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BIPHASIC RESPONSIVENESS OF RAT PIAL ARTERIOLES TO DOPAMINE: DIRECT OBSERVATIONS ON THE MICROCIRCULATION

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The effects of local perivascular application of dopamine to rat pial arterioles, (20–40 μm i.d.) were examined *in situ*, at the microcirculatory level, by use of a high-resolution closed circuit television microscope recording system. Local application of very low, physiological doses (1 to 10 pg) of dopamine to pial arterioles of the anaesthetized rat induces vasodilatation, whereas higher doses induce vasoconstriction. The magnitudes of these biphasic responses obtained in male rats were not significantly different from those obtained in female animals. Our findings support the theory that local release of this neurotransmitter amine from perivascular cells in the brain may promote local increases in cerebral blood flow.

Introduction The caudate-putamen region, as well as cortical projection areas, in the mammalian brain contain dopaminergic systems in close proximity to cerebral microvessels. Although it has amply been demonstrated that large mammalian cerebral arteries contain receptors for the neurotransmitter, dopamine, which may respond with contractile or relaxant responses (Toda, 1976; Edvinsson, Hardebo, Harper, McCulloch & Owman, 1977), there are no direct *in vivo* studies with this neurotransmitter substance, at the terminal arteriolar level in the cerebral microcirculation (Kuschinsky & Wahl, 1978). Such direct *in situ* studies are necessary, especially in view of recent observations in baboons which suggest that systemic administration of the dopamine receptor agonist, apomorphine, can strongly increase cerebral blood flow and oxygen consumption (McCulloch & Harper, 1977).

We have found that direct, local application of very low doses (1 to 10 pg) of dopamine to pial terminal arterioles (20 to 40 μm o.d.) of the anaesthetized rat induces vasodilatation, whereas higher doses induce vasoconstriction.

Methods Fourteen young male and female rats (Wistar strain, 120 to 180 g) were lightly anaesthetized with intramuscular pentobarbitone sodium (Nembutal, 25 mg/kg). After induction of anaesthesia, tracheostomies were performed, and catheters were placed in femoral arteries for blood gas (Po_2,Pco_2), pH and blood pressure determinations. A right parietal-temporal craniotomy was performed by scraping the cranium with a scalpel down to the dura, by a method similar to that described previously (Lassoff & Altura, 1980); the dura was then incised and stripped. Artificial cerebral spinal fluid (CSF) (composition in mEq/l: Na^+ 155, Cl^- 137, HCO_3^- 21, K^+ 3.5, Mg^{2+} 1.3, Ca 2.2 and glucose 6), maintained at a temperature between 36 to 37.5°C and at a pH of 7.3 to 7.4, was allowed to drip onto the exposed brain surface. The brain surface temperature was kept close to 37.5°C and measured with a thermistor probe.

Pial arteriolar diameters (20 to 40 μm o.d.) were examined and measured quantitatively (up to 3000×) with an image-splitting television microscope recording system, similar to that described previously for microvessels (Altura, 1975). The reactivity of selected arterioles was tested before, and after dopamine, by local application of 0.1 ml of a 5% $BaCl_2$ solution. Pial arterioles that failed to yield a 30 to 40% constriction in response to the standard dose of barium were not used in this study. $BaCl_2$ has been shown to produce consistent and reproducible constrictor responses on normal rat pial arterioles (Lassoff & Altura, 1980). Dopamine (dissolved in artificial CSF) was applied locally (10^{-10} to 10^{-1} mg) to the vessels in volumes of 0.1 ml. Periodically throughout the experiments drug-free artificial CSF in 0.1 ml volumes was also tested for vasoactivity. Reapplication of the test dose of $BaCl_2$, at the end of the experiments, insured that the pial arterioles had been reactive throughout the testing of dopamine. Systolic blood pressure was measured throughout the experiments (average mean = 125 mmHg). At selected intervals, arterial blood samples were obtained for pH, Po_2 and Pco_2 measurements. The arterial blood gas values were always found to be normocapnic throughout the experiments (mean Pco_2 = 29.2 mmHg). Paired *t* tests were used for statistical analysis of the differences between mean values (±s.e. mean) before and after agonist application.

Results The perivascular application of 0.1 ml artificial CSF had no significant effect on the diameters of the pial arterioles. Table 1 indicates that low, increasing doses of dopamine (i.e., 1 to 100 pg) significantly increased the vessel calibres 9 to 11%. Higher doses of dopamine (i.e., 1 ng to 100 μg) produced dose-dependent decreases in arteriolar lumen sizes, ranging from

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Table 1 Influence of dopamine on pial terminal arteriolar diameters in intact rats

Test agonist	*Dose*	*Control diameter size* (μm)	*Diameter size after agonist* (μm)	*% change*[a]
$BaCl_2$, 5% (initial)		31.9 ± 1.52	14.7 ± 1.12	−54.0***
Dopamine,	1 pg	30.3 ± 1.69	33.2 ± 2.31	+9.6**
	10 pg	30.2 ± 1.43	33.3 ± 1.72	+10.3***
	100 pg	31.1 ± 1.22	34.5 ± 2.76	+10.9**
	1 ng	32.4 ± 1.16	30.7 ± 2.11	−5.3
	10 ng	32.3 ± 1.56	26.7 ± 2.27	−17.4*
	100 ng	31.4 ± 1.72	26.5 ± 2.18	−15.7**
	1 μg	31.9 ± 1.64	25.1 ± 2.97	−21.4***
	10 μg	31.4 ± 1.75	25.0 ± 2.06	−20.4***
	100 μg	30.0 ± 1.82	22.8 ± 1.83	−24.0***
$BaCl_2$, 5% (final)		30.2 ± 1.43	17.8 ± 1.09	−41.1***, NS

Values are given as means ± s.e. mean. $n = 14$ different rats.
[a]Minus sign signifies vasoconstriction; plus sign signifies vasodilatation.
Significantly different from control: $*P < 0.05$; $**P < 0.025$, $***P < 0.005$.
NS not significantly different from initial $BaCl_2$ response.

17 to 24%. Although not shown, it should be noted that the degrees of the biphasic responses obtained in male rats were not significantly different from those obtained in female animals. No dose of dopamine could produce the degree of vasoconstriction found after application of $BaCl_2$, i.e., 40 to 55%.

Discussion These data clearly indicate that pial terminal arterioles can both dilate and constrict to the perivascular application of dopamine. Despite this biphasic responsiveness, it is doubtful whether the pial arteriolar constrictor action of dopamine has physiological significance, since these responses can not be elicited by doses less than 10 ng. The fact that as little as 1 pg of dopamine can produce significant dilatation seems to suggest that the normal *in situ* physiological response of pial terminal arterioles is probably vasodilatation rather than vasoconstriction. Such findings support the theory that local release of this neurotransmitter amine from perivascular parenchymal cells may indeed promote local increases in cerebral blood flow (McCulloch & Harper, 1977). It is of additional interest that, like the responsiveness of arterioles in other organ regions of the rat (Altura, 1975), the constrictor action of dopamine on pial arterioles is independent of the influence of sex hormones.

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