to have no effect on the peripheral circulation (Ascroft, 1937; Wybauw, 1936a), though a slight tendency to coldness has been described (Hinsey, 1934; Zuckerman and Ruch, 1934). Such a negative result would be expected if sympathetic instead of posterior root fibres formed the link between the central nervous system and the vasodilator fibres of the posterior roots, possibly ending in the pericellular baskets of Dogiel. This ingenious suggestion of Ranson and Wightman (1922a) appears to be excluded because excision of the posterior root ganglia produces no effects on the circulation (Ascroft, 1927) or only a very slight vasoconstriction as indicated by a temperature drop of 0.5° C. (Wybauw, 1936a). The animal experi-

ments therefore offer no positive support for the view that efferent fibres exist in the posterior roots.

The evidence in humans which has appealed to Lewis (1939-42) rests on a series of cases with reflex urticaria reported by Grant *et al.* (1937-8). These authors point out, however, that sympathetic fibres might form the efferent pathway. In view of the known vasodilator function of the sympathetic fibres (Grant and Holling, 1937-8) in at least some of the regions involved by the urticaria, it would seem that this was the most tenable hypothesis. Moreover, it is to be noted that atropine prevented the development of the reflex urticaria in these cases and also in a similar case described by Lewis (1939-42). Atropine, on the other hand, has no effect on the vasodilatation produced by antidromic stimulation (Hunt, 1918). This would argue strongly against the conclusion that the fibres mediating the urticaria are the same as those mediating antidromic vasodilatation. Carmichael *et al.* (1937) have found in man that section of the posterior roots had no effect on the peripheral circulation other than was accounted for by loss of afferent impulses. The observations in man, therefore, offer no support for the view that there are efferent fibres in the posterior roots.

INNERVATION OF CELLS OF THE SKIN.—The conception that the posterior root fibres control the metabolism of the skin cells and so affect the circulation in an indirect fashion was evolved by Gaskell (1916). Against this view is the fact that section of these fibres was not found, in paper G, to cause any change in the growth of the skin and its appendages. Such an effect, however, would not be necessary if, as in the view of Lewis (1939-42), the posterior root fibres governed only a particular function of the skin cells such as the liberation of H-substance. If such were the case degeneration of the excitor fibres should induce a hypersensitive state in the effector organ according to the law of denervation (Cannon, 1939). Ascroft (1937) found no evidence of this following excision of the posterior root ganglia and three subjects have been tested with this in mind. As it was suggested that the fibres in question were cholinergic a solution of 2 per cent. acetylcholine bromide was prepared in normal saline and ionized into the skin under the influence of an anode of 4 cms. in area. Using a current of 25 microamps. for 5 minutes a slight localized reddening occurred on the normal skin of the leg. The reaction of denervated areas with skin of similar texture was in all respects the same, except that here a slight pilomotor and sweating response was found. Saline had no effect. It was concluded, therefore, that no hypersensitivity of the cells supposed to secrete H-substance was present despite the degeneration of the fibres having their cell stations in the posterior root ganglia. Another argument against these fibres innervating effector cells is that neither atropine (Hunt, 1918), curare (Brown and Maycock, 1940), nor nicotine (Ranson and Wightman, 1922b) has been found to abolish the effect. Present observations have also shown

that if 2 ccs. of 0.02 per cent. atropine be infiltrated under the skin or a similar amount of 0.02 per cent. prostigmine, the histamine flare is in no way affected although the sweat response to local faradism (Wilkins *et al.*, 1938) is respectively abolished and augmented. Also against the conception of a release of H-substance by the skin cells under the influence of nervous stimulation is the point that a similar local endocrine function would have to be attributed to skeletal muscle cells as antidromic vasodilatation also occurs in this tissue (Bayliss, 1900-01, Wybauw, 1938).

The necessity of hypothecating an indirect influence of the nerves on blood vessels arises from both anatomical and physiological considerations.

Hinsey (1928) traced the peripheral fibres of the posterior root system after producing degeneration of the sympathetic and motor fibres and found that though they travelled in close contiguity with the terminal blood vessels they did not end on them. He considered therefore that their effects on the vessels were produced by some remote influence. Lewis and Marvin (1927-9) reached a similar conclusion after demonstrating that a fundamental difference exists between antidromic vasodilatation and the vasodilatation induced by stimulation of vasodilator nerves such as the *nervi erigentes*. Thus it is necessary to hypothecate an intermediate step, but no evidence has been found indicating that the cells of the skin are the mediators of the indirect effect of the posterior root fibres.

CHOLINERGIC FIBRES.—The first suggestion that the posterior root fibres produced vasodilatation by the release of acetylcholine came from Dale (1929) who reasoned from the analogy with the Sherringtonian phenomenon which was shown (Dale and Gaddum, 1930) to be due to the peripheral release of acetylcholine. Dale (1933) later withdrew this suggestion after Hinsey and Cutting (1933) showed that the Sherringtonian phenomenon could not be elicited by stimulation of the posterior roots and was dependent on sympathetic pathways. Bülbring and Burn (1936) have confirmed the observation that stimulation of sympathetic fibres induces a contraction in skeletal muscle. The evidence of Wybauw (1936*b*) who found an increase of acetylcholine in venous blood after stimulating the posterior roots is antagonistic to that of Hinsey and Cutting who were, in a sense, using sensitized denervated skeletal muscle while Wybauw was using leach muscle and other tissues to detect acetylcholine. This discrepancy might be resolved if it could be shown that Wybauw was exciting sympathetic cholinergic fibres through a reflex whose afferent arc was formed by those fibres mediating recurrent sensation (Foerster, 1927). That this is not an unlikely explanation follows from the fact that in the cat stimulation of almost any efferent channel will cause sweating (Reid, 1898) and Wybauw used the same preparation as was used by Dale and Feldberg (1934) to demonstrate the release of acetylcholine by sudomotor fibres.

The evidence against acetylcholine itself being the

vasodilating agent is to be found in the paper of Lewis and Marvin (1927-9). These authors found that stimulation of posterior root fibres produced a state of vasodilatation that could persist for at least 6 minutes through a period of circulatory arrest. The evanescent effects of acetylcholine in the absence of eserine clearly rules out the possibility of the direct action of posterior root fibres through cholinergic endings.

In man Grant *et al.* (1935-6) and Lewis (1939-42) have found in their cases of reflex urticaria evidence that the nerve fibres are cholinergic but, as pointed out above, there is doubt as to the identity of these fibres.

It may therefore be concluded that the possibility of the peripheral release of acetylcholine by posterior root fibres is unproved.

NERVOUS RELEASE OF H-SUBSTANCE.—The term "H-substance" has been used by Lewis to mean "any substance (or substances) that is liberated by the tissue cells and exerts on the minute vessels and nerve endings an influence culminating in the triple response" (Lewis 1927*a*). The triple response consists of "local vasodilatation, the flare and eventually local oedema" (Lewis 1927*b*). Whether such a substance is liberated through the mediation of nerves requires consideration. Lewis and Marvin (1927-9) have shown that stimulation of posterior root fibres causes a vasodilatation which has a relatively long latent period, which endures longer than the stimulus, and which persists through a period of ischaemia. These observations were most readily explained on the basis of the release of a stable vasodilating agent and this was assumed to be H-substance. However, evidence was not adduced that this substance could evoke the triple response, and in fact their observations suggest that this was not the case. Thus they showed that the vasodilatation, even after prolonged stimulation of posterior root fibres, did not spread into the territory of adjoining nerves, and this would argue against the presence of a substance capable of initiating a flare. Foerster (1933) has confirmed this observation in man. Moreover, Lewis and Marvin were unable to produce oedema or blistering by stimulation of posterior root fibres alone, and any support for such an occurrence offered by the herpes of zoster or of irritative nerve lesions is insecure (see paper C).

To support his contention Lewis has quoted the results of Ungar. Ungar (1935) found in the dog that stimulation of the distal end of a cutaneous nerve for 2 minutes resulted in an increase in gastric secretion and this response was present after atropinization (Ungar *et al.*, 1935). It is somewhat disconcerting, therefore, to find that arterial occlusion of the limb during and for 8 minutes following stimulation abolished the gastric response. Thus the substance in question is apparently more unstable than those required to explain the vascular effects. It is impossible to be certain in this instance that the released substance was not fixed in the tissues during the period of occlusion, but against this possibility are the observations of Barsoum and Smirk (1936)

demonstrating that vascular occlusion itself leads to the release of H-substance. The explanation of the results of Ungar (1936), which suggest that the posterior root fibres are "histaminergic" and are involved in depressor reflexes, must await further study. Ungar and Parrot (1939) have since concluded that they were dealing with adrenoxine but Kwiatkowski (1943) supports their former interpretation.

The evidence for the release of H-substance by the nerve fibres involved in the flare is also unconvincing. So unconvincing indeed that Lewis (1937), being certain that antidromic stimulation released H-substance, was constrained to question the identity of nerve fibres mediating these two types of vasodilatation. However, there seems little reason to doubt their identity as both sets of fibres belong to the posterior root system, both cause vasodilatation and both are immune to the action of atropine. Recently Lewis (1939-42) has concluded in favour of the view that H-substance is released in the flare because in a subject with a highly sensitive skin small wheals occurred over the area of vasodilatation. It may be noted that Grant *et al.* (1935-6) in a group of patients similar to that of Lewis were unable to produce wheals in this way. An alternative explanation to that of Lewis may be offered, for inasmuch as the blood serum of his patient was shown to be highly potent in causing wheals on her skin when injected intradermally, it is possible that the marked vasodilatation in the area of the flare might have permitted sufficient exudation of plasma to produce the wheals.

It seems certain, therefore, that some substance with vasodilating properties is released by the stimulation of nerves, but it is doubtful whether it is entitled to the name "H-substance."

This review of the literature may be summarized by saying that there is no positive evidence indicative of:—

1. Efferent fibres in the posterior roots.
2. Posterior root fibres exerting their effects on the circulation by cholinergic endings.
3. Skin cells mediating the effects of these fibres.
4. Nervous liberation of H-substance.

AN ALTERNATIVE HYPOTHESIS.—In his latest paper Lewis (1939-42) appears to have been prompted to put forward the hypothesis that the nerve fibres under consideration are efferent because of the difficulty of conceiving that a single fibre subserves both efferent and afferent functions. His present conception does no less violence to the established doctrines of neurophysiology, for it requires certain efferent fibres to be endowed with a unique sensitivity to nocuous stimuli and to histamine while other fibres, whether large or small, efferent or afferent, are not stimulated by histamine with the possible exception of pain fibres, and here it is likely that pain endings are in fact being activated.

The only alternative to endowing a sensory fibre with efferent functions or vice versa appears to be to deny that one of these activities is a specific or intrinsic function of the fibre. It has been seen

above that these fibres belong to the posterior root system and there is no evidence of efferent fibres in this system, nor is there any evidence of any usual type of excitor-effector junction. Therefore it may be assumed that these fibres are afferent. It may also be assumed that they terminate in a branching axone system ending in receptors specially sensitive to products of tissue damage similar to histamine. It was shown by Woollard (1926) and Hinsey (1928) that afferent fibres travel in close association with the terminal vessels. The products of metabolism of these fibres would therefore have exceptional access to the vessels, and these products of metabolism would have the requisite vasodilating properties as judged by the action of metabolites of other tissues. Axonal vasodilatation is therefore attributed to the metabolites of sensory nerve fibres.

The above conception appears to outrage no physiological principles and to be capable of reconciling all the facts. Its main disadvantage is that it does not appear to be easily susceptible of proof. At first sight it would appear that the hyperæmic response of the flare is greatly in excess of the needs of the nervous filaments, but it may be recalled that the hyperæmia in response to activity in other tissues such as glands and muscles (Barcroft and Kato, 1916) is also excessive as judged by the approach of the O_2 content of the venous blood to that of the arterial blood. This point, therefore, should not be given undue weight, particularly as it has been shown that activity of nerve fibres, as in cerebral white matter, does induce a dilatation of the vessels in their vicinity (Serota and Gerard, 1938). Moreover it is not impossible that nerve fibres, and perhaps unmyelinated fibres in particular, may release peculiar catabolic products of high vasodilating potency. The presence of such substances in nerve fibre is indicated by the work of Lorente de N6 (1938) who found acetylcholine (i.e. a substance causing contraction of leach muscle) in fibres at sites distant from their ultimate terminations, while Kwiatkowski (1943) has offered similar evidence for a substance considered to be histamine. If these were released on excitation of the fibres the explanation of the results of Wybauw (1936b) and Ungar (1935) would be made clear. This idea might also be supported by reference to the observations of Gerard (1932) and Abrams and Gerard (1933) that substances leave the cell body and pass down the axone. At some point these must be extruded, and it is conceivable that this process would be accentuated by the changes in membrane permeability associated with the conduction of the nerve impulse. Perhaps the development of refractoriness that occurs after periods of anti-dromic stimulation could be explained by the exhaustion of the supplies of this substance.

This hypothesis does not necessarily restrict all cases of axonal vasodilatation to one type of fibre and pain fibres would seem to be a not unlikely pathway. However, it has been deduced from the case reported above that axonal vasodilatation is

mediated at least in part by fibres which do not give rise to a conscious sensation.

It may be mentioned that the view point supported here is not far removed from that originally presented by Langley (1923-4), who considered that metabolites from the muscle spindles might be the cause of the antidromic vasodilatation in muscle. Moreover, Gaskell (1916) favoured and Lewis (1927c) was not inimicable to the view that metabolites were the cause of the vasodilatation in the skin. The fundamental alteration in theory suggested here merely transfers from the skin cells to the nerve fibres the onus of producing the metabolites.

It is proper though perhaps unnecessary to indicate the defects of the method used in reaching this conclusion. The method entails in the first place selection from a vast literature of observations that appear to be pertinent and in the second place of evaluation of these observations. It is obvious that an incalculable human element is introduced in both these procedures. Thus it is not easy to tell how far the prejudices of the moment have caused a distorted picture to be presented. The fundamental difficulty arises from the impossibility of reconciling the desire of an advocate to do full justice to his cause and the desire of a judge to see full justice done to all. Of some reassurance that the latter attitude has been successfully maintained is the apparent usefulness of the concept in integrating seemingly unrelated phenomena. Of these, three in particular may be mentioned which are explicable on the basis that intense stimulation of nerve fibres causes them to liberate a vasodilator substance near their terminations :—

1. The vasodilatation that occurs in the atropinized submaxillary gland following stimulation of the chorda tympani.
2. The reversal of the vasoconstrictor effect of sympathetic stimulation by ergotoxine.
3. The flare response and anti-dromic vasodilatation which have formed the subject of this paper.

Summary

A case of ulnar nerve section with an unusual distribution of the median nerve has been reported. Evidence was found that axonal vasodilatation was mediated at least in part by fibres other than those associated with sensation.

A criticism of a recent elaboration of the theory of axonal vasodilatation was made.

An alternative hypothesis was formulated attempting to explain the phenomena of antidromic vasodilatation and axonal vasodilatation within the concepts of classical neurophysiology.

This hypothesis was based on the assumption that potent vasodilating substances might be liberated from nerve fibres near their terminations.

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