THE REACTION OF THE PIAL ARTERIES TO SOME CHOLIN-LIKE AND ADRENALIN-LIKE SUBSTANCES

BY

V. LUNN and M. FOG

From the Laboratory of Neurophysiology, Rigshopsitalet, Copenhagen

(RECEIVED 25TH FEBRUARY, 1939)

THE demonstration of the neuro-humoral transmission of nervous impulses has opened possibilities for the study of the nature and the extension of vasomotor innervation. Until recently it was open to discussion whether the cerebral vessels were innervated by the sympathetic and the parasympathetic system or not. During the last years, however, experimental and histological investigations have already indicated that a vasomotor innervation is present.

From the histological work undertaken by Busch (1938), Chorobski and Penfield (1932), Hassin (1930), Stöhr (in Penfield, 1931), and McNaughton (1938) it is clear that nerves may be traced along the pial vessels to the arterioles and capillaries. Both myelinated, presumably sensory, and unmyelinated nerves follow the large vessels and terminate eventually within a vessel wall. Only an occasional non-myelinated nerve is to be demonstrated in the precapillary arterioles and the capillaries. The nature of these latter is undecided, as is also their terminal relation to the smooth muscle. Experiments favour the existence of both a sympathetic and a parasympathetic cerebral vasomotor innervation (Cobb and Finesinger, 1932 ; Fog, 1934 and 1939 ; Forbes, Nason, Cobb, and Wortman, 1937 ; and Schmidt and Hendrix, 1938). Stimulation of the cervical sympathetic as well as application of adrenalin causes a moderate but distinct constriction of the pial arteries ; a dilatation effect may be brought about by stimulation of the seventh cranial nerve and of the ganglion geniculatum ; the response of the vessels to acetylcholin is a dilatation. Compared with the reaction of the arteries in other areas, such as the skin and splanchnic regions, the responses of the cerebral vessels to a similar stimulus are small. Further, it appears that only arteries larger than 50–100μ react to stimulation of the sympathetic, the smaller vessels remaining unchanged. This applies equally to an electrical and to a chemical stimulus. On the other hand, it has not been determined if a similar difference in reaction between large and small vessels occurs to a dilating stimulus.

The purpose of the experiments described in this paper was to study in detail the action of some adrenalin-like and cholin-like substances on pial vessels of various sizes. Previous investigations included either the direct application

J Neurol Psychiatry: first published as 10.1136/jnnp.2.3.223 on 1 July 1939. Downloaded from http://jnnp.bmj.com/ on September 29, 2023 by guest. Protected by copyright.

of solutions of adrenalin, acetylcholin, etc., on the surface of the brain or the intravenous or intra-arterial injections of similar substances. When a solution of a chemical agent is applied extravascularly its possible action can only be exerted after it has passed through the adventitial wall of the vessel. Consequently it is possible that a lack of action might be due to a delayed or insufficient penetration. On the other hand, intravenous administration results in the combined effects from a variation of the general blood pressure and from the direct chemical action. In consequence it was decided to perform direct injections into the pial vessels of solutions of the substances in question.

Method

Cats, anæsthetized with brombutylmalonylureid ("Pernocton") and under artificial ventilation, were used. The cranium was trephined over the parietal-occipital area; a flow of warm Ringer's solution (37°–38° C.) over the brain surface was kept up during the experiment. A glass cannula (size from 30 to 50μ) was introduced into the pial artery under the microscope, by means of a Buchthal micromanipulator (1936). From a special apparatus (Fig. 1) the solution was infused into the

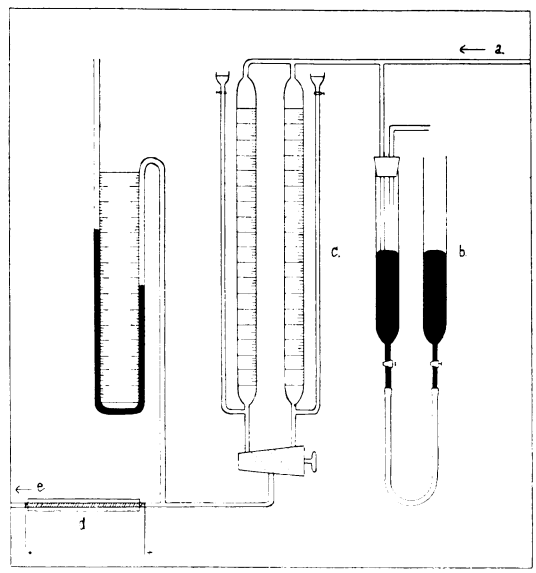

Fig. 1.—Apparatus for injection under constant pressure and temperature: *a*, leading from the oxygen tank; *b*, regulation of pressure; *c*, burettes for solutions to be injected; *d*, electrical heating apparatus; *e*, leading to the cannula.

vessel under conditions of constant pressure and temperature (37° C.). The arteries chosen for observation were branches of the cannulated vessels, situated 3–500μ from the site of the cannula. The changes in diameter of the vessel were measured by means of an ocular micrometer and indirectly registered on a kymograph (Fog, 1934). It was established that the diameter remained constant for a period of some minutes before the infusion. Any given artery was never tested with more than one of the various solutions. The systemic blood pressure and the time were recorded on the drum throughout the experiment.

J Neurol Psychiatry: first published as 10.1136/jnnp.2.3.223 on 1 July 1939. Downloaded from http://jnnp.bmj.com/ on September 29, 2023 by guest. Protected by copyright.

Results

As adrenalin-like agents, solutions of adrenalin (" Medicinalco "), para-oxyphenylmethylaminoæthanol (" Sympatol," Merck), β-phenylisopropylamin-sulphate (benzedrine-mecodrin), isopropyl-mecodrinsulphate, and β-phenyl-æthylaminhydrochloride (" Medicinalco ") were used. The vasomotor effect of " Sympatol " is supposedly less pronounced but more protracted than that of adrenalin.

As recent work pointed to β-phenylisopropylamin (benzedrine) being a cerebral stimulant, it was decided to study its possible vasomotor effect on cerebral vessels. According to Barger and Dale (1910) benzedrine is closely related to ephedrine, the effect of which in blood-vessels is less pronounced than that of adrenalin and " Sympatol."

In search for substances which might retain the central effect of benzedrine without its peripheral action, Dr. Erik Jacobsen has produced several preparations with a similar chemical constitution. Two of these, isopropylbenzedrine and β-phenylæthylaminhydrochlorid, have been used in our experiments.

The cholin-like agents investigated were acetylcholin, carbaminoylcholin-chloride (" Doryl," Merck), and acetylmethylcholin (" Mecolyl," Merck). The two last cholin esters were used in order to obtain a protracted effect, as acetylcholin is known to be inactivated rapidly by cholinasterase. " Mecolyl " is ordinarily considered to have a more specific action on the blood vessels than " Doryl."

(1) *Adrenalin.*—Concentration 1 : 100,000. 11 experiments.

The main result was that arteries of less than 40–50μ in diameter showed no constriction (Fig. 2). A slight dilatation was commonly observed, the degree

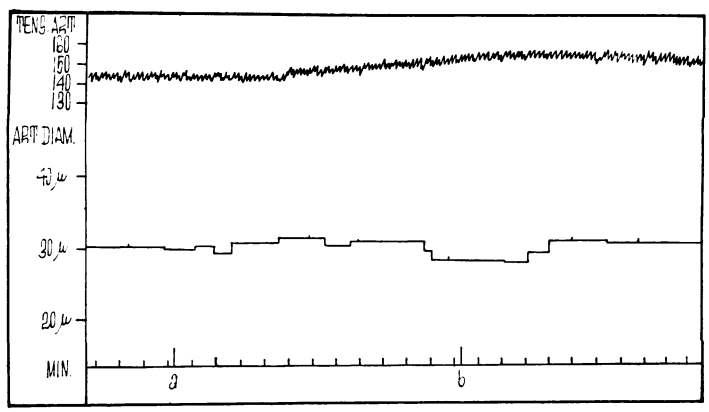

Fig. 2.—*a–b*, injection of 1·8 c.c. adrenalin 1 : 100,000. Artery of 30μ. No reaction.

of which was similar to that occurring in the control experiments. Arteries of more than 50μ invariably showed a considerable constriction, averaging 13 per cent. of diameter (Fig. 3), which continued for about 3 minutes after the injection stopped.

(2) *Sympatol.*—6 experiments.

As preliminary experiments revealed that the use of solutions of a con-

J Neurol Psychiatry: first published as 10.1136/jnnp.2.3.223 on 1 July 1939. Downloaded from http://jnnp.bmj.com/ on September 29, 2023 by guest. Protected by copyright.

centration of 1 : 100,000 usually caused a complete blanching of the brain surface, concentrations of 1 : 500,000 were used. With this concentration the drug did not produce any changes in diameter of arteries smaller than

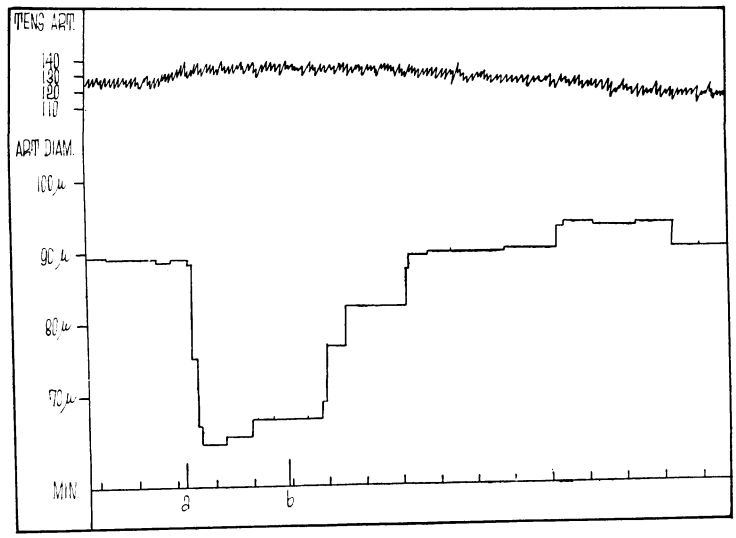

Fig. 3.—*a–b*, injection of 0·6 c.c. adrenalin 1 : 100,000. Artery of 88μ. Constriction.

50μ. Arteries of 59–94μ constricted averaging 9 per cent. of diameter (Fig. 4) and the lumen did not regain its original size until about 5 minutes after the injection had been discontinued.

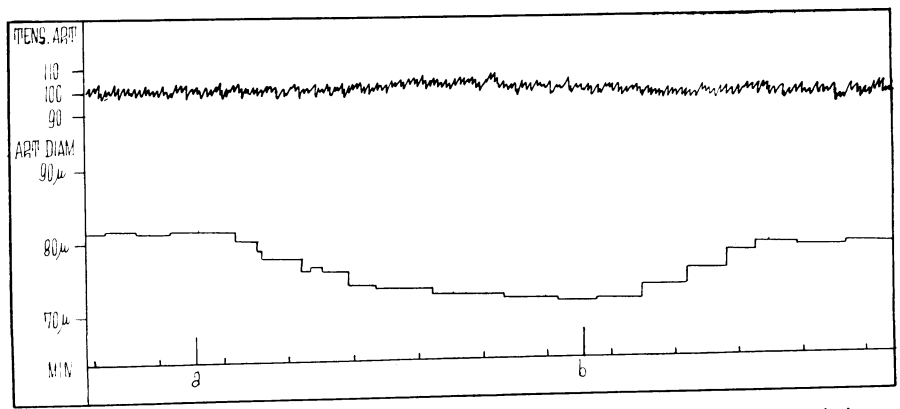

Fig. 4.—*a–b*, injection of 1·2 c.c. "Sympatol" 1 : 500,000. Artery of 82μ. Constriction.

(3) *Mecodrin.*—6 experiments.

The substance was used in concentrations of 1 : 200,000 in order to cause distinct reactions. Small arteries of less than 60μ were unaffected, but larger vessels constricted, averaging 9 per cent. of diameter (Fig. 5). The constriction was of a similar duration to that obtained by "Sympatol."

J Neurol Psychiatry: first published as 10.1136/jnnp.2.3.223 on 1 July 1939. Downloaded from http://jnnp.bmj.com/ on September 29, 2023 by guest. Protected by copyright.

(4) *Isopropylmecodrin.*—Concentration 1 : 20,000. 4 experiments.

One artery of 47μ dilated 5 per cent. of its original diameter, while three vessels of more than 50μ all constricted to a degree similar to that found in the " Mecodrin " experiments.

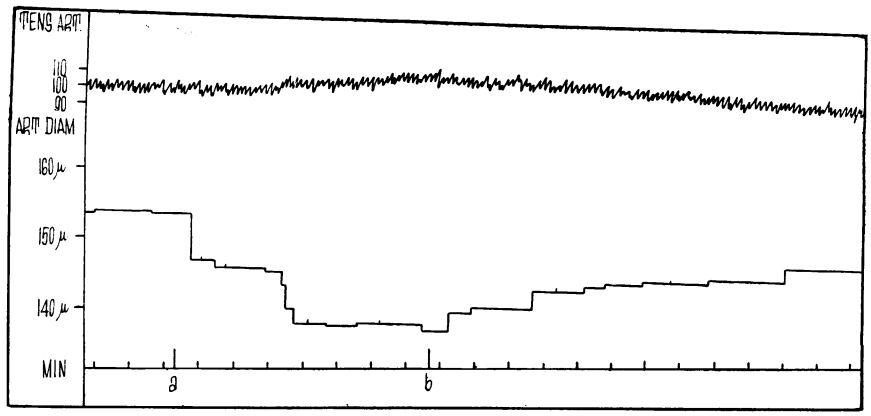

Fig. 5.—*a–b*, injection of 1·05 c.c. of " Mecodrin " 1 : 20,000. Artery of 154μ. Constriction.

(5) *β-phenylæthylaminohydrochloride.*—Concentration 1 : 20,000.

In five experiments no reaction at all was observed in arteries varying from 51μ to 242μ in diameter.

(6) *Acetylcholin.*—Concentration 1 : 500,000. 6 experiments.

One artery of 38μ in diameter did not change ; all larger vessels dilated

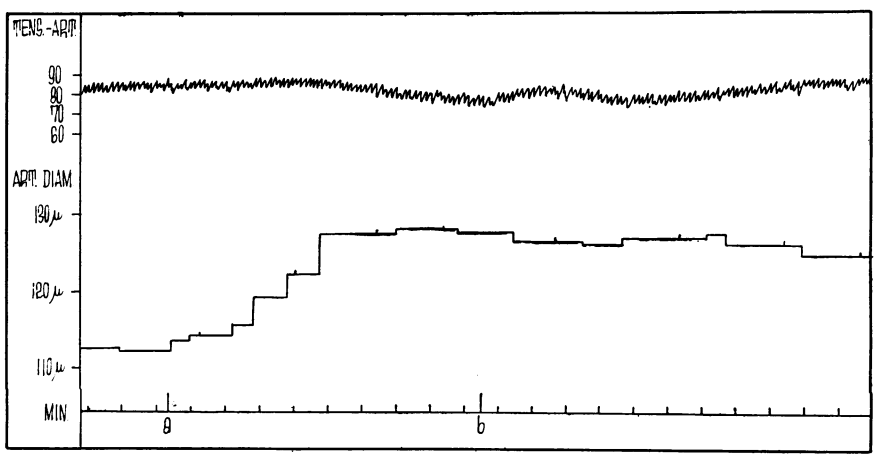

Fig. 6.—*a–b*, injection of 1·8 c.c. of acetylcholin 1 : 500,000. Artery of 113μ. Dilatation.

(averaging 9 per cent. of diameter (Fig. 6)). The dilatation decreased slowly in the course of about 15 minutes.

(7) *Doryl.*—Concentration 1 : 500,000. 9 experiments.

The dilating effect was present in vessels down to lumen of 30μ ; only three vessels (22μ, 26μ, and 27μ) remained unchanged. The changes in diameter

J Neurol Psychiatry: first published as 10.1136/jnnp.2.3.223 on 1 July 1939. Downloaded from http://jnnp.bmj.com/ on September 29, 2023 by guest. Protected by copyright.

considerably exceeded those obtained with acetylcholin and averaged 18 per cent. of diameter (Fig. 7). The vessels remained dilated for about 15 minutes.

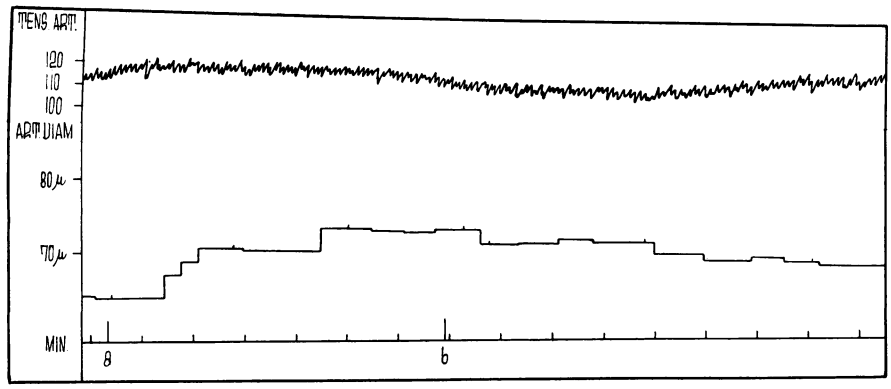

Fig. 7.—*a–b*, injection of 1·3 c.c. of carbaminoylcholinchloride (Doryl) 1 : 500,000. Artery of 65μ. Dilatation.

(8) *Mecolyl.*—Concentration 1 : 500,000. 6 experiments.

In two experiments arteries less than 30μ showed no reaction. Vessels of more than 50μ dilated, but the changes in diameter did not amount to those produced by " Doryl."

(9) *Control experiments.*

In 14 cases injection of Ringer's solution were made under the same conditions of pressure and temperature as in the previous experiments. It was constantly found that the small vessels dilated moderately. Contrarily, the larger arteries remained unaffected. In consequence the positive reactions of the series 1 to 8 must be considered as elicited through the chemical properties of the various agents.

During the experiments it was common to find a variation of the systemic pressure in the direction which was typical for the mode of action of the drug in question. The changes, however, were slight and occurred later than the responses of the pial vessels. It follows that changes of blood pressure cannot be responsible for the local vasomotor effect.

It is well known that mechanical iritants generally will cause a local reaction of the pial arteries (Florey, 1925). In some experiments we found that a vessel constricted vigorously at the moment of puncture. In such instances it was impossible to introduce the cannula. This event, however, seemed to be dependent on the relation between the size of the artery and that of the cannula. When very pointed cannulas were employed (40–50μ) and the diameter of the vessels punctured exceeded 150μ, no local change was observed.

Comments

This study demonstrates that both adrenalin-like and cholin-like substances will produce changes in the diameter of vessels in a similar direction as occurs in vessels elsewhere. It is noticeable that the common effect of the three cholin-like agents tested was distinctly more prolonged than that observed in

J Neurol Psychiatry: first published as 10.1136/jnnp.2.3.223 on 1 July 1939. Downloaded from http://jnnp.bmj.com/ on September 29, 2023 by guest. Protected by copyright.

the experiments with adrenalin-like substances. Further, it is evident that the vasomotor reactions are only to be elicited in the larger arteries. However, the action of the cholin-like substances may be traced more peripherally than that of the adrenalin-like substances. The dilating effect of the cholin-like substances occurs in vessels of about 30μ in diameter, whereas the constricting action of the other substances occurs in vessels of 50μ. " Sympatol " used in concentration of 1 : 100,000 causes a marked blanching of the brain surface. This is probably due to an obstruction of the larger arteries which consequently deprives the smaller vessels of any blood supply.

Whether the chemica
that of nervous stimulat
dilating effect of stimula
been investigated in arte
ever, previous experimen
as small a size as observ
sympathetic chain. Thes
stimulation and electrica
identical effects.

It has been clearly de
of chemical agents exert
adrenalin-like group, "
solutions of adrenalin h
than those of " Sympat
above, it is commonly b
action than " Sympatol
dently does not apply
" Sympatol," " Mecod
agents.

Of the cholin-like
The efficiency of " Do
The two last-named su
dilating reaction lasts
following the applicati

It may be conclude
to evoke pronounced v

In 53 experiments
like substances were i
on eight cats as contr
of temperature and p

All adrenalin-like
50μ in diameter ; ve

The cholin-like s
the smaller arterioles

... be considered identical to

ERRATA

Page 163, for *lines* 13 to 25, read the following :—

Clark, W. E. Le G., Beattie, J., Riddoch, G., and Dott, N. M. (1938). " The Hypothalamus." Oliver & Boyd, London.
Collin, R. (1924*a*). *C. R. Soc. Biol.*, **91**, 1334.
—— (1924*b*). *Rev. Franç. Endocrin.*, **2**, 2.
—— (1924*c*). *Ibid.*, **2**, 381.
—— (1925*a*). *Ibid.*, **3**, 16.
—— (1925*b*). *Ibid.*, **3**, 213, 277.
—— (1926*a*). *C. R. Soc. Biol.*, **95**, 107.
—— (1926*b*). *Ibid.*, **95**, 686.
—— (1927). *Ibid.*, **97**, 381.
—— (1928). *Arch. gén. exp.*, **28**, 102.
—— (1933). *Ann. Méd.*, **33**, 239.
Celestino da Costa, A. (1925). *C. R. Soc. Biol.*, **92**, 1246.

J Neurol Psychiatry: first published as 10.1136/jnnp.2.3.223 on 1 July 1939. Downloaded from http://jnnp.bmj.com/ on September 29, 2023 by guest. Protected by copyright.

In the control experiments only a slight dilatation was observed.

The most pronounced constricting effect was observed with the use of para-oxyphenylmethylaminoæthanol (" Sympatol "), which in a concentration of 1 : 100,000 caused a complete obstruction of the large arteries. Among the cholin-like substances carbaminoylcholinchloride (" Doryl ") elicited the most pronounced dilating effect.

" Mecodrin " and its derivatives were kindly given by the " Medicinalco " Company.

REFERENCES

Buchthal, F. (1936), *J. sci. Instrum.*, **13,** 20.
Barger, G., and Dale, H. H. (1910), *J. Physiol.*, **41,** 19.
Busch, E. (1938). *Acta Psychiat. Neurol.*, **13,** 131.
Chorobski, J., and Penfield, W. (1932). *Arch. Neurol. Psychiat.*, **28,** 1,257.
Cobb, S., and Finesinger, J. E. (1932). *Ibid.*, **28,** 1,243.
Florey, H. (1925). *Brain*, **48,** 43.
Fog, M. (1934). *Om piaarteriernes vasomotoriske reaktioner*. Danish Dissertation.
—— (1939). *Arch. Neurol. Psychiat.*, **41,** 109.
Forbes, H. S., Nason, G. I., Cobb, S., and Wortman, R. C. (1937). *Ibid.*, **37,** 776.
Hassin, G. B. (1930). *The Vegetative Nervous System*, p. 437. Baltimore.
McNaughton, F. L. (1938). *The Circulation of the Brain and Spinal Cord*, p. 178. Baltimore.
Schmidt, C. F., and Hendrix, J. P. (1938). *Ibid.*, p. 229.
Stöhr, P., *in* Penfield, W. (1931). *Cytology and Cellular Pathology of the Nervous System*, p. 381. New York.

J Neurol Psychiatry: first published as 10.1136/jnnp.2.3.223 on 1 July 1939. Downloaded from http://jnnp.bmj.com/ on September 29, 2023 by guest. Protected by copyright.