THE USE OF CHOLINERGIC BLOCKING AGENTS

IN THE TREATMENT OF CRANIO-CEREBRAL INJURIES

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ACETYLCHOLINE is the mediator of preganglionic nerve impulses in both the sympathetic and parasympathetic nervous systems.[6,9] In this respect its action is similar to the effect of nicotine. Hence, the stimulating action of acetylcholine on ganglia has been termed "nicotinic."

Acetylcholine is also liberated at the end organ upon stimulation of the parasympathetic nervous system. The similarity between its action in that location and the effect of muscarine has given rise to the term, "muscarinic." This is in contrast to the release of an epinephrine-like substance at the end organ upon stimulation of the sympathetic nervous system (Fig. 1).

The administration of acetylcholine produces responses which include hypotension, diaphoresis and increased gastro-intestinal motility. They are known as cholinergic responses. Atropine is a cholinergic blocking agent which antagonizes the muscarinic action of acetylcholine.

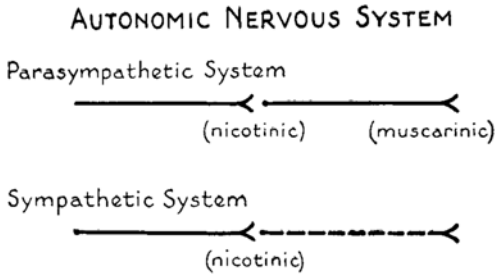

FIG. 1. Acetylcholine is released at the ganglia of both the parasympathetic and sympathetic nervous systems and at the end organ of the parasympathetic system. Its action at the ganglia is called nicotinic, while its postganglionic action is called muscarinic.

Cranio-cerebral injuries frequently produce signs that mimic cholinergic stimulation: hypotension, diaphoresis and occasionally gastro-intestinal motility. Because these phenomena are so similar to the muscarinic action of acetylcholine, it has appeared logical to treat them with anti-muscarinic agents. Ward[15] has reported encouraging results in the treatment of cranio-cerebral injuries by the daily use of large amounts of atropine sulfate (0.1 mg. per kg.).

Acetylcholine normally occurs intracellularly in the brains of mammals. Dikshit[4] demonstrated that extracts prepared from the brains of cats and rabbits have the same pharmacologic actions as acetylcholine. When administered intravenously, a decrease in blood pressure resulted and upon introduction into the ventricles of the brain, respirations were inhibited. The perfused frog heart was also depressed. He found that extracts made from the basal ganglia contained 0.4 gamma per cent of acetylcholine and the

cerebrum and cerebellum contained lesser amounts. Chute, Feldberg and Smyth[3] perfused the cat's head and found that 2 cc. solution of the perfused eserinized blood had the same acetylcholine content as 2 cc. solution of acetylcholine diluted 1–400 million. When the brain was removed and the perfusion repeated no acetylcholine was present.

Acetylcholine is not a constituent of normal cerebrospinal fluid but Tower and McEachern[14] recovered varying quantities of acetylcholine in the cerebrospinal fluid of epileptics and patients who had sustained severe cranio-cerebral injuries. They noted that recovery was associated with a decrease in acetylcholine in the cerebrospinal fluid. Employing contraction of the frog's rectus abdominis muscle for biological assay, Bornstein[1] measured 2.7 to 10.0 gamma of acetylcholine in the cerebrospinal fluid of animals that had received concussive trauma to the head. When the same quantity of acetylcholine was introduced into the cisterna magna of animals, they became quiet and listless but no alterations in blood pressure were noted. Feldberg and Schriever[7] have taken exception to the view that acetylcholine could be recovered from the cerebrospinal fluid unless the animal had been eserinized to prevent the destruction of acetylcholine by cholinesterase. Their experiments indicate that eserine, and eserine in combination with adrenalin, administered intravenously, will produce acetylcholine in the cerebrospinal fluid.

The instillation of acetylcholine into the nervous system has resulted in varying reports. Kremer[10] stated that in man the lumbar intrathecal injection of as much as 500 mg. of acetylcholine gave no response. Suh and his associates[13] injected acetylcholine into the cisterna magna and applied it directly to the floor of the 4th ventricle and reported an increase in blood pressure and augmentation of respiration. Dikshit[5] reported a slight inhibition of respiration and occasional cardiac irregularity when small doses of acetylcholine (0.5 gamma) were introduced intraventricularly in cats. Silver and Morton[12] observed sharp falls in the blood pressure when 2.0 to 4.0 gamma were introduced into the hypothalamic region of cats. Similar injections into the lateral ventricle occasionally produced the same blood-pressure effect together with drowsiness and nausea. Henderson and Wilson[8] observed sweating, nausea, vomiting, peristaltic rushes and altered consciousness in humans who had received 2.5 to 7.5 mg. of acetylcholine intraventricularly.

METHOD

In this study an attempt was made to determine if acetylcholine can be identified in the cerebrospinal fluid following a cranio-cerebral injury and if parasympathetic responses to injury are successfully combated with antimuscarinic agents.

Twenty-three dogs, weighing from 10 to 22 kg., were used as the experimental animals. Anesthesia was obtained by intravenous Nembutal.

Two methods of biological assay[11] were employed. The contraction of the

eserinized leech muscle was used to determine the presence of acetylcholine in the cerebrospinal fluid removed by cisternal aspiration. In two instances, quantitative assays were done to measure the concentration of acetylcholine. The gastro-enterectomized cat's blood pressure was also employed to determine the presence of acetylcholine in cerebrospinal fluid aspirated from the cisterna magna of dogs. Continuous tracings from the carotid artery were recorded. In one instance a quantitative assay was made.

Trauma was inflicted by striking the vertex of the skull with a mallet or by cortical incisions made through a small craniectomy and dural incision. Atropine sulfate and banthine in varying dosages were employed to treat the traumatized animals. Atropine sulfate blocks the muscarinic action of acetylcholine (Fig. 1). Banthine is an autonomic blocking agent that inhibits the neural stimuli at the sites of the parasympathetic and sympathetic ganglia as well as the muscarinic effects.[2]

EXPERIMENTAL DATA

Biological assay employing the eserinized leech muscle to determine presence of acetylcholine was done upon the cerebrospinal fluid obtained by cisternal puncture of 4 of the animals. A cisternal puncture was done prior to subjecting the brain to trauma. Assay of this fluid did not yield a contraction of the leech muscle. Cranio-cerebral injuries were inflicted upon the animals and the fluid was again assayed. In 2 animals, samples taken at 20 and 40 minutes following trauma yielded no contraction of the eserinized leech muscle. The contractions occurred, however, in fluid collected 1 hour after trauma. In the cerebrospinal fluid obtained from one of the animals, the contraction was equal to that resulting from 5.2 gamma of acetylcholine per 100 cc. In another the response was equal to that obtained in a solution containing 6 gamma acetylcholine per 100 cc.

Biological assay using the fall in blood pressure of a cat was used in 7 of the dogs. As with the leech muscle, the cerebrospinal fluid aspirated from the cisterna magna prior to intracranial trauma failed to give an acetylcholine response. However, the cerebrospinal fluid procured 1 hour following a cerebral insult was positive in 5 instances (Fig. 2). In 1 of the 2 who failed to show an acetylcholine response, the cerebrospinal fluid was grossly bloody. Cholinesterase which is normally present in blood may have inactivated any acetylcholine that appeared in the cerebrospinal fluid. The response obtained from one of the samples was equivalent to that resulting from a solution of 40 gamma acetylcholine per 100 cc. After the cat was atropinized, the fluid which had previously been capable of causing a drop in the cat's blood pressure was unable to do so (Fig. 3).

The instillation of 5 to 50 gamma of acetylcholine had no effect upon the blood pressure of the untraumatized, anesthetized dog, whether given into the cisterna magna, the lateral ventricle or brain substance. Four of the dogs had a marked drop in blood pressure when 10 mg. of acetylcholine were injected into the cisterna magna. Ordinarily, this was greater in an animal

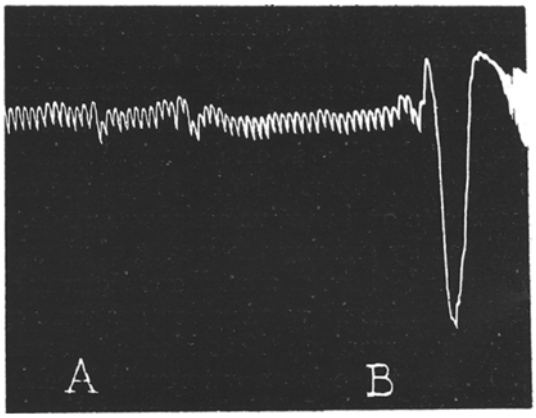

FIG. 2. Assay of cerebrospinal fluid of dog for acetylcholine using the blood pressure of gastroenterectomized cat. (A) Normal cerebrospinal fluid, 2 cc., given intravenously produced no response in blood pressure. (B) The same quantity of cerebrospinal fluid collected 1 hour after cranio-cerebral trauma produced a marked fall in blood pressure.

who had also received cerebral trauma. The administration of 2 mg. of atropine sulfate hastened the return to a normal blood pressure and blocked the muscarinic action of subsequent administration of intrathecal acetylcholine. On several occasions, the same or larger quantities of acetylcholine injected intrathecally into an atropinized animal produced a rise in blood pressure (Fig. 4).

In 1 dog, the administration of 10 mg. of acetylcholine into a lateral ventricle produced the typical parasympathetic blood pressure decline. A prompt recovery occurred when atropine sulfate (0.25 mg.) was given intravenously.

To determine the effect of injecting a substance not containing acetylcholine into the brain, 1 cc. of normal saline was introduced into a cerebral hemisphere. This gave only a slight blood pressure response (Fig. 5A) and was in no way comparable to the marked drop in blood pressure that occurred when 1 cc. of a 1–100 solution of acetylcholine (10 mg.) was injected into a cerebral hemisphere (Fig. 5B). The recovery from intracerebral acetylcholine was prompt when atropine sulfate (1.2 mg.) was given intravenously

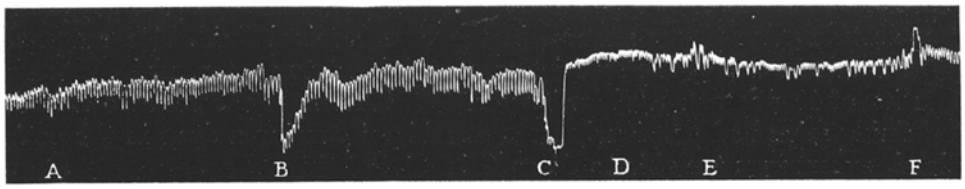

FIG. 3. Assay of cerebrospinal fluid of dog for acetylcholine using the blood pressure of gastroenterectomized cat. All substances were given intravenously. (A) Normal cerebrospinal fluid, 1 cc., had no effect on the blood pressure. (B) 1 cc. cerebrospinal fluid collected 1 hour after cranio-cerebral trauma caused drop in blood pressure. (C) 1 cc. solution of 1:2,500,000 acetylcholine caused a drop in blood pressure similar to B. (D) Atropine, 1 mg. (E) After atropinization, administration of 1 cc. of cerebrospinal fluid obtained 1 hour after trauma gave no acetylcholine response. (F) Acetylcholine, 2 cc. of 1:10,000 solution, produced a slight rise in blood pressure.

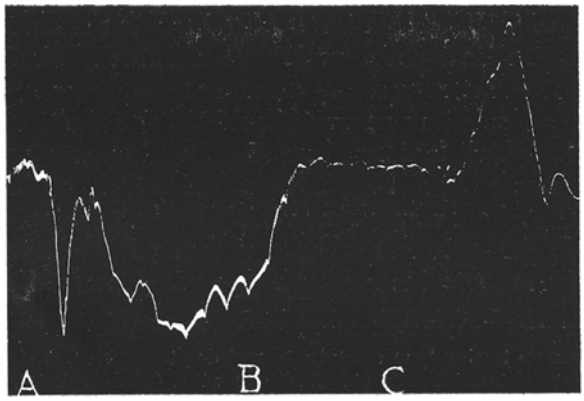

FIG. 4. Blood pressure tracing from carotid artery of dog to show effect of intrathecal administration of acetylcholine. (A) Acetylcholine, 10 mg., introduced into cisterna magna. (B) Atropine, 2 mg. administered intravenously. (C) Acetylcholine, 10 mg., introduced into cisterna magna.

(Fig. 5D). Thereafter, when the same quantity of acetylcholine was injected into the cerebrum, the response was similar to that seen when 1 cc. of normal saline was introduced (Fig. 5E).

To study the effect of a cholinergic blocking agent which also acts at the ganglia of the autonomic nervous system, banthine was used alone and in combination with atropine. After obtaining the drop in blood pressure by intracisternal administration of acetylcholine, 50 mg. of banthine were injected intravenously. In 2 animals no beneficial effects were noted. However, in 1 animal banthine was given in combination with atropine (atropine 0.25 mg. and banthine 10 mg.) and the combined agents brought a prompt recovery in blood pressure and prevented the muscarinic action of acetylcholine when 20 mg. were given intracisternally. Upon premedication with atropine (0.75 mg.) and banthine (30 mg.), the intrathecal injection of acetylcholine (50 mg.) produced the nicotinic response, i.e., a rise in blood pressure.

In an attempt to imitate the muscarinic effects of acetylcholine without

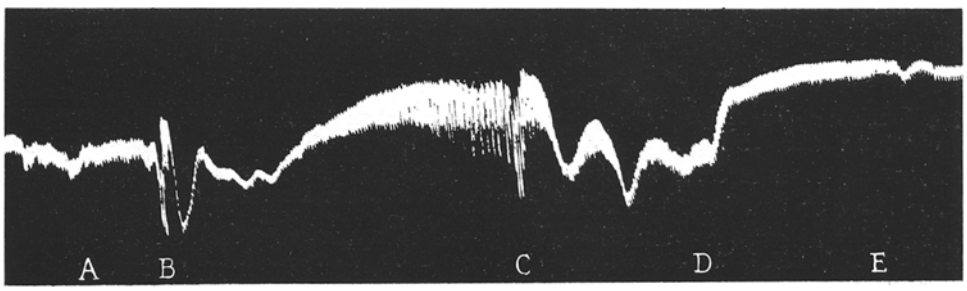

FIG. 5. Blood pressure tracing from carotid artery of dog to show effect of intracerebral administration of acetylcholine. (A) Normal saline, 1 cc., injected into cerebrum had very slight effect upon blood pressure. (B) Acetylcholine, 10 mg. (1 cc. of 1:100 concentration), given intracerebrally produced marked blood pressure drop. (C) Acetylcholine, 20 mg. (2 cc. of 1:100 concentration), given intracerebrally produced greater blood pressure drop. (D) Atropine, 1.2 mg., given intravenously brought prompt rise in blood pressure. (E) Acetylcholine, 10 mg. (1 cc. of 1:100 concentration), given intracerebrally after atropinization produced very slight blood pressure drop.

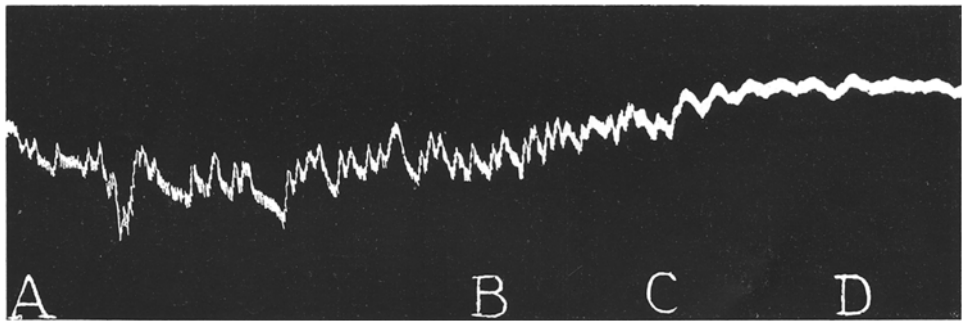

FIG. 6. Blood pressure tracing from carotid artery of dog to show effect of cerebral trauma and response to systemic atropine medication. (A) Cerebral trauma. (B) Atropine, 0.12 mg., administered intravenously. (C) Atropine, 0.12 mg., administered intravenously. (D) Atropine, 0.12 mg., administered intravenously.

introducing acetylcholine, 3 additional animals received concussive trauma or cerebral incisions. In the presence of extensive trauma, cardiac irregularities and decreases in blood pressure appeared. These disappeared promptly upon the administration of relatively small doses of atropine (0.36–0.5 mg.) as shown in Fig. 6. If, however, a considerable subdural hematoma appeared, the drop in blood pressure might be replaced by a hypertensive episode, probably the response to an increased intracranial pressure. The cardiac irregularities resulting from extensive cerebral trauma were lessened by section of the vagus nerves in the neck (Fig. 7B, C). In the same animal 10 mg. of acetylcholine given intracisternally caused no muscarinic effect. However, upon increasing the dosage five-fold, the muscarinic response again appeared and was subsequently blocked by atropine.

DISCUSSION

Many cranio-cerebral injuries produce the symptoms of shock for only a short time. Recovery may promptly result upon the institution of ade-

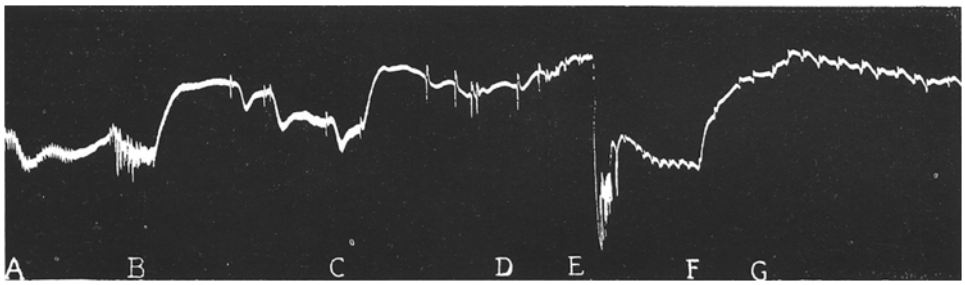

FIG. 7. Blood pressure tracing from carotid artery of dog to show effect of vagotomy, intrathecal acetylcholine and response to atropine. (A) Cerebral trauma produced low blood pressure. (B) Section of right vagus nerve in neck produced temporary rise in blood pressure. (C) Section of left vagus nerve in neck produced more prolonged rise in blood pressure. (D) Acetylcholine, 10 gm., introduced into cisterna magna caused no drop in blood pressure. (E) Acetylcholine, 50 mg., introduced into cisterna magna caused drop in blood pressure. (F) Atropine, 0.6 mg., administered intravenously produced a prompt recovery. (G) Acetylcholine, 50 mg., introduced into cisterna magna did not alter blood pressure after atropinization.

quate nursing care and supportive measures. With the development of increased intracranial pressure as it occurs, for example, if there is an intracranial hematoma, the low blood pressure and rapid pulse are replaced by a gradual rise in systolic blood pressure, increase in pulse pressure and a decrease in cardiac rate. In those patients, treatment is directed toward the removal of the hematoma.

However, many patients who have sustained cerebral insults continue in a state of shock and management often consists of blood transfusions and drugs which stimulate the sympathetic nervous system. Such procedures may have only a transient effect. It appears logical to employ anti-muscarinic agents to combat the signs that simulate a profound parasympathetic discharge.

SUMMARY

Acetylcholine apparently is liberated from traumatized central nervous tissue and some of it diffuses into the cerebrospinal fluid where minute quantities can be measured. When relatively large quantities are introduced into the brain, ventricles or cerebrospinal fluid system, characteristic muscarinic responses of blood pressure are observed. The same responses are not noted when similar amounts of normal saline are injected. Cerebral trauma also produces cardiac irregularities and decreased blood pressure. Cholinergic blocking agents, particularly atropine sulfate, have a beneficial effect upon the parasympathetic responses that accompany cerebral trauma because they block the muscarinic responses of acetylcholine.

REFERENCES

1. Bornstein, M. B. Presence and action of acetylcholine in experimental brain trauma. *J. Neurophysiol.*, 1946, *9:* 349–366.
2. Bulletin of the Pharmacy and Therapeutics Committee. New approved drugs. *Univ. Mich. Med. Bull.*, 1951, *17:* 88–89.
3. Chute, A. L., Feldberg, W., and Smyth, D. H. Liberation of acetylcholine from the perfused cat's brain. *Quart. J. exp. Physiol.*, 1940, *30:* 65–72.
4. Dikshit, B. B. Action of acetylcholine on the brain and its occurrence therein. *J. Physiol.*, 1934, *80:* 409–421.
5. Dikshit, B. B. Action of acetylcholine on the "sleep centre." *J. Physiol.*, 1935, *83:* 42P.
6. Feldberg, W., and Gaddum, J. H. The chemical transmitter at synapses in a sympathetic ganglion. *J. Physiol.*, 1934, *81:* 305–319.
7. Feldberg, W., and Schriever, H. The acetylcholine content of the cerebro-spinal fluid of dogs. *J. Physiol.*, 1936, *86:* 277–284.
8. Henderson, W. R., and Wilson, W. C. Intraventricular injection of acetylcholine and eserine in man. *Quart. J. exp. Physiol.*, 1936, *26:* 83–95.
9. Kibjakow, A. W. Über humorale Übertragung der Erregung von einem Neuron auf das andere. *Pflüg. Arch. ges. Physiol.*, 1933, *232:* 432–443.
10. Kremer, M. Action of intrathecally injected prostigmine, acetylcholine, and eserine on the central nervous system in man. *Quart. J. exp. Physiol.*, 1942, *31:* 337–357.
11. MacIntosh, F. C., and Perry, W. L. M. Biological estimation of acetylcholine. In: *Methods in medical research.* R. W. Gerard, Ed. Chicago: Year Book Publishers, Inc., 1950, *3:* 78–92.
12. Silver, G. A., and Morton, H. G. The central action of acetylcholine. *J. Pharmacol.*, 1936, *56:* 446–450.
13. Suh, T. H., Wang, C. H., and Lim, R. K. S. The effect of intracisternal applications of acetylcholine and the localization of the pressor centre and tract. *Chin. J. Physiol.*, 1936, *10:* 61–78.
14. Tower, D. B., and McEachern, D. Acetylcholine and neuronal activity in craniocerebral trauma. *J. Clin. Invest.*, 1948, *27:* 558–559.
15. Ward, A., Jr. Atropine in the treatment of closed head injury. *J. Neurosurg.*, 1950, *7:* 398–402.