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THE SPINAL ORIGIN OF FIBRES
CAUSING VASODILATION IN THE
CAT'S SUBMAXILLARY GLAND.

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INTRODUCTION

In 1884, Dastre and Morat demonstrated vasodilator fibres running to the buccofacial region in the dog via the cervical sympathetic. Bowditch and Warren, in 1886 obtained vasodilation in the hind limb of the dog upon stimulating the peripheral part of the cut sciatic with induction shocks of low frequency. Burn, in 1932, obtained similar effects after stimulating the lower abdominal sympathetic chain in a canine heart-lung-lower limb preparation. He noticed vasodilation when shocks of low intensity were applied for short periods, and vasoconstriction when stronger shocks of greater duration were applied. He further observed that maintaining a normal concentration of adrenaline in the blood augmented both vasodilator and constrictor response.

In 1907, Carlson obtained vasodilation in the cat submaxillary gland following stimulation of the cervical sympathetic. This action could be obtained after the use of shocks too weak to cause visible secretion, and was also seen after administration of atropine in sufficient dosage to
prevent visible section. McLean, in 1908, obtained vasodilation from this gland after intravenous administration of adrenaline. The augmented flow was observed to be, at its maximum, partly independent of general blood pressure effects. Carlson and McLean attributed this phenomenon to the presence of vasodilator fibers in the cervical sympathetic supply to the organ.

Another hypothesis to explain glandular vasodilation had been advanced by Henderson and Lowe. They were of the opinion that this vasodilation was due to increase of size in the capillary rather than the arteriolar bed, and that it was caused by the action of metabolites formed during secretion, rather than by direct nervous effect on the arterioles. Evidence for this view was afforded by Barcroft in 1907. He showed that vasodilation in the cat submaxillary gland was synchronous with increased secretion of saliva, and that even after atropinization, sufficient in degree to prevent any visible secretion, increased gaseous metabolism could be detected during times of increased venous outflow. Gesell, in 1918, noticed that secretion in the gland produced typical
deflection curves with the D'Arsonval galvanometer. Stimulation of the chorda tympani causes vasodilation and secretion. He used currents weak enough to produce vasodilation but no visible secretion, yet the typical deflection curve, reduced in intensity, was observed. This indicated some glandular activity stimulating currents too weak to give the D'Arsonval deflection also failed to give vasodilation. Hence, they concluded that glandular vasodilation was due to the action of metabolites on the capillary bed.

Langley, in 1892, showed that vasoconstriction fibres to the head and neck region of the cat took their spinal origin at the 2, 3, 4 and 5 T levels, and that secretory fibres to the submaxillary gland came from the 2, 3, 4 T and a few from the 5 T in 75% of the animals studied. He also found similar origin for sympathetic cardio-accelerator fibres.

Stryker, Ranson, Sherrington and others obtained vasodilation in skeletal musculature by stimulating dorsal nerve roots after previous section and degeneration of the ventral roots. Similar effects were noted when acetyl choline was injected. Gasser and Hinsey found that the nerve fibers causing this were of the finely medullated type, 3-5 micra in diameter. Ken Kure and his associates, in 1928, while
seeking the position and origin of this nervous element noticed that after sectioning the dorsal root different degenerative effects ensued in distal and proximal segments. In the distal part, large myelinated fibres were in a healthy state, but the small varieties were degenerated. In the proximal segment an opposite effect obtained; here the large fibres were degenerated and certain smaller fibres were in good condition. He traced these fibres to their cell bodies which were situated in the spinal cord, between the substantia gelatinosa and the anterior horn. He is of the opinion that these are the nerve cells carrying the impulses from the central nervous system responsible for the Sherrington and allied phenomena. He classes these fibres with the parasympathetic system.

So far as we are aware, antidromic conduction has not been found to be responsible for vasodilation in glandular tissue. Accordingly, we sought to determine whether or not fibres taking origin in upper thoracic dorsal roots, and reaching the gland via the cervical sympathetic might be responsible for the vasodilation observed by Carlson. We
have also attempted to separate secretory from direct vascular effects. Taking Langley's work as a basis for the origin of secretory fibres, we thought that any evidence showing vasodilator fibres to come from any other levels than those supplying secretory fibres would indicate that the effects were produced by direct nervous action rather than secondary chemical reaction.

In brevis, we have attempted to answer the following questions:

1. Have dorsal root components any part in submaxillary gland vasodilation?

2. From which spinal levels do the fibers causing vasodilation arise?

3. Can secretory be separated from vasodilator effects?
METHODS.

Mature oats, 2-5 kilograms in weight were the material for our work. Ether or nembutal were the anaesthetics. The animals were curarized when strong stimulating currents were employed in order to eliminate muscular movements. Heparin was used as an anticoagulant in several experiments but its use was later abandoned since it is a very expensive drug. A control experiment showed it to have no effect on blood pressure.

METHOD I. The animal was anaesthetized and tied on a catboard. Provisions were made to prevent undue loss of body heat. An incision, one centimeter lateral to the midline, was made from the angle of the jaw to a point just cephalad from the clavicle. A dissection was then made to expose the gland. Its venous outflow was traced to the anterior or posterior facial veins. All other tributaries to these and to the external jugular were ligated. The cervical sympathetic trunk on the same side was isolated from the vagus and prepared for stimulation with induced current. The external jugular vein was then cannulated so as to enable us to record the venous outflow from the gland. The outflow
was recorded by drops on a kymograph chart in relation to stimulation of the cervical sympathetic trunk. To prevent thrombosis in the system, a cannula, connected to a burette filled with 10% sodium citrate solution, was introduced into the anterior facial vein just below the ligature. The solution, if washed through at regular intervals prevented clotting and washed out any formed blood elements present. These experiments confirmed the Carlson vasodilation.

METHOD II. The animal was prepared as in the first procedure, but additional dissection was done. Upper thoracic dorsal and ventral roots, homolateral to the neck dissection were separated, ligated and sectioned centrally. Records of outflow were taken as affected by stimulation of these and of the cervical sympathetic. The secondary coil of the inductorium was between 7 and 13 centimeters from the primary during stimulations. Monopolar platinum electrodes were used for the spinal roots and ordinary ones for the sympathetic. Due to the brevity of the roots in this region it was deemed impossible to separate effects of dorsal root from ventral root stimulation, due to the spread of the current. This method was then abandoned. The segments studied in this group were the second to the fifth thoracic.
METHOD III. This was one of preliminary extirpation and degeneration of the nervous elements involved. In an operation undertaken with aseptic precautions several ventral roots were sectioned or dorsal root ganglia excised in the upper thoracic region. Sufficient time for degeneration was allowed, and the animal then employed in an acute experiment. Venous outflow from both glands was recorded simultaneously in relation to stimulation of the cervical sympathetic on either side. Flow was recorded from both sides to compare the normal with the operated, and as a check on cardiac and other effects to be discussed later. In several of these experiments ergotamine tartrate was used in an attempt to paralyze the sympathetic constrictor fibres, thus making any dilator response more obvious. Adrenaline was also used because of its known effect in increasing the responses to sympathetic stimulation.

In all cases where the animal suffered dorsal root excision a careful post mortem examination was done to make sure that no ventral root injury had been done in the previous aseptic operation.

In those animals having several dorsal roots removed from the upper thoracic region no changes were observed in response to cervical sympathetic stimulation on the operated
side. This vasodilation was about equal on both sides.

With animals having several ventral roots sectioned in the lower cervical and upper thoracic region different results were obtained.

In one animal with the eighth cervical and first and second thoracic ventral roots cut, in another with the first and second thoracic, and another with the first and third thoracic similarly treated, stimulation of the cervical sympathetic resulted in a reduced vasodilator response on the operated side. Animals with sections at lower levels showed no significant differences.

METHOD IV. Feeling assured that the dorsal root component was not concerned in the vasodilation, we decided to stimulate whole spinal roots and disregard dorsal root effects providing the root was sectioned to prevent central reflex effects. The animals were prepared much as in method II. We curarized these animals and gave artificial respiration. Since we were using stronger stimulating currents it was thought advisable to include this step so as to avoid muscular movements in the animal which might give rise to a simulated vasodilation.
In these experiments we found that stimulating the first, second and third thoracic usually gave rise to vasodilation. The fourth thoracic also did this in one instance. In another experiment, stimulation of the third and fourth thoracic caused a decided vasoconstriction. In an animal in which stimulation of the first and second thoracic ventral roots gave only slight dilation, subsequent stimulation of the sympathetic caused a strong constriction. We were surprised to observe in several experiments that stimulation of the eighth cervical gave rise to strong vasodilation. All vasodilator and constrictor responses were abolished after the cervical sympathetic was sectioned.

METHOD V. These were control experiments.

A. Venous outflow from the left submaxillary gland of a curarized cat was measured in relation to stimulating the eighth cervical and first thoracic ventral roots of the right side. No significant changes were observed.

B. Venous outflow from the left submaxillary gland was measured after stimulation of the right cervical sympathetic trunk. No increased rate was observed on the left side,
while on the right side a strong vasodilation was observed.
RESULTS.

Plate one.

Top line of tracing shows flow of blood in drops from the submaxillary gland. Middle line shows stimuli: numbers in centimeters show distance of secondary coil from the primary, degrees refer to its angle in relation to the primary. The bottom line is a time tracing in five second intervals.

The effect of increasing the strength of cervical sympathetic stimulation is shown.
Plate two.

Top line of each tracing shows drops of blood from right submaxillary gland. The second line records the flow from the left. The third line is signal, and the bottom is time in five seconds.

The first chart is from an animal in which the right seventh and eighth cervical ventral roots had been cut. The second is from an animal in which the right eighth cervical and first and second thoracic ventral roots had been sectioned. The third is from an animal in which the right second, third and fourth thoracic ventral roots had been sectioned.
Plate three.

Chart one is from an animal in which the right first and second thoracic dorsal root ganglia had been removed. The second chart is from an animal in which the same operation had been done at the second, third and fourth thoracic levels. The top line of each tracing records the venous outflow in drops from the right submaxillary gland, the second line records the same for the left gland.
Plate four.

This chart shows the effect of direct stimulation of the ventral roots of a curarized cat at the eighth cervical (a), and first to fourth thoracic levels (B,C,D, and E respectively) with the cervical sympathetic intact.
Plate five.

This chart is from the same animal from which plate four is taken and shows the effect of sectioning the corresponding cervical sympathetic trunk on vasodilator response to ventral root stimulation.
Plate six.

The first three show the effects of stimulating the eighth cervical, and first and second thoracic ventral roots on blood flow from the gland. The two bottom charts show the effect of stimulating the third and fourth thoracic ventral roots. Both cats were curarized.
Plate seven.

The top tracing shows the effect of increasing the strength of stimulation of the cervical sympathetic: vasoconstrictor and vasodilator effects are mixed.

The second line of tracings shows vasodilation from the right submaxillary gland after stimulating the right cervical sympathetic gland. The two bottom tracings show the effect of stimulating the right cervical sympathetic on blood flow from the left submaxillary gland.
DISCUSSION.

True vasodilation is a condition in which the arterial blood supply to a part is increased by an increase in the size of the arterioles in the part. This phenomenon is followed by a resumption of the normal or resting rate of flow. The author has had to distinguish between this and other changes simulating true vasodilation. They are herein-after described.

An increased cardiac output such as might obtain after stimulating the cardio-accelerator fibres in the cervical sympathetic would tend to cause an increased flow of blood from the gland. This effect has been observed accompanying vasodilation by means of bilateral simultaneous blood flow records.

If the blood vessels in one part of the body are constricted as are the splanchnics during muscular exertion, the result is an increased amount of blood flowing through other parts, e. g., the skeletal musculature. Hence, if in stimulating these spinal roots we have been causing constriction to other parts of the general system, such as the upper extremity, head or neck, then it is conceivable that the increased
blood flow through the submaxillary gland might be due to constriction in other parts. However, if such were the case, the flow after stimulation would be reduced since more of the blood would go to fill up the other emptied structures. This was not observed to be the case, for after the dilation was abated, the previous normal rate of flow was observed. Further, any great vasoconstriction would result in an increased venous outflow from the gland on the opposite side, and this also was observed not to be the case.

Henderson and Loewi, as previously mentioned in the introduction, think that vasodilation in glands is due to the action of metabolites on the capillary bed. The mechanism suggested is that certain secretory products flow into the lymph, are absorbed from there by the blood capillaries and cause the latter to dilate. We believe that the vasodilation we have observed after stimulating the eighth cervical and first thoracic ventral roots is probably due to the action of vasodilator fibres since Langley has shown that secretory fibres to the submaxillary gland do not originate from these two levels. As to the vasodilation obtained after stimulating the second, third and fourth thoracic roots, we certainly
cannot claim to have shown that the effect is not the result of metabolites. Atropinization, or records of blood flow and salivary secretion taken simultaneously would have been of no value to us since the work of Barcroft and Gesell has shown that an increase over the resting metabolism may occur without visible secretion being formed.

When one stimulates a ventral root all the nerve fibres therein may be stimulated, hence any muscles innervated by that segment contract and squeeze out blood. This causes an increased amount of circulating blood, and might in its outflow from the submaxillary gland seem to be a true vasodilation. This augmented venous outflow is followed by a period of decreased flow. Thus it is distinguished from real vasodilation. This effect is prevented by administration of curare in an amount sufficient to prevent stimulation of a muscle by its nerve.

We have observed increased venous outflow to show some variations. When the sympathetic trunk is stimulated, vasodilator, vasoconstrictor, and secretory nerve fibres are affected simultaneously. When a low strength current is used, vasodilation is observed, so the vasodilators apparently have a lower threshold. This affect has been observed by Carlson.
Stronger stimulating currents usually bring into play the vasoconstrictor fibres so that the effect is alternate dilation and constriction. We have not seen vasoconstriction alone even with high strength currents save once. For a certain range of strengths of current (secondary coil between 5 and 13 centimeters distant; 2 batteries in the primary circuit), the effect of increasing the strength of the stimuli is to augment the vasodilator response. Infrequently, currents between 5 and 10 centimeters, and frequently currents with the coil between 0 and 5 centimeters result in the appearance of vasoconstrictor effects.

When the spinal roots are stimulated in a curarized preparation, the effect of increasing the strength of current is an increase in the type of response noted. Thus when the eighth cervical, first and second thoracic ventral roots are stimulated over several strengths of current, the greatest response, vasodilation, is obtained with the strongest current. Vasoconstrictor effects do not usually appear with these segments. With the third, fourth and fifth thoracic segments vasoconstriction is more frequently seen, and the constrictor response varies with the strength of current. The effects produced with nerve root stimulation have been, therefore,
either dilation or constriction, and not a mixture of the two.

Considerable variations in the resting rate of the venous outflow are seen in different animals and in the same animal at varying stages. Larger healthy cats show a greater rate of flow than do small ones. The greater the surgical trauma inflicted during preparation the lower will be the rate of flow. Exsanguination which rapidly occurs in the smaller animals results in a slowed flow which is not raised to normal after intravenous administration of saline or epinephrine.

When simultaneous records of flow from both glands are taken the resting rate from each gland is approximately the same. Where the rates have been different, changes in flow have been judged in relationship to the resting output, rather than compared to the flow on the opposite side. The cause of these unequal rates is usually intravascular clotting, a condition not much benefited by citrate washings. In most of the experiments where simultaneous records were taken an equal or nearly equal basal output from either gland was seen.

After each stimulation, sufficient time was allowed before the succeeding stimulation was administered, in order that a resumption of the regular flow rate might occur.

When the venous output is not affected by stimulation
of the sympathetic or its roots it shows a gradual lessening. This effect is due to two things: The blood tends to clot in the cannula and its connected tube, and the red blood cells settle out, leaving a semisolid debris in the underside of the cannula. This effect is illustrated by figure number 4. The flow is fast at first, is greatly augmented upon stimulation, then resumes the normal flow and gradually lessens until the tube is completely occluded with thrombi. Often citrate was washed through the system (marked by a single line in the signal) the normal rate of flow was resumed.

It is apparent from our results that the dorsal root components take no part in submaxillary vasodilation. While the Heidenhain and Sherrington phenomena are easily demonstrable, it should be borne in mind that they are obtained, to date, only in skeletal muscle, and only during certain stages of degeneration. Therefore, it is probable that this effect is not one occurring normally in the animal body. We have no evidence for direct antidromic vasodilation in the cat submaxillary gland.

Since vasodilator fibres exist, and since in submaxillary innervation they do not arise from dorsal roots, they must come from the cord via the ventral roots. This we believe to have shown in our work. It was surprising to find vaso-
dilator response after stimulating the eighth cervical ventral root. Heretofore the concept has been that this root did not contribute preganglionic fibres to the sympathetic, but received only postganglionic axons for distribution to the glands and vessels of the upper extremity. From our work it would seem that the eighth cervical gray ramus contains a preganglionic element which runs to the stellate ganglion, and out the sympathetic to the submaxillary gland. The reason for cutting the cervical sympathetic after positive effects with nerve root stimulation was to determine whether or not the nerve fibres traveled to the gland via the sympathetic. This was found to be the case as is shown in the chart.
CONCLUSION.

I. Stimulation of the eighth cervical, and first and second thoracic ventral roots results in vasodilation in the cat's submaxillary gland. Stimulation of the third and fourth ventral roots may cause either vasodilation or constriction.

II. Vasodilation obtained from stimulating the eighth cervical and first thoracic is probably a direct vasodilator effect. That obtained from the others may be due to metabolites formed during increased salivary secretion.

III. The usual effect of stimulating the cervical sympathetic in the cat is vasodilation in the gland.

IV. The vasodilator fibres arise in the ventral rather than the dorsal roots.

V. When the cervical sympathetic trunk is stimulated weaker currents tend to cause vasodilation and stronger stimuli tend to cause vasoconstriction. (This confirms previous reports e.g., Carlson and Burn). Stimulation of the ventral roots causes either vasodilation or vasoconstriction, regardless of the strength of current employed.
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