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Drug-Induced Contractile Responses in the Isolated Posterior Communicating Cerebral Artery of the Cat *

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The isolated posterior communicating cerebral artery of the cat has been shown to have the ability to produce a contractile response to the following drugs; norepinephrine (NE), tyramine (Ty), 5-hydroxytryptamine (5-HT), histamine (H), acetylcholine (Ach) and potassium (K^+). The changes in the contractile response were dose-dependent. The order of potencies of these vasoactive agents with respect to ED_{50} was: 5-HT > NE > Ach = H = Ty > K^+. With regard to their ability to induce maximal contractile responses the order was: H = Ach > 5-HT = Ty > NE = K^+. These results show that cerebral arteries are more sensitive to 5-HT than to NE, as opposed to extracranial arteries in which NE is generally the most potent vasoconstrictor agent.

The presence of receptors to norepinephrine (5, 9, 12, 14), acetylcholine (1, 4, 12), 5-hydroxytryptamine (10, 12, 14) and histamine (6, 8, 14), among other agonists in the cerebral blood vessels, has been demonstrated *in vivo* as well as *in vitro*. Nevertheless, the vascular responses induced by these agents are still controversial, e.g., intravascular administration of acetylcholine (1, 4) increased the cerebral blood flow, whereas it elicited a contractile effect when applied to the isolated middle cerebral artery of the cat (12), both effects being blocked by atropine. On the other hand, few reports exist in which the various agonists were compared in the same experimental design. The aim of the present study was to compare the vasoconstrictor effects of several drugs and potassium in the isolated posterior communicating cerebral artery of the cat.

Materials and Methods

Cat brains were carefully removed and posterior communicating cerebral arteries

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dissected into cylindrical segments 4 mm long. The cylinder was set up for isometric recording in an organ bath according to the method described by NIELSEN and OWMAN (12). Briefly, the method consists in passing two fine stainless steel pins through the lumen of the vascular segment. One pin is fixed to the organ bath wall while the other is connected to a strain gauge for isometric recording. The latter pin is parallel to the former and movable, allowing the application of resting tension at right angles to the long axis of the vascular cylinder. The recording system included a Universal Transducing Cell UC3, a Statham Micro-Scale Accessory UL5 and Beckman Type RS recorder. A resting tension of 0.5 g was applied to the tissue and readjusted every 15 min during a 90-120 min equilibration period, before accumulative dose-response curves for the different agonists were made.

The organ bath which contained 3 ml of Krebs-Henseleit solution a 37° C was continuously bubbled with a 95 % oxygen-5 % carbon dioxide mixture which gave a pH of 7.3 to 7.4. The composition of the Krebs-Henseleit solution was (mM): NaCl, 115; KCl, 4.6; $CaCl_2$, 2.5; KH_2PO_4, 1.2; $MgSO_4 . 7H_2O$, 1.2; $NaHCO_3$, 25; glucose, 11.1. Ethylenediamine tetracetic acid (EDTA, 3×10^{-5} M), was added to prevent oxidation of unstable substances, Drugs were dissolved in physiologic saline solution containing ascorbic acid 0.01 % (w/v).

The following drugs, purchased from Sigma, were used: 5-hydroxytryptamine creatinine sulfate, l-norepinephrine bitartrate, histamine hydrochloride, acetylcholine hydrochloride and tyramine hydrochloride. Drug concentrations are expressed in final molar concentration in the bath.

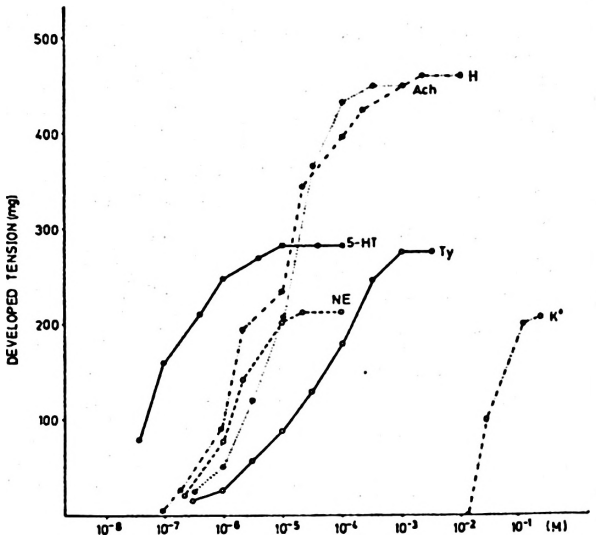

Fig. 1. *Dose-response curves showing the contraction of the isolated posterior communicating cerebral artery of the cat to the following agonists: 5-Hydroxytryptamine (5-HT), Acetylcholine (Ach), Tyramine (Ty), Norepinephrine (NE), Histamine (H) and potassium (K^+).*
The drugs were applied in accumulative manner. The number of arterial segments used in each dose-response curve is listed in table I.

Table I. *ED_{50} and maximal contractile responses of the isolated posterior communicating cerebral artery of the cat for the following agents: 5-Hydroxytryptamine (5-HT), Acetylcholine (Ach), Tyramine (Ty), Norepinephrine (NE) Histamine (H) and Potassium (K^+).*

Agonist	ED_{50} (M)	Maximum response mg ± S.E.M.	N
5-HT	$(1.8 \pm 0.6) \times 10^{-7}$	283±57	6
NE	$(1.9 \pm 0.2) \times 10^{-6}$	214±48	7
Ach	$(2.3 \pm 0.7) \times 10^{-5}$	435±71	4
H	$(4.3 \pm 0.4) \times 10^{-5}$	460±111	7
Ty	$(5.5 \pm 1.0) \times 10^{-5}$	277±27	8
K^+	$(7.9 \pm 2.1) \times 10^{-2}$	208±42	8

N: Number of arterial segments used for each dose-response curve.

Results and Discussion

Under the *in vitro* conditions used, the posterior communicating cerebral artery of the cat showed dose dependent contractile responses to all the drugs tested in the present study. These responses were obtained with histamine (H), ace-

tylcholine (Ach), 5-hydroxytryptamine (5-HT), tyramine (Ty), norepinephrine (NE) and potassium (K^+). The dose-response curves for these agents are illustrated in figure 1 and the ED_{50} values ± S.E.M. for these drugs, as well as the maximal responses induced by them, are given in table I. From these results it can be observed that the relative order of potencies with respect to ED_{50} was: 5-HT > NE > Ach = H = Ty > K^+ and with regard to their ability to induce maximal contractile responses, the order was: H = Ach > 5-HT = Ty > NE = K^+.

In agreement with previous data from other isolated cerebral arteries of cat (12), goat (14) and dog (2, 13), the sensitivity to 5-HT was greater than that to NE. We found the relative potencies of 5-HT, NE, H and K^+ also similar to those reported for the middle cerebral artery of the goat (14), and basilar atrery of the dog (2), but the maximum contractile responses induced by these agents in our experiments were considerably smaller, possibly due to differences between the diameters of the arteries mentioned above.

The increases in tension elicited by Ach in our experiments are in accordance with other results obtained in isolated cerebral vessels of the cat (12) and dog (2). Nevertheless, when cat pial arteries are previously given a tonic contraction by 5-HT Ach produces a dilatory effect (7).

The behaviour of the cerebral arteries when tested against the agonists used seems to be almost exclusive of these vessels. Only the human umbilical arteries (3) show a similar pattern of both relative potencies and relative maximum contractile responses and in this vascular bed 5-HT is also the greatest vasoconstrictor, far greater than NE. On the other hand, in various extracranial arteries of the dog (11, 13) it has been found that the order of maximal contractile responses to NE, 5-HT and K^+ differ with respect to cerebral arteries of the same animals, which means that NE has the greatest intrinsic activity (efficacy).

Four consistent facts seem to emerge from comparative analyses of the responsiveness of the posterior communicating cerebral artery to vasoconstrictor agents: 1) the potency of 5-HT is greater than that of all other drugs tested, including tyramine; 2) the maximal contractile response induced by NE is smaller than those obtained with the other amines tested; 3) the order of potencies and the order of maximal responses were similar to those previously obtained in human umbilical arteries (3); 4) the order of maximal responses that we found were different from those shown above (11, 13) for the various extracranial arteries in which NE has usually the greatest efficacy.

In conclusion, these results show that cerebral arteries are more sensitive to 5-HT than to NE, as opposed to extracranial arteries in which NE is generally the most potent vasoconstrictor agent. Furthermore, these results suggest that the factors controlling the cerebral and peripheral blood flow are probably different.

Resumen

La administración de noradrenalina (NE), tiramina (Ti), 5-hidroxitriptamina (5-HT), histamina (H), acetilcolina (Ach) y potasio (K^+) dio lugar a una respuesta vasoconstrictora dosis-dependiente en la arteria comunicante posterior aislada de gato. El orden de potencias considerando la DE_{50} fue: 5-HT > NE > Ach = H = Ti > K^+. Mientras que con respecto a su capacidad para inducir respuestas máximas el orden fue: H = Ach > 5-HT = Ti > NE = K^+. Estos resultados demuestran que las arterias cerebrales son mucho más sensibles a la 5-HT que a la NE a diferencia de las arterias extracraneales en las que NE es generalmente el más potente agente vasoconstrictor.

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