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REFLEX VASO-MOTOR RESPONSES OF THE PAW OF THE CAT

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Hallion & Conte, as early as 1894, using plethysmographs, recorded on a smoked drum the volume changes occurring in the fingers and feet. They showed that a decrease of volume followed a nocuous stimulus or a deep breath and concluded that these changes represented active reflex vaso-constriction. Since that time many records have appeared in the literature, but it is only in recent years that observers have introduced more sensitive methods of recording volume changes. Information about the methods which have been introduced can be obtained from papers by Goetz [1935], Stürup, Bolton, Williams & Carmichael [1935] and Hertzman [1937].

In the following investigations a sensitive method has been used similar to that described by Stürup *et al.* [1935] to record the changes in the paw volume of cats. Small changes of volume are easily recorded and the time relations of the change accurately charted. We consider that the method will give much information of the mechanisms of vaso-constriction both at the periphery and at the reflex centres. A short summary of this work has been published previously [Downman, Goggio, McSwiney & Young, 1939].

Method

Glass plethysmographs of about 50 c.c. capacity were applied over the paws of the cat, reaching up to the wrist joint of the front paw and over the greater part of the metatarsus of the hind paw. The plethysmographs were connected to a brass capsule with rubber tubing, a side tube controlled by a spring clip allowing for equalization of pressure when necessary. A light plane mirror of polished silvered glass was mounted eccentrically upon a thin rubber membrane covering the end of the capsule. A beam of light was projected through a vertical slit on to the mirror and the movements of the reflected beam were recorded on photosensitive paper.

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The sensitivity of the system could be varied within wide limits by using rubber membranes of differing thickness on the capsules. It was most convenient to use a membrane which gave a deflexion equal to the width of the camera slit (58 mm.) for a volume change of 0·03–0·05 c.c. A less sensitive membrane would not record very small changes of volume; with a more sensitive membrane the deflexions due to each heart beat became inconveniently large.

Systemic blood pressure was recorded optically from the central cut end of a carotid artery. The arterial cannula was connected to a metal capsule carrying a thick rubber membrane with a stainless steel mirror attached; the mirror deflected the beam of light on to the camera slit. The system was filled with normal saline containing carrageen as anti-coagulant [Elsner, Braser & Bürgel, 1937; Elsner, 1938; Little, personal communication].

Respiratory movements were recorded optically by means of a rubber balloon held in contact with the epigastrium.

Typical calibration figures were of the following order:

Volume of glass plethysmograph	55 c.c.	
Volume of connecting tube and capsule	11 c.c.	
	66 c.c.	
Volume of tissue in plethysmograph	30 c.c.	(hind paw of 2·7 kg. cat)
Dead space	36 c.c.	

The volume of tissue enclosed varied with the size of the animal, but was of the same order of magnitude for all animals.

Plethysmographs shaped to the form of tissue under investigation were also made by the following method. X-ray films were cleaned in hot water and the base dissolved in acetone to form a viscous solution. A layer of artificial silk-stocking material was applied to a wax model of the tissue and then painted over with the solution. When dry, alternate layers of fabric and solution were applied until a wall 2–3 mm. thick had been built up; the wax was scooped out and a glass side tube was cemented into a hole bored through the wall. The resulting structure was very rigid and withstood boiling. This method is rapid and can be adapted to produce any desired shape.

Anaesthesia

In the majority of experiments urethane (1·5 g./kg. body weight), nembutal (80 mg./kg.), or pernocton (0·4 c.c. 10 % solution per kg.) were used to produce anaesthesia. In a few cases anaesthesia was maintained with chloralose or dial (Ciba).

Urethane was administered intravenously or subcutaneously. In the former case preliminary ether anaesthesia was given, and the trachea cannulated. The anaesthetic was made up in normal saline as a 20 % solution. It was

seldom possible to administer the full dose in less than 30 min. owing to respiratory difficulties attendant upon a faster rate of administration; at a later stage in the experiments the respiratory rate was often very high, reaching 120 per min. in some animals. Reduction of the dose produced satisfactory anaesthesia but good vaso-motor responses were not obtained from the paws. In some animals responses were obtainable after about 5 hr. had elapsed from the intravenous injection of urethane. After a further period of about 2 hr. sensitivity was usually lost, and did not return. The respiratory difficulties consequent upon the use of intravenous urethane could generally be avoided by giving the same dose subcutaneously. We found that these animals were more sensitive to weak afferent stimulation than were those in which urethane had been given intravenously. The disadvantage of this method was that it was generally necessary to wait for 10–14 hr. before a response could be elicited; the period of sensitivity lasted slightly longer than in the case of intravenous urethane.

Nembutal was dissolved in normal saline and administered intraperitoneally; deep anaesthesia was obtained within 10 min. In some animals reflex responses were obtained within 1 hour, but in others it was necessary to wait up to 3 hr. The animals were sensitive to weak afferent stimulation, and once sensitivity had appeared it did not pass off within the time required for the longer experiments (about 8–10 hr.), though in some animals anaesthesia became too light towards the end of this period.

Pernocton (supplied in 10 % solution) was diluted with 5–10 times its volume of normal saline and administered intravenously under ether anaesthesia. A slow rate of injection (2 c.c. diluted solution per minute) avoided difficulties with respiration. Reflex responses were usually obtainable within 2 hr. of administration of the anaesthetic; after a further variable time it was usually found that anaesthesia became too light, and the reflex responses were lost. In these circumstances a second injection of pernocton (equal to one-quarter of the original dose) generally restored both the required depth of anaesthesia and the reflex responses.

Positive results were also obtained with chloralose and dial anaesthesia. The chloralose (75–80 mg./kg. body weight) was injected as an approximately 2 % solution in saline into the femoral vein exposed under preliminary ether anaesthesia. Dial (Ciba) 0·65–0·70 ml./kg. was injected intraperitoneally. In our hands, however, these anaesthetics were not as reliable as the others, few of the animals remaining sensitive over long periods.

On the whole pernocton gave the most satisfactory results, the depth of anaesthesia being more easily controlled than when using urethane or nembutal. The use of nembutal had the advantage of dispensing with preliminary ether anaesthesia and avoided the possibility of the accumulation of mucus in the respiratory tract.

Results

Sensory stimulation caused a sharp decrease of volume of the paws of anaesthetized and of decerebrate cats. The decrease of volume reached its maximum in a short interval of time and was followed by a slow return to the initial volume. In a sensitive animal the responses of the front and hind paws were synchronous. In some animals, however, the responses were limited to the hind paws, the front paws showing no change of volume. The decrease of volume of the paw was accompanied by a diminution of the amplitude of the pulsations, the return to the initial volume by an increase of amplitude up to its original size.

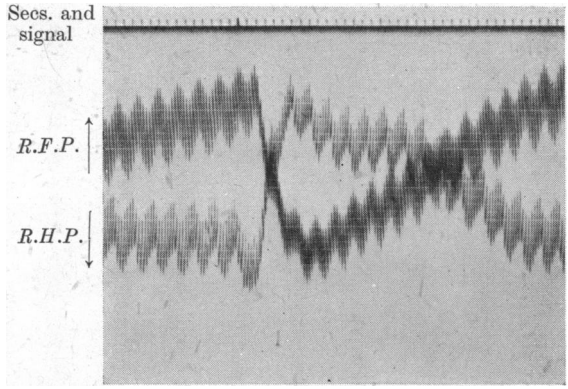

Fig. 1. Change of volume of front and hind paws following pinch of central end of cut left radial nerve. The smaller regular waves correspond with respirations. Urethane anaesthesia. Pinch at signal. *R.F.P.* = right front paw; *R.H.P.* = right hind paw. Arrows show direction of increase of volume. Time in seconds.

The volume change could be elicited by many types of stimulus, such as a noise, pinching the skin, irritation of exposed nerves, manipulation of the viscera; flicking the pinna with the finger was found to be a good test for sensitivity. In spite of the variety of stimuli there was no difference in the form or time relations of the responses.

Nature of the response

The diminution of volume is not caused by reflex movements; similar changes were obtained in the curarized decerebrate animal. The response could have been due to increased circulatory adrenaline, but this explanation cannot be accepted, because the latent period was too short, the decrease of paw volume after intravenous injection of adrenaline never taking place in less than 7·5 sec. Furthermore, the removal of both adrenal glands did not alter the response in magnitude or time relations.

The response is not secondary to alterations of blood flow to the limb, because clamping of the common iliac artery, though modifying the response,

did not prevent its occurrence in the ipsilateral hind paw. The volume change is also independent of alterations of systemic blood pressure. It usually preceded the recorded pressure changes in time, and was not apparently influenced by the direction of the change. In some animals it was accompanied by a rise, in others (especially under urethane) by a fall, and in some experiments there was no apparent change of blood pressure in the carotid artery.

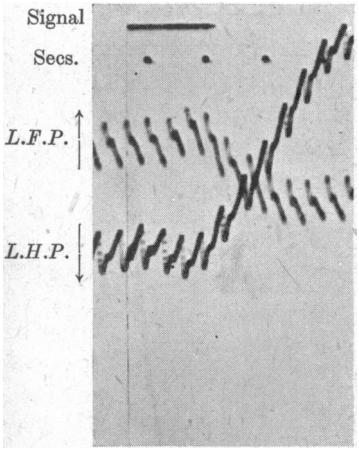

Fig. 2.

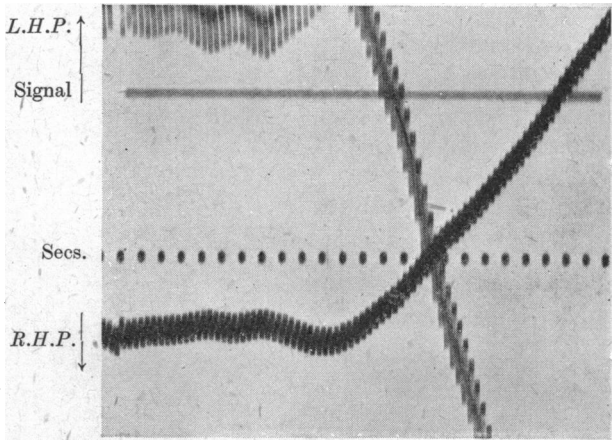

Fig. 3.

Fig. 2. Volume changes of left front and hind paws taken on more rapidly moving paper to show length of latent period. At beginning of signal line the central end of the cut radial nerve was stimulated by a single break induced shock, using a Lucas pendulum. Pernocton anaesthesia. Time in seconds.

Fig. 3. Volume changes of hind paws following injection of 1 μg. adrenaline in 1 ml. saline into left radial vein during signal. Pernocton anaesthesia. Time in seconds. Smaller pulses of right paw are due to use of stiffer rubber membrane carrying mirror.

A tight rubber ligature round the paw immediately proximal to the pads abolished the change of paw volume. This may be explained by the arrest of the circulation through the pads by the mechanical effect of the ligature. The abolition of the response is unlikely to be due to local damage to nervous paths, because release of the ligature was followed by its immediate return. If the pad of one digit was left out of the ligature the response was not abolished, showing that the previous results were not due to inhibition of nervous centres by the nocuous stimulus.

It is concluded, therefore, that the change of paw volume represents an active constriction of the vessels of the pads. Other possible causes, such as movement, changes of blood flow to the limb, and activity of the adrenal glands, have been controlled.

Features of the afferent side of the reflex arc

The wide range of effective stimuli has been referred to. A flick with the finger or a pinch of the pinna, pinching the skin of the body and loud, sharp sounds were effective. When using a Lucas pendulum it was necessary to remove it to another room as the sound of the fall of the arm was an effective stimulus to sensitive animals. Centripetal stimulation of the cut radial, saphenous, sciatic, vagus or splanchnic nerves was effective. The nerves were stimulated by pinching, faradization, or by single break induction shocks using the Lucas pendulum. The vagus was stimulated in the neck and the splanchnic nerves below the diaphragm. The response was also elicited by pulling on the root of the mesentery, distending a balloon in the pylorus (pressure 50–80 mm. Hg) or by pinching the small intestine.

When a graded series of induction shocks was given to an afferent nerve, increasing the current strength caused the decrease of paw volume to become maximal, but the blood pressure might fall, rise or show no change. Further increase of current strength caused no greater decrease of paw volume, but in some animals a previous fall of blood pressure was converted to a rise, or an existing rise augmented.

In a series of experiments the response was elicited by stimulation of the central cut end of a cutaneous nerve with weak faradic current. Increasing the duration of the stimulus up to approximately 60 sec. made no difference to the duration of the response, return to initial volume occurring during stimulation. When the strength of the faradic current was increased above a limiting value an increase in the duration of the stimulus now caused increased duration of the response, paw volume not returning to its base line until after the cessation of the stimulus.

Spinal nerve roots were exposed in the lumbar region by laminectomy. Single break shocks, faradization and pinching the central cut end of a dorsal root caused decrease of volume of both hind paws. Stimulation of the peripheral cut end of the root did not produce a response.

It is seen that the reflex can be elicited by stimulation of afferent nerves and end-organs situated in many different parts of the body.

Efferent pathways for the reflex

Section of the sympathetic pathway to the forelimb, either by removal of the stellate ganglion or section of the thoracic sympathetic chain proximal to the ganglion, abolished the response of the ipsilateral front paw. Stimulation of the distal cut end of the chain or pinching the stellate ganglion produced a response of the paw. Removal of both 4th lumbar sympathetic ganglia abolished the responses of both hind paws. Stimulation of the distal cut end

of either chain below this level caused decrease of volume of both hind paws, after the spinal cord of the lumbar region had been destroyed.

Stimulation of the distal cut end of a mixed nerve supplying the limb also caused responses of the corresponding paw in the curarized decerebrate cat.

Pinching the first, second or third anterior spinal roots of the lumbar region elicited a decrease of volume of the ipsilateral hind paw. The response persisted when the posterior roots were severed, and also when the corresponding segment of the cord was isolated and split in the mid-line. These results show that the impulses pass centrifugally, and that the response is not set up by impulses passing back into the cord.

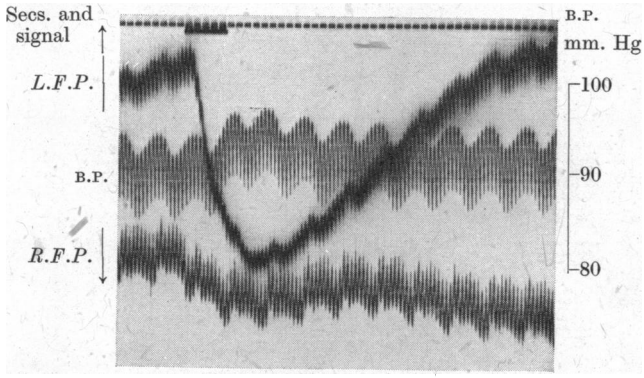

Fig. 4. Abolition of volume change by removal of right stellate ganglion. At signal faradization of central end of cut left saphenous nerve. Volume of front paws: blood pressure recorded from central end of cut left carotid artery. Time in seconds. Urethane anaesthesia.

It is concluded that the reflex vaso-constriction of the pads is mediated on the efferent side through the sympathetic system. The fibres leave the cord in the anterior roots, pass into the sympathetic chains and reach the pads after travelling along the mixed nerve trunks. Precise definition of the course and relay stations of the fibres was not attempted. The absence of a response to stimulation of the peripheral cut end of a dorsal nerve root suggests that there is no efferent pathway mediating vaso-constrictor reflexes of the paws along the sensory nerves. At the same time no vaso-dilatation was produced but this may have been due to the vessels being already maximally dilated.

Time relations of the response

In our experiments the reflex response had a latent period of 0·5–2·5 sec. Considerable variations were noted from time to time in the same animal on stimulation of the same afferent nerve, these variations depending mainly upon altered conditions of the peripheral blood vessels. It was observed that alteration of the latent period by as much as 0·5 sec. paralleled changes in tone of the vessels, the latent period being shorter if the vessels were con-

stricting at the time of the stimulus and longer if they were dilating. In a typical experiment the latent period was 0·67 sec. when the vessels were constricting and 1·12 sec. when they were dilating; these figures are averages of several observations taken over a short period when little variation occurred in each group. The latent period was increased by deepening the anaesthesia or by exhibiting curarine. Following the latent period the paw volume decreased rapidly, reaching a minimum in 2·5–10 sec. The time taken for return to the initial volume ranged from 8 to 50 sec.

The volume changes consequent upon direct stimulation of the sympathetic efferent pathway have the same general form and time relations as the reflex response. The stellate ganglion and the lumbar sympathetic chains were stimulated by pinching or by break induction shocks. After a latent period the volume reaches a minimum rather more rapidly than the reflex response; the minimum was attained in an average time of 3·2 sec. from the beginning of the change (range 0·8–6 sec.) against 4·2 sec. (range 2·5–10 sec.). The differences between the reflex and direct latent periods will be discussed in the next section.

Central reflex time

The latency of the reflex response was invariably greater than the latency of the response to direct stimulation of the sympathetic chains. The error incurred by including the time of conduction along the afferent nerve was less than the error of the method; altering the length of nerve involved did not appreciably alter the latent period.

A survey of the observations showed that the shortest differences recorded were of the order of 0·4 sec. The method involved the estimation of the latent period before and after the exposure and section of the chains; although care was taken that the state of the vessels was apparently the same during corresponding observations, there was sufficient variation in the periphery to make many of the times much longer. It is clear that accurate estimates of the central reflex times require a method which will allow more rigid control of these factors.

Summation

Single break induced shocks were given to nerve trunks at intervals of 20 and 50 m./sec. Spatial summation of responses was indicated when subliminal and submaximal stimuli were applied to the same or to different sensory nerves. The same result obtained on stimulation of preganglionic and postganglionic fibres to the hind limb. The preganglionic fibres were stimulated in the lumbar chains, while the postganglionic were stimulated by applying the two electrodes to the distal halves of the cut sciatic nerve after splitting the nerve longitudinally.

At present it is not possible to discuss the significance of these findings. Spontaneous variations in the periphery precluded the construction of accurate

curves relating summation of effects to stimulus interval. Further analysis is needed to define the site of summation and the factors underlying its production.

Discussion

Using a sensitive optical recording method we have found a short-lived volume change in the paws of anaesthetized cats following many types of sensory stimulation. The records of the volume changes show the same spatial and temporal features as the records of digital volume changes in man. Stürup *et al.* [1935] find a latent period of 2–3 sec. in man, while in cats the duration is 0·5–2·0 sec.; other investigators have not recorded their findings, but from the published records the latent period is in all cases a matter of a second or more. Following the latent period there is a sharp decrease of volume, followed by a slower return. So strong are the resemblances between the records obtained from man and the cat that one is tempted to assume that identical physiological phenomena are being recorded in the two species.

The basis of the response is a vascular change. Skeletal muscle activity was precluded by the use of curarine, and the only means of producing such rapid changes of volume is by shift of fluid from the paws. Hallion and Conte deduced an underlying vasoconstriction from the accompanying change of shape of the arterial pulse tracing. Hertzman & Dillon [1939] and Burton [1939] emphasize the decrease of amplitude of the pulsations accompanying the reduction of volume, and it can be seen in the published tracings of other workers. Wilkins, Doupe & Newman [1938], Burton [1939], and Burton & Taylor [1939], have shown that there is a reduction of inflow of blood into the finger during the decrease of volume. More direct evidence is provided by Mulinos & Shulman [1939]; from direct observation of the capillaries of the nail bed they concluded that the reduction of flow depended upon some happening on the arterial side of the capillary. The persistence of the volume change when the main artery to the limb was occluded, found also by Bolton, Carmichael & Stürup [1936], and Lieb, Mulinos & Taylor [1936], indicates that the change of volume is not secondary to a reduction of blood flow above the level of the paw itself. Our evidence is that the greater part, if not the whole, of the volume change arises in the pads. We may deduce therefore that the volume change is dependent upon a change in skin vessels. The precise site of this change and the relative part played by the different vessels remains to be cleared up.

There can be no doubt that the vaso-constriction is of neurogenic origin. Not only does it occur with the limb circulation temporarily stopped but also in the acutely adrenalectomized animal. Furthermore, the latent period of the vaso-constriction caused by a constrictor drug (adrenaline) injected into the internal jugular vein was in our hands never less than 7·5 sec. Finally, interruption of the nervous pathway abolishes the response. In man, for example,

Stürup *et al.* [1935] and Peters [1939] could not obtain the response in the finger following avulsion of the brachial plexus, and we have found that the response is abolished by section of the sympathetic chain at the appropriate level.

The connector neurones leave the spinal cord with the anterior roots. Centrifugal stimulation of anterior roots in the lumbar region caused decrease of volume of the corresponding hind paw while centrifugal stimulation of the cut posterior roots did not. Section of the sympathetic supply to the limb also abolishes the response. We have found that removal of the stellate ganglion or the lumbar sympathetic chain prevented the change of paw volume although stimulation of the peripheral cut end of the nerve demonstrated that the vessels were still reactive. Stürup *et al.* [1935], Bolton *et al.* [1936], and Burton [1939] have found that cervical or lumbar ganglionectomy is followed by absence of vaso-constriction of the corresponding digits. The impulses then pass down fibres in the somatic nerves; we have found that stimulation of the peripheral end of the cut sciatic nerve produces a decrease of hind-paw volume. Malmejac & Haimovici [1936] showed that in dogs section of the nerves to the muscles and veins of the hind limb decreased the change of paw volume, and that subsequent denervation of the arterial walls abolished the small residual response. The experimental findings indicate that the impulses leave the cord, pass into the sympathetic chain and are relayed out to the paw or digit along fibres which run in the somatic nerves. This course represents the final common path of the reflex vaso-constriction in both man and cat. The work of Malmejac & Haimovici [1936] shows that a small part of the diminution of paw volume may be dependent upon the peri-arterial nerve net. Bearing in mind the conclusion of Gilding [1932] that this sympathetic plexus does not conduct impulses to the peripheral vessels, it seems probable that the small decrease of volume is secondary to a constriction of the main artery due to impulses conducted along this pathway. The majority of the conducting fibres, however, run in the somatic nerves. Applying further the conclusions of Gilding [1932] it seems that these fibres leave the main nerve trunk to reach the pads or digital skin in the local sensory nerves, but no direct confirmation of this is recorded.

Stimulation of cut posterior roots produced a response only when the central end was stimulated; no change in paw volume followed stimulation of the peripheral cut end. As we have pointed out, the absence of dilatation may have been due to an already maximal dilatation of the skin vessels. The anaesthetic itself may have played some part in this; de Waele, van de Velde & Braeye [1933] have shown that deepening of ether narcosis abolishes the classical effect.

The pathway through the central nervous system has not been traced. Bolton, Williams & Carmichael [1937] found that in two cases of spinal cord lesions there was no evidence of reflex activity through intact sympathetic ganglia alone but that a path in the cord is involved, while Bolton *et al.* [1936] showed that total transection of the cord by crushing in man prevented the appearance

of the reflex to deep breathing below the lesion level. We have not, however, been able to demonstrate a reflex pathway confined to the spinal cord. Certainly destruction of the cord abolishes the responses but so also does acute section in the cervical, dorsal, or lumbar regions in the anaesthetized animal. The cause of this may be, on the one hand, the acute upset of the cord. Sherrington [1906] showed in dogs that all reflexes, including vaso-pressor, were lost for some hours below the transection after withdrawal of the anaesthetic, the return of vascular reflexes requiring even some days. Although we used strychnine in an attempt to heighten any trace of the reflex, following the suggestion of Bayliss [1923], it is probable that we did not wait long enough to demonstrate it. On the other hand, the central path may be long; the long central reflex time indicates this, but the effect of the anaesthetic has not been determined. However long it may be, the path is complete in the brain stem below the level of the superior colliculi, shown by the persistence of the response after decerebration at this level. In man the cerebral cortex is not involved, typical responses occurring in spite of an extensive decortication [Williams & Scott, 1939] and diverse cerebral lesions [Stürup *et al.* 1935].

Reverting to the afferent side of the reflex arc, it is seen that the receptive field of the reflex is large and is not limited to the end-organs in any one area of the body. Impulses set up in this field converge on the centre to cause discharge of impulses along the final common path. It is noteworthy that the response is as easily elicited in man as in animals; sudden noises, stimulation of the skin and distending a balloon in the intestine are effective in both species. At present it is not possible to say whether any specific type of end-organ is involved. It is interesting to note also that the same methods of indirect stimulation produce marked vaso-constriction in the paw as produce dilatation of the pupil in the chloralosed cat.

The resemblances between the reflex in animals and man suggest that one and the same reflex is involved, and analysis shows that the anatomical plan is the same. Final discrimination of the site of action of the impulses is still needed. At what level this reflex path is complete within the brain stem is still undefined; certainly it is complete below the superior colliculi. Many more details of the anatomy require investigation, but the establishment of the reflex allows of its use as an index of changes in the central nervous system; for example, it will form an index of the arrival of impulses at the lateral horn cell or of changes of state of the cell itself.

Summary

1. Reflex changes of paw volume of anaesthetized cats have been recorded by a sensitive optical method.

2. Various methods of sensory stimulation cause a transient decrease of paw volume. This is due to active constriction of the vessels of the pads.

3. The final common path of the reflex is represented by the sympathetic nerve supply of the limb. The central paths have not been traced but are complete below the level of the superior colliculi.

4. The latent period of the response is long; the central reflex time also appears to be long.

5. The reflex response can be used as an index of changes in the centres, and gives evidence of summation there.

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