**α-Adrenergic Receptors in Cerebral Microvessels of Normotensive and Spontaneously Hypertensive Rats**

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SUMMARY. In rat cerebral microvessels, we characterized α1- and α2-adrenergic receptors, using [3H]prazosin and [3H]-p-amino-clonidine as radioligands. [3H]Prazosin binding to the cerebral microvessels was saturable and of high affinity (dissociation constant of 78 pM), with a maximum binding of 48 fmol/mg protein. [3H]Prazosin binding reached equilibrium within 15 minutes and was dissociated by the addition of 10 μM phentolamine. The inhibitory effects of isomers of norepinephrine and epinephrine on the binding showed that L-isomers were over 10 times more potent than d-isomers. [3H]-p-Amino-clonidine binding to the cerebral microvessels was saturable and of high affinity (Kd = 0.61 nM) with a Bmax of 73 fmol/mg protein. The binding reached equilibrium within 30 minutes, and was dissociated by the addition of 100 μM L-norepinephrine. L-Isomers of norepinephrine and epinephrine were over 10 times more potent than d-isomers in displacing the binding. Thus, both [3H]prazosin and [3H]-p-amino-clonidine bindings to the cerebral microvessels were characterized by saturability, high affinity, reversibility, and stereospecificity. Furthermore, the specificity of both binding sites was pharmacologically evaluated by the inhibitory effects of various adrenergic agonists and antagonists on the bindings. These data indicate the existence of α-adrenergic receptors in the cerebral microvessels and are consistent with the hypothesis that the cerebral microcirculation is regulated by adrenergic innervation. Furthermore, the receptors were measured in cerebral microvessels of spontaneously hypertensive rats and Wistar-Kyoto controls. The number of α1-receptors in the cerebral microvessels of spontaneously hypertensive rats was significantly higher than that of Wistar-Kyoto rats, without any difference in the affinity constant to the ligands. No difference in α2-receptors was observed between spontaneously hypertensive and Wistar-Kyoto rats. These results suggest that the neuronal regulatory mechanisms of the cerebral microcirculation are altered in hypertension. (Circ Res 56: 402-409, 1985)

**Methods**

VARIOUS experimental observations suggest that brain microvasculature is under neuronal control of the central adrenergic system. In fact, morphological studies show that brain capillary endothelium is closely associated with adrenergic fibers originating from the locus coeruleus (Swanson et al., 1977), whereas physiological data indicate that α- and β-adrenergic receptors are involved in regulatory mechanisms of brain microvasculature. In particular, it is suggested that the two populations of receptors play an important role in mediating changes of cerebral blood flow and blood-brain barrier (BBB) permeability to molecules such as water and glucose (Raichle et al., 1975; MacKenzie et al., 1976a, 1976b; Bates et al., 1977; Grubb et al., 1978; Schwartz, 1978; Abraham et al., 1979). Furthermore, biochemical experiments demonstrated the presence of norepinephrine, its synthesizing and catabolizing enzymes (Lai et al., 1975), and adrenergic receptors in cerebral microvessels. β-Adrenergic receptors linked to adenylate cyclase in the microvessels were well characterized (Herbst et al., 1979; Nathanson and Glaser, 1979; Kobayashi et al., 1981a, 1981b, 1982a, 1982b, 1982c). The existence of α-adrenergic receptors was also reported (Peroutka et al., 1980; Kobayashi et al., 1982a); however, the properties of the receptors were not fully analyzed.

On the other hand, several studies indicate that hypertension affects cerebral microvessel functions. In particular, increased BBB permeability and impairment of cerebral blood flow autoregulation have been described (Johansson, 1976; Strangaard et al., 1973, Hatzinikolou et al., 1981). Recently, we reported that the number of β-receptors located in the cerebral microvessels is decreased by about 30% in both genetic and experimental hypertensive rats (Magnoni et al., 1983). To investigate further the involvement of the adrenergic system in brain microvascular regulatory mechanisms in hypertension, we have measured α1- and α2-adrenergic receptors in the cerebral microvessels of normotensive and spontaneously hypertensive rats.
pressure, measured by the tail cuff method, was 190 ± 5 
mm Hg in SHR and 120 ± 3 mm Hg in WKY (means ± 
SEM, n = 7).

Brain microvessels were prepared as described previ-
ously (Kobayashi et al., 1981a). In each experiment, 20-
40 rats per group were used. Rats were killed by decapi-
tation. Gray matter of cerebral cortices was rapidly cleaned 
from pial membrane and white matter, minced by scissors, 
and homogenized by hand in a Teflon-glass homogenizer 
gassed (95% O2, 5% CO2) Ringer’s solution that con-
stisted of 137 mM NaCl, 5 mM KCl, 3 mM CaCl2, 1.2 mM 
MgCl2, 12 mM NaHCO3, 5 mM glucose, 1% bovine serum 
albumin (BSA), and 15 mM HEPEs (pH 7.4). The homoge-
enate was passed through 700-, 200-, and 100-μm nylon 
meshes and centrifuged at 1,000 g for 10 minutes. The 
resulting small pellet was suspended in Ringer’s solution. 
The floated thick layer was suspended in the supernatant 
and recentrifuged at 1,000 g for 15 minutes. The pellet 
was suspended in Ringer’s solution and combined with 
the first suspension. The suspension was passed through 
a column of glass beads (0.2-0.5 mm in diameter) and 
washed extensively with Ringer’s solution. The microves-
sels attached to the glass beads were released by gentle 
agitation in Ringer’s solution, collected, and washed three 
times by centrifugation in the buffer used for binding assay.

α1-Adrenergic receptors were measured as described 
previously (Barnes et al., 1979; Kobayashi et al., 1982a). 
The microvessels were incubated in triplicate with various 
concentrations of [3H]Prazosin in 50 mM Tris-HCl buffer 
(pH 7.5) at 25°C for 15 minutes. [3H]Prazosin bound to 
the microvessels was separated from free ligand by filtra-
tion through GF/B glass fiber filter (Whatman), and the 
filters were washed four times with 5 ml of cold 50 mM 
Tris-HCl buffer. The filtration step was accomplished 
within 15 seconds. The radioactivity was measured in 
toluene base scintillation cocktail with an efficiency of 
43%. The specific binding of [3H]Prazosin was defined as 
total binding minus nonspecific binding which was deter-
mined in the presence of 10 μM phentolamine.

α2-Adrenergic receptors were measured using [3H]-p-
amino-phenolamine ([3H]PAC; Rouot and Snyder, 1979; 
Kobayashi et al., 1982a). The assay mixture consisted of 
various concentrations of [3H]PAC, 0.001% ascorbic acid, 
50 mM Tris-HCl buffer (pH 7.5), and the microvessels. 
Incubation was carried out at 25°C for 30 minutes. The 
specific binding of [3H]PAC was defined as total binding 
minus nonspecific binding which was determined in the 
presence of 100 μM l-norepinephrine.

γ-Glutamyltranspeptidase (γ-GTP), a marker enzyme 
of brain capillary, was measured according to the method 
of Orlovski and Meister (1965), using γ-glutamyl-p-ni-
troanilide as a substrate. The samples were incubated in a 
reaction mixture composed of 5 mM L-γ-glutamyl-p-ni-
troanilide, 10 mM MgCl2, and 100 mM Tris-HCl buffer 
(pH 9.0), in a final volume of 1 ml. After 60 minutes of 
incubation at 37°C, the reaction was terminated by the 
addition of 2 ml of 1.5 M acetic acid. The enzymatic 
reaction leads to the formation of p-nitroaniline which 
was determined by direct spectrophotometric measure-
ment. The absorbance, at 410 nm, was recorded against 
a reference solution containing the same components except 
substrate.

Protein concentration was measured according to the 
method of Lowry et al. (1951).

The maximum binding and the dissociation constant 
values of the specific binding of [3H]Prazosin and [3H]- 
PAC to the cerebral microvessels were analyzed by a linear 
least squares regression method on the Scatchard analysis.

Clonidine was kindly donated by Boehringer Ingelheim, 
phentolamine was from Ciba Geigy, and prazosin was 
from Pfizer. [3H]Prazosin (20.2 Ci/mmol) was purchased 
from Amersham and [3H]-p-amino-clonidine (56.6 Ci/ 
mmol) was from New England Nuclear. d-Norepinephrine 
was from Adams Chemical and d-epinephrine was from 
ICN Pharmaceuticals. Other drugs were from Nakai 
Chemicals.

Results

The purity of the cerebral microvessels of Sprague-
Dawley rats was checked by phase-contrast micros-
copy and by measurement of γ-glutamyltranspepti-
dase activity, and they were highly purified as 
described previously (Kobayashi et al., 1981a).

The specific binding of [3H]Prazosin to the cere-
bral microvessels was a linear function of amount 
of protein in the preparation up to 250 μg/tube (data 
not shown). A higher concentration of protein inter-
fered with the binding assay by slowing the passage of 
the incubation medium through the filter.

The specific binding of [3H]Prazosin to the cere-
bral microvessels is shown in Figure 2. Equilib-
rium was attained within 15 minutes. After addition 
of phentolamine at the final concentration of 10 μM, 
the binding was dissociated with a half-time of 10 
minutes showing the reversibility of [3H]Prazosin 
binding to the cerebral microvessels. From the data, 
association rate (Ko), of 0.00098/pm · min and dis-
sociation rate (Kd) of 0.072/min were calculated.

The KD value obtained by the equation KD = Kd/ 
Ko was 73 pm. This value is in good agreement with 
the Kd value calculated by the Scatchard analysis 
(Fig. 1b).

The specific binding of [3H]PAC to the cerebral 
microvessels was saturated at 5 nM of [3H]PAC 
concentration (Fig. 3a). The KD value calculated by 
the method of Scatchard was 0.61 ± 0.03 nM (n = 4), 
and the Bmax value was 74 ± 2 fmol/mg protein, 
indicating the high affinity characteristic of the bind-
ing (Fig. 3b). Further increases in [3H]PAC concen-
tration, up to 20 nM, did not produce any increase 
in the specific binding, indicating the [3H]PAC 
labeled single class of receptors in the cerebral mi-
icrovessels.

The time course of the [3H]PAC binding to the 
cerebral microvessels is shown in Figure 4. Equilib-
rium was attained within 30 minutes. After the 
addition of l-norepinephrine at the final concentra-
FIGURE 1. Saturation curve (panel a) and Scatchard plot (panel b) of [3H]prazosin binding to cerebral microvessels. Values are representative of five separate experiments with Sprague-Dawley rats, and are the means of triplicate determinations which varied less than 10%. ■, total binding; △, nonspecific binding; ●, specific binding; F, free concentration of [3H]prazosin; B, [3H]prazosin binding to the cerebral microvessels.

FIGURE 2. Time course of specific [3H]prazosin binding to cerebral microvessels. The concentration of [3H]prazosin was 100 pM. Incubation was started by the addition of cerebral microvessel preparation of Sprague-Dawley rats, and was terminated by filtration at the times indicated (O). Dissociation (●) was started by adding 10 μM phentolamine, after equilibrium had been reached. Each point is the mean of three to five separate experiments with standard errors ranging from 5 to 20%.

FIGURE 3. Saturation curve (panel a) and Scatchard plot (panel b) of [3H] PAC binding to cerebral microvessels. Values are representative of four separate experiments with Sprague-Dawley rats, and are the means of triplicate determinations which varied less than 10%. ■, total binding; △, nonspecific binding; ●, specific binding; F, free concentration of [3H]PAC; B, [3H]PAC binding to the cerebral microvessels.

The dissociation of 100 μM, the binding was dissociated with a half-time of 17 minutes, indicating that the [3H]PAC binding to the cerebral microvessels is reversible. From the data, K_eq of 0.194/μM • min and K_off of 0.095/μM • min were calculated. The K_d value obtained by K_off division by K_on was 0.49 μM. This value was comparable with the K_d value calculated by the Scatchard analysis (Fig. 3b).

To characterize the stereospecificity of the binding sites, the inhibitory effect of L- or D-isomers of norepinephrine and epinephrine on [3H]prazosin and [3H]PAC bindings to the cerebral microvessels was investigated (Table 1). L-Norepinephrine was 17 times more potent than its d-isomer, and L-epinephrine was 22 times more potent than its d-isomer. The inhibitory effect of L-norepinephrine to the [3H]PAC binding to the microvessels was 38 times more potent than its d-isomer, and L-epinephrine was 17 times more potent than that its d-isomer. Thus, both the [3H]prazosin
and [3H]PAC bindings to the cerebral microvessels were characterized by their stereospecificity.

Inhibitory effects of various adrenergic agonists and antagonists on [3H]prazosin and [3H]PAC bindings to the cerebral microvessels were shown in Table 1. [3H]Prazosin binding was inhibited by prazosin > phentolamine > yohimbine > epinephrine > clonidine, and > norepinephrine, whereas [3H]PAC binding was inhibited by phentolamine > clonidine > epinephrine > norepinephrine > yohimbine > and > prazosin. Ratio between the inhibitory constant (Ki) value for [3H]prazosin binding and the Ki value for [3H]PAC binding of each drug was calculated to demonstrate the characteristics of each ligand binding. The α1-selective antagonist, prazosin, was 40,000 times more potent in inhibiting [3H]prazosin binding than in inhibiting [3H]PAC binding to the cerebral microvessels, whereas the α2-selective agonist, clonidine, was 182 times more potent in inhibiting [3H]PAC binding than in inhibiting [3H]prazosin binding. These data indicate that [3H]prazosin bound to the cerebral microvessels with characteristics of α1-adrenergic receptors, and [3H]PAC bound with characteristics of α2-adrenergic receptors.

The purity of the cerebral microvessel preparations from WKY and SHR was controlled by phase-contrast microscopy (Fig. 5). The preparations were practically free from neuronal and glial elements. At this level of magnification, no morphological difference between the preparations from WKY and SHR is detectable. Table 2 shows that γ-GTP activities of WKY and SHR are comparable, both in the brain homogenate and in the microvessel preparation. γ-GTP activity was more than 30 times higher in the microvessels than in the brain homogenate, indicating that both preparations were highly purified. There was no difference between WKY and SHR in recovery of the microvessels per unit of tissue weight.

Table 6a shows the specific binding of [3H]prazosin to the cerebral microvessels from WKY and SHR. At various concentrations of [3H]prazosin, binding is higher in the preparation from SHR than in that from WKY. Scatchard analysis (Fig. 6b) shows that the Bmax value for SHR is 50% higher than that of WKY, without a change in KD value: Bmax 43 ± 3 and 66 ± 5 fmol/mg protein (P < 0.01); KD, 81 ± 5 and 83 ± 7 pm, for WKY and SHR, respectively.

Table 1

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Ks for [3H]prazosin binding (a)</th>
<th>Ks for [3H]PAC binding (b)</th>
<th>a/b</th>
</tr>
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<tbody>
<tr>
<td>Agonists</td>
<td></td>
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<tr>
<td>1-Norepinephrine</td>
<td>540 ± 40</td>
<td>20 ± 5</td>
<td>27</td>
</tr>
<tr>
<td>d-Norepinephrine</td>
<td>9000 ± 1100†</td>
<td>750 ± 80†</td>
<td>12</td>
</tr>
<tr>
<td>1-Epinephrine</td>
<td>200 ± 50</td>
<td>3.3 ± 0.3</td>
<td>61</td>
</tr>
<tr>
<td>d-Epinephrine</td>
<td>4300 ± 900*</td>
<td>55 ± 14†</td>
<td>78</td>
</tr>
<tr>
<td>Clonidine</td>
<td>310 ± 60</td>
<td>1.7 ± 0.3</td>
<td>182</td>
</tr>
<tr>
<td>Antagonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>0.045 ± 0.008</td>
<td>1800 ± 600</td>
<td>0.000025</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>2.1 ± 0.4</td>
<td>1.4 ± 0.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>110 ± 50</td>
<td>30 ± 8</td>
<td>3.7</td>
</tr>
</tbody>
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The IC50 values were determined graphically, and the Ki values were calculated from the equation, Ks = IC50/(1 + S/KD), where S is the concentration of [3H]prazosin (100 pm) or [3H]PAC (0.7 nm) used in the assay, and KD is the dissociation constant calculated by the Scatchard analysis (78 pm for [3H]prazosin binding and 0.61 nm for [3H]PAC binding, as indicated in the text). The values given are expressed as nm and are the means ± SEM of three to six separate experiments, performed in triplicate, using Sprague-Dawley rats.

* P < 0.01, † P < 0.001 significant difference from value for its l-isomer analyzed by the method of Cochran and Cox (1959) for two groups of different variance.
FIGURE 5. Phase-contrast microscope observation of cerebral microvessel preparations of WKY and SHR. Left, WKY; right, SHR. Bars show 50 μm.

TABLE 2
Recovery and γ-GTP Activity in Cerebral Microvessels Prepared from WKY and SHR

<table>
<thead>
<tr>
<th></th>
<th>WKY</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>420 ± 35</td>
<td>395 ± 42</td>
</tr>
<tr>
<td>γ-GTP activity</td>
<td>95 ± 12</td>
<td>106 ± 9</td>
</tr>
<tr>
<td>Brain homogenate</td>
<td>3980 ± 35</td>
<td>3850 ± 50</td>
</tr>
</tbody>
</table>

Recovery was expressed as μg protein of microvessels per g of cerebral cortex. γ-GTP activity was expressed in nmol product per mg protein per hr. The data are means ± SEM of four separate experiments.

Figure 7 shows the specific binding of [3H]PAC to the microvessel preparations. No difference in [3H]-PAC binding between WKY and SHR is observed: Bmax, 70 ± 6 and 75 ± 6 fmol/mg protein; KD, 0.64 ± 0.04 and 0.69 ± 0.05 nm for WKY and SHR, respectively.

The binding of [3H]prazosin to the cerebral microvessels prepared from normotensive Wistar rats (Bmax, 47 ± 3 fmol/mg protein; KD, 78 ± 5 pm, n = 3) and the binding of [3H]PAC (Bmax, 73 ± 5 fmol/mg protein; KD, 0.63 ± 0.04 nm, n = 3) were not different from the values of WKY (data not shown in figure).

Discussion

Our data show the existence of α1- and α2-adrenergic receptors in the rat cerebral microvessels which are labeled by [3H]prazosin and [3H]PAC, respectively. Both binding sites were characterized by saturability, high affinity, reversibility, and stereospecificity. Furthermore, the specificities of

FIGURE 6. [3H]Prazosin-specific binding to cerebral microvessels (panel a) and its Scatchard plot (panel b) of WKY and SHR. The assay conditions are described in Methods. O, WKY; □, SHR. Each point shows the mean of four experiments which varied less than 10%.
both binding sites were pharmacologically evaluated by the inhibitory effect of various adrenergic agonists and antagonists on the bindings. $[^3H]$Prazosin binding to the cerebral microvessels showed the pharmacological properties of $\alpha_1$-adrenergic receptors, and $[^3H]$PAC binding satisfied the properties of $\alpha_2$-adrenergic receptors. Harik et al. (1980) reported the existence of $\beta$-adrenergic receptors in the cerebral microvessels of the rat and pig, whereas they did not find the $\alpha_1$-adrenergic receptor sites by use of $[^3H]$-WB4101. However, Peroutka et al. (1980) demonstrated the presence of a considerable number of $\alpha_1$-receptor sites in the bovine cerebral microvessels, using the same radioligand, and we also reported the existence of $\alpha_1$-receptors which were labeled by $[^3H]$-prazosin (Kobayashi et al., 1982a). Characterization of the $[^3H]$prazosin-binding sites in this report ascertains the existence of the $\alpha_1$-adrenergic receptors in the cerebral microvessels. These results, together with reports of the existence of $\beta$-adrenergic receptor sites (Kobayashi et al., 1981a, 1981b, 1982a-c; Peroutka et al., 1980) and $\beta$-adrenergic-sensitive adenylate cyclase activity (Herbst et al., 1979; Nathanson and Glaser, 1979) in the cerebral microvessels, are consistent with the hypothesis that functions of the brain microvessels are controlled by adrenergic innervation.

In a previous report, it was found that $[^3H]$-clonidine bound to the $\alpha_2$-receptors with different affinity components (U’Prichard et al., 1979), whereas $[^3H]$PAC bound to the receptors uniformly (Rouot and Snyder, 1979). In our system, the straight line in the Scatchard analysis showed that $[^3H]$PAC labeled $\alpha_2$-receptors of the cerebral microvessels with one affinity component, as in other tissues (Rouot and Snyder, 1979).

Preskorn et al. (1980) reported that tricyclic antidepressants, which are the blockers of the neuronal uptake of norepinephrine, increased the permeability for water from blood to the brain, and this blood-brain permeability of water was decreased by the $\alpha$-adrenergic antagonist, phentolamine (Raichle et al., 1975). These results suggest that $\alpha$-receptors located on the cerebral microvessels are involved in the regulation of blood-brain barrier functions.

The number of $[^3H]$prazosin-binding sites in SHR was significantly higher than in control, indicating an increase of $\alpha_1$-receptors, whereas no difference in $\alpha_2$-receptors labeled by $[^3H]$PAC was observed between SHR and WKY. Furthermore, a reduction of $\beta$-receptor density in the cerebral microvessels of SHR and DOCA-salt hypertensive rats has been demonstrated previously (Magnoni et al., 1983).

Morphological changes of the capillaries, such as increased diameter, endothelial cell degeneration, and deposition of collagen, were reported in experimental hypertensive animals and in humans with essential hypertension (Garcia et al., 1981). Physiological experiments indicate that the acute elevation of systolic blood pressure induces a disruption of the blood-brain barrier, characterized by increased cerebral blood flow, extravasation of markers which normally do not pass the blood-brain barrier, and cerebral edema (Johansson et al., 1970, Johansson, 1976; Heistad and Marcus, 1979). Impaired capacity of cerebral blood flow autoregulation and cerebral edema also have been described in patients with severe hypertension (Byrom, 1954; Stranggaard et al., 1975; Healton et al., 1982).

In this report, we suggest the possibility that changes of $\alpha_1$- and $\beta$-adrenergic receptors in the cerebral microvessels may be involved in the changes of cerebral microvasculature observed in hypertension.

Catecholamines are implicated in the pathogenesis of hypertension. In fact, changes in the functions of peripheral adrenergic neurons and increased plasma catecholamine levels have been reported in hypertension, as well as alterations in the central nervous system (Reid et al., 1975; Nagaoka and Lovenberg, 1976, 1977; Brody et al., 1980). Synthesis, content, and turnover of catecholamines are modified in various brain regions of hypertensive rats (Nakamura et al., 1971a, 1971b; Goldberg et al., 1975; Versteeg et al., 1976; Nagaoka et al., 1977; Gianutsos and Moore, 1978; Saavedra et al., 1978).
in concomitance with changes in adrenergic receptors (Cantor et al., 1981; Myers et al., 1981). Alterations in hypertension of both central and peripheral adrenergic system may therefore concur in determining the changes of α- and β-receptors in the brain capillaries.

It is interesting to note that the number of α₁- and β-adrenergic receptors is modified in opposite directions, indicating that the two populations may be independently regulated. Experimental observations show that α- and β-receptors mediate opposite effects in cerebral microvasculature. β-Receptor stimulation increases and α-receptor stimulation decreases cerebral blood flow and glucose uptake into the brain (Raichle et al., 1975; MacKenzie et al., 1976b; Schwartz, 1978; Abraham et al., 1979). The same events have been described in the rat auditory system (Savaki et al., 1978). In this line, the higher level of α₁-receptors and the reduced level of β-receptors in the cerebral microvessels of hypertensive rats could produce the same functional changes in response to catecholamine system. These events may be the consequence of specific changes in neuronal regulatory mechanisms of cerebral microvasculature induced by hypertension.

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Received February 8, 1983; accepted for publication December 17, 1984.

Circulation Research / Vol. 56, No. 3, March 1985

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INDEX TERMS: Cerebral microvessels • α-Adrenergic receptors • Brain microcirculation • Neuronal regulation • Spontaneously hypertensive rats
alpha-Adrenergic receptors in cerebral microvessels of normotensive and spontaneously hypertensive rats.
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Circ Res. 1985;56:402-409
doi: 10.1161/01.RES.56.3.402

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