in human intestine by radioimmunoassay[10] where it is present in highest concentration in the lamina propria and muscularis externa. This peptide has also been demonstrated in brain[13] suggesting that PHI may act as a neurotransmitter or neuromodulator peptide. The plasma half life of PHI was calculated to be 3.1 min, similar to the reported plasma half life of VIP of 1.03 min[14]. The relatively short half life of PHI may possibly be more in favor of PHI being a neurotransmitter rather than a circulating hormone, being considerably shorter, for example, than the hormonal peptides, GIP and glucagon.

The plasma levels of PHI achieved during this study are comparable to the level at which the very similar peptide VIP results in facial flushing, hypotension and tachycardia[15]. No such effects were observed during the PHI infusion, suggesting that these 2 peptides, despite having similar sequences alter either in their biological activities or potency. At the plasma levels achieved during this study, no effect was noted on secretion of gastric acid and pepsin, and this contrasts with the findings on animal studies on the effects of the members of this family of peptides. In addition, infusion of PHI in man did not effect release of pancreatic glucagon or insulin in this study, and this contrasts with the stimulation observed in the isolated rat pancreas[7].

As this is the 1st study in which porcine PHI has been infused in man, there is no data on its possible other bioactivity. It is possible that the dose of PHI infused may have been too low to produce an effect. The dose however, probably produced pharmacological blood levels as normal basal levels of PHI in healthy controls are less than 20 pmoles/l, and the plateau levels achieved during the infusions reported here were more than 10 times this level. On the other hand, PHI may be a neurotransmitter or neuromodulator rather than a circulating hormone to be released by local nerves in the gastric mucosa. It is thus possible that the local cellular concentration of PHI may be much higher than that achieved after the exogenous PHI infusion in this study.

1 Acknowledgment. JMA is in receipt of a Wellcome Trust Training Fellowship. The work was generously supported by the Medical Research Council.
2 Requests to SRB., 2nd Floor Francis Fraser Labs, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London, W12 OHS (England).
3 Tatemoto, K., and Mutt, V., Nature, Lond. *285* (1980) 417.
4 Tatemoto, K., and Mutt, V., Proc. natl Acad. Sci. USA *78* (1981) 6603.
5 Dimaline, R., and Dockray, G.J., Life Sci. *27* (1980) 1947.
6 Jensen, R.T., Tatemoto, K., Mutt, V., Lemp, G.F., and Gardner, J.D., Am. J. Physiol. *241* (1981) G498.
7 Szecowka, J., Tatemoto, K., Mutt, V., and Efendic, S., Life Sci. *26* (1980) 435.
8 Anagnostides, A.A., Manolas, K., Christofides, N.D., Yiangou, Y., Welbourn, R.B., Bloom, S.R., and Chadwick, V.S., Gut *23* (1982) A914.
9 Ghiglione, M., Christofides, N.D., Yiangou, Y., Uttenthal, L.O., Tatemoto, K., and Bloom, S.R., Neuropeptides *3* (1982) 79.
10 Christofides, N.D., Yiangou, Y., Aarons, E., Ferri, G.-L., Tatemoto, K., Polak, J.M., and Bloom, S.R., Dig. Dis. Sci. *28* (1983) 507.
11 Bloom, S.R., and Long, R.G., eds, Radioimmunoassay of gut regulatory peptides. W.B. Saunders, London 1982.
12 Goldstein, A., Aronow, L., and Ralman, S.M., in: Principles of drug action, 2nd edn, p.311. John Wiley, New York 1974.
13 Christofides, N.D., Yiangou, Y., McGregor, G.P., Aarons, E., Woodhams, P.L., Tatemoto, K., and Bloom, S.R., Biomed. Res. *1982*, 573.
14 Domschke, S., Domschke, W., Bloom, S.R., Mitznegg, P., Mitchell, S., Lux, G., Strunz, U., and Demling, L., in: Gut Hormones, 1st edn, p.475. Ed. S.R. Bloom. Churchill, Livingstone 1978.
15 Holm-Bentzen, M., Christiansen, J., Petersen, B., Fahrenkrug, J., Shultz, A., and Kirkegaard, P., Scand. J. Gastroenterol. *16* (1981) 429.

0014-4754/83/101129-03$1.50+0.20/0


## Dopamine vasodilates human cerebral artery

N. Toda

*Department of Pharmacology, Shiga University of Medical Sciences, Seta, Ohtsu 520-21 (Japan), December 20, 1982*

*Summary.* In human large pial arteries, dopamine-induced relaxations appear to be mediated via dopaminergic receptors, and predominate over contractions mediated via alpha-adrenoceptors.

Regional and species differences in the response of the vasculature to dopamine have been demonstrated in vivo and in vitro[1,2]. These differences are mainly associated with variable magnitudes of activation of postsynaptic dopamine receptors and alpha-adrenergic receptors in the vascular smooth muscle. Isolated mesenteric, renal, splenic and coronary arteries from dogs and rabbits[2-7], as well as isolated dog and cat cerebral arteries treated with high concentrations of alpha-adrenergic antagonists, respond to dopamine by relaxation, possibly mediated via dopamine receptors[8,9]. However, an analysis of dopamine action has not been made in primate cerebral arteries, despite evidence indicating the effectiveness of dopamine in treating acute brain ischemia[10]. The present study was undertaken to compare the effect of dopamine and norepinephrine in isolated human cerebral arteries and to clarify the mechanism of dopamine action.

Four basilar, 5 middle cerebral and 3 vertebral arteries were obtained during autopsy of 4 patients (13-, 49-, 55- and 71-year-old males). The arteries were helically cut into strips, approximately 20 mm long. The specimen was vertically fixed under a resting tension of 2 g in a muscle bath containing modified Ringer-Locke solution, which was maintained at $37 \pm 0.3$ °C and was aerated with a mixture of 95% $O_2$ and 5% $CO_2$. Detailed procedures have been described in an earlier report[11]. Preparations were allowed to equilibrate for 60 to 90 min, before the start of experiments. Cumulative dose-response curves for dopamine and norepinephrine were obtained.

Human cerebral arteries under resting conditions responded with a slight contraction to high concentrations of dopamine ($2 \times 10^{-5}$ to $10^{-4}$ M). However, when the arteries were contracted partially with prostaglandin (PG) $F_{2\alpha}$ or serotonin, dopamine ($5 \times 10^{-8}$ to $5 \times 10^{-6}$ or $2 \times 10^{-5}$ M)

Experientia 39 (1983), Birkhäuser Verlag, CH-4010 Basel/Switzerland

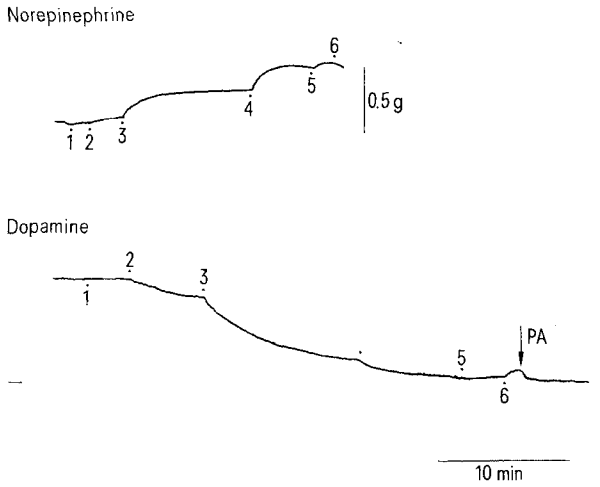


Figure 1. Responses of human middle cerebral arteries to norepinephrine and dopamine. Two strips were obtained from the same cerebral artery segment. The horizontal line just left of the lower tracing represents the level prior to the addition of $10^{-7}$ M prostaglandin (PG) $F_{2\alpha}$. Concentrations of norepinephrine from 1 to $6 = 2\times10^{-8}$, $10^{-7}$, $5\times10^{-7}$, $2\times10^{-6}$, $10^{-5}$ and $5\times10^{-5}$ M, respectively. Concentrations of dopamine from 1 to $6 = 5\times10^{-8}$, $2\times10^{-7}$, $10^{-6}$, $5\times10^{-6}$, $2\times10^{-5}$ and $10^{-4}$ M, respectively. PA = $10^{-4}$ M papaverine.

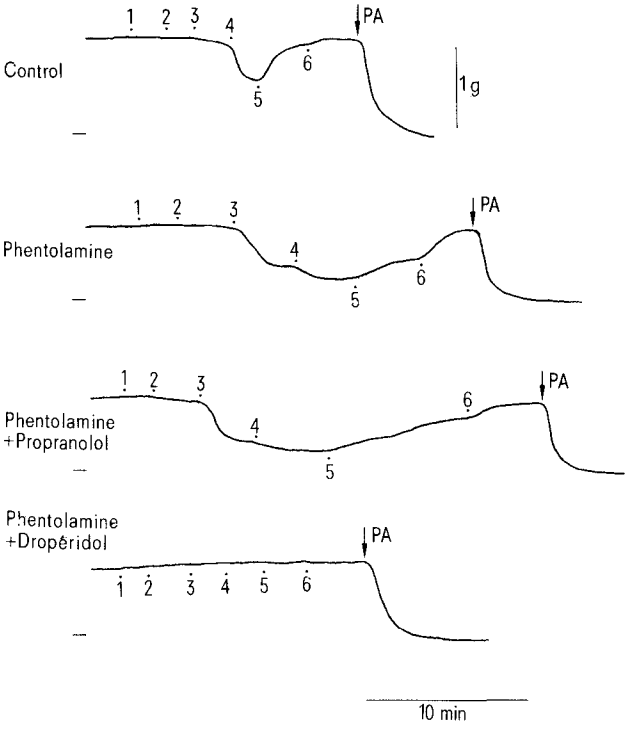


Figure 2. Modification by phentolamine, propranolol and droperidol of the relaxant response of a human vertebral artery strip to dopamine. Concentrations of dopamine, same as those in figure 1. Concentrations of phentolamine, propranotol and droperidol = $10^{-6}$, $10^{-6}$ and $3\times10^{-5}$ M, respectively. PA = $10^{-4}$ M papaverine.

produced a concentration-dependent relaxation and at the higher concentrations produced a contraction (fig. 1). In contrast, norepinephrine ($2\times10^{-8}$ to $10^{-5}$ M) contracted human cerebral arteries dose-dependently under resting conditions (fig. 1) and when contracted with $PGF_{2\alpha}$. Relaxations induced by low concentrations of dopamine were potentiated and contractions induced at high concentrations were reversed to relaxations by treatment for 30 min with $10^{-6}$ M phentolamine (fig. 2) or $10^{-9}$ M prazosin. Norepinephrine-induced contractions were attenuated by these alpha-antagonists.

Relaxations induced by dopamine in concentrations of $2\times10^{-7}$, $10^{-6}$ and $5\times10^{-6}$ M in middle cerebral arteries obtained from 4 individuals averaged $10.0\pm4.9$, $36.5\pm10.7$ and $58.8\pm13.5\%$, respectively, relative to relaxations induced by $10^{-4}$ M papaverine, which maximally relaxes isolated arteries[12]. Dopamine-induced relaxations were not influenced by treatment with $10^{-6}$ M propranolol (fig. 2) and $10^{-6}$ M atropine; therefore, beta adrenergic and muscarinic mechanisms are excluded. Treatment for 30 min with $3\times10^{-5}$ M droperidol markedly attenuated or abolished the relaxation induced by dopamine (fig. 2) in 3 out of 3 preparations but did not alter the relaxant response to adenosine and papaverine. Selective antagonism of dopamine-induced relaxation by droperidol has also been demonstrated in an earlier report with dog coronary and renal arteries[13]. These findings indicate that the predominant relaxation induced by dopamine in human cerebral arteries is associated with activation of dopamine receptors, and conractions induced by high concentrations of dopamine are mediated by alpha-adrenoceptors, as are contractions induced by norepinephrine.

Dopamine-induced relaxation is more evident in human cerebral arteries as compared with the response of other isolated human arteries (unpublished data). In contrast, isolated human renal arteries contract in response to dopamine[14]. The present study clearly demonstrated a dopamine-induced vasodilatation in human large pial arteries. Since high concentrations of dopmaine are present in human plasma[15], circulating dopamine may play some role in regulating the cerebral circulation. Moreover, dopamine may be a useful therapeutic agent for certain cerebral vascular disorders, such as spams of large cerebral arteries.

1 Goldberg, L.I., Pharm. Rev. *24* (1972) 1.
2 Goldberg, L.I., and Toda, N., Circulation Res., suppl. *36* and *37* (1975) 1.
3 Toda, N., and Goldberg, L.I., Cardiovasc. Res. *9* (1975) 384.
4 Toda, N., Hojo, M., Sakae, K., and Usui, H., Blood Vessels *12* (1975) 290.
5 Schmidt, M., and Imbs, J.L., J. cardiovasc. Pharmac. *2* (1980) 595.
6 Brodde, O.-E., Meyer, F.-J., Schemuth, W., and Freistuhler, J., Archs Pharmac. *316* (1981) 24.
7 Hilditch, A., and Drew, G.M., Eur. J. Pharmac. *72* (1981) 287.
8 Toda, N., Br. J. Pharmac. *58* (1976) 121.
9 Edvinsson, L., Hardebo, J.E., McCulloch, J., and Owman, Ch., Acta physiol. scand. *104* (1978) 349.
10 Kwak, S., and Nakamura, H., in: Cerebral Ischemia - An Update -, p. 179. Eds Z. Ito, T. Kutsuzawa and N. Yasui. Excerpta Medica, Amsterdam 1983.
11 Toda, N., Am. J. Physiol. *243* (1982) H145.
12 Toda, N., J. Pharmac. exp. Ther. *191* (1974) 139.
13 Toda, N., and Hatano, Y., Eur. J. Pharmac. *57* (1979) 231.
14 Ueda, S., Yano, S., and Sakanashi, M., J. Cardiovasc. Pharmac. *4* (1982) 76.
15 Jonson, G.A., Baker, C.A., and Smith, R.T., Life Sci. *26* (1980) 1591.

0014-4754/83/101131-02$1.50 + 0.20/0