GABAergic Control of Arteriolar Diameter in the Rat Retina

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PURPOSE. To investigate the role of γ-aminobutyric acid (GABA) in the regulation of arteriolar diameter in the rat retina.

METHODS. The actions of GABA on arteriolar diameter were examined using ex vivo retinal whole-mount preparations and isolated vessel segments. In most experiments, arterioles were partially preconstricted with endothelin (ET)-1. The expression levels of GABAA and GABAB receptors on isolated rat retinal Müller cells were assessed by immunohistochemistry.

RESULTS. GABA (0.1–1 mM) evoked vasodilatation or vasoconstriction of arterioles in whole-mount preparations. No such effects were observed with isolated vessel segments. In whole mount samples, the GABAA receptor agonist muscimol caused vasomotor responses in only a small proportion of vessels. In contrast, arteriolar responses to the GABAB receptor agonists baclofen and SKF97541 more closely resembled those observed with GABA. No responses were seen with the GABAB receptor agonist 5-methylimidazoleacetic acid. GABA-induced vasodilator responses were, for the most part, repeatable in the presence of the GABAB receptor antagonist bicuculline. These responses, however, were completely blocked in the presence of the GABAA receptor inhibitor 2-hydroxysaclofen. Strong immunolabeling for both GABAA and GABAB receptors was detected in isolated Müller cells. In the absence of Et-1-induced preconstriction, most vessels were unresponsive to bicuculline or 2-hydroxysaclofen.

CONCLUSIONS. GABA exerts complex effects on arteriolar diameter in the rat retina. These actions appear largely dependent upon the activation of GABAA receptors in the retinal neuropile, possibly those located on perivascular Müller cells. Despite these findings, endogenous GABA appears to contribute little to the regulation of basal arteriolar diameter in the rat retina.

Keywords: GABA, retinal arterioles, vascular tone

As the principal inhibitory neurotransmitter in the retina, γ-aminobutyric acid (GABA) plays an important role in the processing of visual information. GABA is used by subpopulations of horizontal and amacrine cells, where it is involved in the lateral inhibition of cone photoreceptors, bipolar cells, and ganglion cells.1 GABAergic signaling in the retina has been reported to underlie several essential mechanisms of visual information processing, including the center-surround receptive field organization of retinal ganglion cells and the motion and direction sensitivity of some retinal neurons.2 Aside from its role as an inhibitory neurotransmitter, GABA has also been implicated as an important neurotrophic factor during retinal development, modulating neuronal survival, differentiation, and formation of photoreceptor synapses.3,4 Although the neurophysiological and neurotrophic actions of GABA in the retina are well recognized, fewer studies have examined the contribution of GABAergic mechanisms to the regulation of the retinal microcirculation. In the brain, previous work has demonstrated that GABA evokes a concentration-dependent dilatation of isolated large cerebral artery segments5 and elicits a net vasodilatory effect on parenchymal microvessels in hippocampal brain slice preparations.6,7 More recently, GABA has been shown to serve as an important mediator of functional hyperemia in the brain, a process whereby neuronal activation triggers a local increase in cerebral blood flow.7,8 To date, however, there has been only one detailed study evaluating the vasomotor effects of GABA on the retinal vasculature. In porcine retinal arterioles, GABA was found to induce vasorelaxation through a complex pathway involving the activation of GABAA receptors in perivascular retinal tissue and inhibition of glutamate, ATP, and prostaglandin E2 signaling.9

Initial studies from our own laboratory have indicated that GABAergic regulation of rat retinal arterioles may differ appreciably from that observed previously in the porcine retina.10 In the present study, we sought to address this issue in more detail by performing experiments using both freshly isolated rat retinal whole-mount preparations and isolated vessel segments. We show that high concentrations of GABA applied to the rat retina can exert a dual effect on arteriolar diameter, inducing either vasodilatation or vasoconstriction. Similar to reactions in porcine retinal arterioles, these reactions were entirely dependent upon the presence of the adjacent retinal neuropile. In contrast, however, both types of GABA-induced vasomotor responses appear to be mediated primarily through the activation of GABAA receptors rather than GABAB receptors, most likely those located on perivascular Müller glia. Despite these findings, we obtained little evidence to suggest that endogenous GABA makes a significant contribution to the...
regulation of basal arteriolar diameter in the intact rat retina, at least under the ex vivo conditions used in our experiments.

**MATERIALS AND METHODS**

All animal use was performed under license from the United Kingdom Home Office under the Animals (Scientific Procedures) Act 1986 and complied with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

**Retinal Whole-Mount Preparation**

Ex vivo retinal whole mounts were prepared from adult male Sprague-Dawley rats (175–250 g; Harlan, Bicester, UK). Animals were killed by overdose of sodium pentobarbital (300 mg/kg of body weight, given intraperitoneally) and eyes enucleated. Following hemisection of the eyes along the ora serrata, the cornea, lens, and vitreous body were removed, and whole neural retinas were gently peeled away from the sclera. Retinas were transferred to a dissecting dish containing prewarmed (37°C), oxygenated (95% O₂, 5% CO₂) Kreb’s solution. Four radial cuts were made, equidistant around the circumference of the retinas to prevent them from curling or folding up during the whole-mounting procedure. Individual retinas were then transferred to a circular glass-bottomed recording bath (0.17-mm-thick base) mounted on the stage of an upright microscope (Eclipse FN1 model; Nikon, Kingston upon Thames, UK). The retinas were mounted whole, vitreous side up, using a nylon mesh and a tungsten wire ring, and continuously superfused at 4 mL/min with oxygenated Kreb’s medium at 37°C.

**Retinal Whole-Mount Imaging**

Retinal arterioles within whole-mount preparations were visualized using a water-immersion objective at ×20 magnification, with differential interference contrast (DIC) optics, and a charge-coupled–device camera (C7500; Hamamatsu, Hamamatsu, Japan). Arterioles were easily distinguished from venules based on their morphological features. Arterioles in the rat retina possess thick walls with a monolayer of circularly arranged vascular smooth muscle cells (Fig. 1A). In contrast, the venules are thin-walled with only a sporadic covering of mural myocytes (Fig. 1B). Capillaries were apparent as small-caliber vessels (4–10 μm in diameter), forming an interconnected network between the arterioles and venules (Fig. 1C). Drugs were delivered via a gravity-fed multichannel perfusion system ending with a single-outlet needle (350 μm in diameter) positioned adjacent to the vessel of interest. Images were captured and analyzed using NIS-Elements AR 3.0 image processing software (Nikon). The average luminal diameter of arterioles was calculated manually at each time point from 10 equispaced width measurements made along the entire vessel length in the field of view.

**Experimental Protocols**

A maximum of 4 arterioles were used from each animal (2 from each retina), and at least 5 animals were used per experimental protocol.

Due to the absence of myogenic tone in retinal whole mounts, arterioles were partially preconstricted with 10 nM endothelin (Et)-1 to enable both vasodilator and vasoconstrictor responses to be observed. Other drugs were not applied until a stable level of preconstriction had been achieved.

![Figure 1](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933598/)

**Figure 1.** Differential interference contrast images of an arteriole (A), venule (B), and capillary network (C) at the vitreal surface of the rat retina. Scale bars: 10 μM.

![Figure 2](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933598/)

**Figure 2.** Protocols used for neurotransmitter and GABA receptor agonist experiments (A) and GABA receptor antagonist experiments (B).
usually within ~15 minutes). All experiments with GABAergic compounds and other neurotransmitters were subsequently performed in the continued presence of Et-1.

For experiments using ATP, glutamate, GABA, and GABA agonists, drugs were applied until a stable response had occurred (~4–5 minutes), and vascular diameters were measured at the end of each minute (Fig. 2A). Drugs were then washed for 2 minutes in the continued presence of Et-1.

GABA antagonist experiments involved repeated GABA applications, first in the absence and then in the presence of the antagonist of interest (Fig. 2B). GABA was initially applied for 5 minutes, and vessel diameters were measured at the end of each minute. GABA was then washed out for 5 minutes, and GABA antagonists applied during the final minute of washout, prior to the addition of GABA plus antagonist, for 5 minutes.

**Isolated Retinal Arteriole Preparation**

Techniques used for retinal arteriole isolation have been described previously in detail. Isolated arterioles were placed in a recording chamber and visualized using the same microscopy set up as that used for the whole-mount studies. Arterioles were anchored with tungsten wire slips (50-μm diameter; 2-mm length), superfused with oxygenated Kreb’s medium at 37°C and preconstricted with 10 nM Et-1 prior to experimentation. Measurements of vessel diameter were made from digitized images, using NIS-Elements AR 3.0 software (Nikon).

**Müller Cell Immunohistochemistry**

Freshly enucleated rat eyes were placed in low Ca²⁺ Hanks’ solution, and the anterior segment lens complexes were removed. The posterior eyecup was fixated in 4% paraformaldehyde for 30 minutes and washed repeatedly in phosphate-buffered saline (PBS) for 4 hours. After fixation, eyecups were permeabilized with 0.5% Triton X-100 and blocked with 5% donkey or goat serum (Sigma-Aldrich, Poole, UK) for 4 hours at room temperature. Eyecups were incubated in primary antibody at a dilution of 1:1000 in permeabilization buffer overnight at 4°C and then washed extensively for 4 hours at room temperature. Incubation and wash steps were subsequently repeated using a 1:200 dilution of secondary antibody (Alexa Fluor 594 donkey anti-rabbit or goat anti-guinea pig immunoglobulin G (IgG; Invitrogen, Paisley, UK). Eyecups were incubated in primary antibody at a dilution of 1:1000 in permeabilization buffer overnight at 4°C and then washed extensively for 4 hours at room temperature. Incubation and wash steps were subsequently repeated using a 1:200 dilution of secondary antibody (Alexa Fluor 594 donkey anti-rabbit or goat anti-guinea pig immunoglobulin G (IgG; Invitrogen, Paisley, UK). Eyecups were then detached and incubated for 30 minutes in an enzyme solution consisting of 0.2 to 0.5 mg/mL papain (Sigma-Aldrich, Poole, UK) and 0.1 mg/mL DNase (Sigma-Aldrich) in PBS at 35°C. After washing in PBS, retinas were triturated using a fire-polished Pasteur pipette (internal tip diameter, ~0.3 mm) until single Müller cells were dissociated. Aliquots (200
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Solutions and Drugs

The Kreb's solution contained (mM): 133 NaCl; 4.7 KCl; 7.8 D-glucose; 2 CaCl₂; 2 MgCl₂; 1.35 NaHPO₄; and 6.3 Na₂HCO₃; maintained at pH 7.4 with 95% O₂–5% CO₂. Low-Ca²⁺ Hank’s solution was composed of (mM): 140 NaCl; 5 KCl; 5 D-glucose; 0.1 CaCl₂; 1.3 MgCl₂; and 10 HEPES at pH 7.4 with NaOH.

Et-1 (human and porcine), U46619, DL-2-Amino-5-phosphono pentanoic acid (DL-APV), GABA, muscimol, (-)-bicuculline methiodide, R-baclofen, SKF97761, and 2-hydroxysaclofen were purchased from Tocris Bioscience (Bristol, UK). Adenosine 5′-triphosphate (ATP) and glutamate were purchased from Sigma-Aldrich. GABA agonists were used at concentrations at least 4× above their respective half maximal effective concentration (EC₅₀) values. All GABAergic compounds were prepared as stock solutions in dimethylsulfoxide (DMSO). The final bath concentration of DMSO never exceeded 0.1%. At that concentration, DMSO had no effect on vessel diameter in any of the experimental protocols used in this study. 5-Methylimidazoleacetic acid was synthesized as previously described and dissolved directly in Kreb’s solution.

Data Analysis

Summary data are presented as either percentages or means ± SEM. Statistical analyses were performed using Prism 5 for Windows (GraphPad Software, San Diego, CA; Microsoft, Redmond, WA). Vessel diameter data were normally distributed as determined by the D’Agostino and Pearson omnibus normality test. To evaluate whether a significant vasodilator or vasoconstrictor response had occurred, the average vessel diameter immediately prior to drug addition was compared with the average diameter at each minute during the test period, using repeated measures one-way ANOVA with the Newman-Keuls post hoc test. All other comparisons were made using Student’s t-test, as indicated. Numbers in text (n) represent the number of arterioles examined. Differences in mean values were accepted as statistically significant at a P level of 0.05. In figures, significant differences are indicated as *P < 0.05; **P < 0.01; ***P < 0.001.
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RESULTS

Choice of Preconstrictor and Validation of the Retinal Whole-Mount Preparation

Et-1 (10 nM) was chosen as the preconstrictor agonist for this study as preliminary experiments showed that this peptide produced reliable and stable vasoconstrictor responses in rat retinal arterioles embedded within whole-mount preparations (mean arteriole diameters were 17.8 ± 1.9 μm and 11.5 ± 1.9 μm before and after 15 minutes’ exposure to Et-1; n = 15; P < 0.001, paired t-test). In previous work examining GABAergic regulation of arteriolar tone in the porcine retina, vessels were initially preincubated in the N-methyl-D-aspartate (NMDA) receptor antagonist DL-APV and subsequently preconstricted using the thromboxane A2 receptor agonist U46619 (in the continued presence of DL-APV). In rat retinal whole-mount preparations, however, we found that preincubation with 100 μM DL-APV followed by application of 1 μM U46619 failed to reach the retinal tissue as all of the arterioles tested responded with a reliable and stable vasoconstrictor response. Application of 100 μM U46619 failed to elicit any significant vasoconstrictor responses (Fig. 3A).

To investigate whether the GABA-evoked vasomotor responses observed were dependent upon the presence of an intact retinal neuropile, we undertook a set of experiments in which the remaining 53% of vessels (Fig. 4A). When the concentration of GABA was increased to 1 mM, a larger percentage of vessels responded, with 59% displaying vasodilation, 18% vasoconstriction, and 23% no response (Figs. 4A–E). Vasodilator, but not vasoconstrictor, responses to both concentrations of GABA were typically reversible following washout (compare Figs. 4D and 4E, respectively). In some whole-mount preparations, both vasodilator and vasoconstrictor responses to GABA were observed across different arterioles.

GABA-Evoked Vasomotor Responses

The effect of GABA on arterioles preconstricted with Et-1 in retinal whole-mount preparations was subsequently examined. Application of 100 μM GABA evoked vasodilation in 39% of vessels, vasoconstriction in 8%, and no response in the remaining 55% of vessels (Fig. 4A). When the concentration of GABA was increased to 1 mM, a larger percentage of vessels responded, with 59% displaying vasodilation, 18% vasoconstriction, and 23% no response (Figs. 4A–E).

Effects of GABA Receptor Agonists and Antagonists

To investigate the role of different GABA receptor types in mediating GABA-evoked vasomotor responses in the rat retina, we began by testing the effects of several GABA receptor-specific agonists with preconstricted arterioles in retinal whole-mount preparations (Fig. 5). Muscimol (10 μM), a GABA_A receptor agonist, caused vasodilation in 6% of vessels, vasoconstriction in 6%, and no response in the remaining 88% of vessels. In contrast, arteriolar responses to GABA_B receptor agonists more closely resembled those observed with GABA. Baclofen (100 μM) elicited vasodilation in 50% of vessels, whereas the remaining 50% exhibited no response. Application of SKF977541 (100 μM) induced vasoconstriction in 39% of vessels, vasoconstriction in 8%, and...
no response in the remaining 53%. The selective GABA<sub>C</sub> receptor agonist 5-methylimidazoleacetic acid (100 μM) failed to evoke a vasomotor response in any of vessels tested.

To more specifically examine the contribution of individual GABA receptor types to GABA-evoked changes in retinal arteriolar diameter, we performed a set of experiments using GABA receptor antagonists. As no responses were observed with the GABA<sub>C</sub> receptor agonist in our previous experiments, all later experiments focused only on the involvement of GABA<sub>A</sub> and GABA<sub>B</sub> receptors. In addition, because only a small number of vessels exhibited GABA-induced vasoconstrictor responses, this work was limited to an analysis of vasodilator reactions. Initial control experiments in the absence of any antagonists showed that vasodilator responses to 1 mM GABA were fully repeatable after a 5-minute washout period (Fig. 6). Following 1 minute’s incubation of the whole-mount preparations with the GABA<sub>A</sub> receptor blocker bicuculline (100 μM), 70% of vessels that had previously exhibited a vasodilator reaction to 1 mM GABA displayed a second, similarly sized response (Fig. 6). In contrast, in the presence of the GABA<sub>B</sub> receptor antagonist 2-hydroxysaclofen (100 μM), all vessels that had previously been responsive to GABA failed to exhibit a vasodilator response (Fig. 6).

Müller Glia Expression of GABA<sub>A</sub> and GABA<sub>B</sub> Receptors

The failure of GABA to evoke any vascular responses in isolated arterioles suggests it acts via intermediary, GABA-responsive neuroglial cells in the retina. Recent studies have shown that Müller cells play a pivotal role in mediating neurovascular signaling in the rat retina, and therefore we undertook immunolabeling studies to examine the expression levels of both GABA<sub>A</sub> and GABA<sub>B</sub> receptors on isolated rat retinal Müller cells. Isolated Müller cells were identified by their length (~100 μm) and by their characteristic bipolar morphology (Fig. 7). As demonstrated in fluorescence photomicrographs of Figures 7A and 7B, strong immunostaining for both GABA<sub>A</sub> and GABA<sub>B</sub> receptors was detected in rat retinal Müller cells. Both receptor proteins appeared to be evenly distributed across the entire cell length. When secondary control experiments were undertaken, all immunoreactivity disappeared (Fig. 7C).

GABAergic Control of Basal Arteriolar Diameter

In the final series of experiments, the possible contribution of endogenous GABA to the resting diameter of retinal arterioles was examined. In these experiments, bicuculline (100 μM) or 2-hydroxysaclofen (100 μM) was applied to retinal whole-mount preparations where the arterioles had not been preconstricted with Et-1. Blockade of GABA<sub>A</sub> receptors with bicuculline caused vasoconstriction in 1 of 20 arterioles, whereas blockade of GABA<sub>B</sub> receptors with 2-hydroxysaclofen induced vasoconstriction in 4 of 31 arterioles (Fig. 8).
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DISCUSSION

Results from the present study revealed that exogenous GABA can exert both vasodilator and vasoconstrictor effects on rat retinal arterioles through a pathway dependent upon the adjacent retinal neuropile. Our results, at least qualitatively, resemble previous findings in the isolated rat retina, showing that light and glial cell stimulation can evoke both vasodilator and vasoconstrictor responses in retinal arterioles. Results are also broadly consistent with previous findings in the brain, where heterogeneity in both blood flow and vasomotor responses to GABAergic stimulation have been reported.

In an attempt to delineate the class of receptor responsible for mediating the effects of GABA on vasomotor responses in rat retinal arterioles, experiments were carried out using relevant agonists and antagonists. Based on these studies, our data strongly suggest that the complex effects of GABA on the diameter of rat retinal arterioles occur principally through GABAA receptors but notwithstanding a contribution by GABAB receptors. Our findings that both GABAA and GABAB receptor agonists are capable of triggering both vasodilator and vasoconstrictor responses in rat retinal arterioles contrast with those of previous studies in rat hippocampal brain slice preparations, where selective activation of each receptor type evokes distinct vasomotor responses. Application of the GABAA receptor agonist muscimol elicited vasodilation in hippocampal microvessels, whereas the GABAB receptor agonist baclofen elicited vasoconstriction. Discrepancies between brain and retinal microvessels could be attributed to differences in GABAergic signaling mechanisms operating in different regions of the central nervous system, but our receptor pharmacology data are also markedly different from those in previous studies examining GABA-induced vasorelaxation in the porcine retina. GABA-evoked dilation of porcine retinal arterioles has been reported to be mediated by the GABAA receptor in perivascular retinal tissue, with no involvement of GABAB or GABAC receptors. Although differences between our results and those of Bek and Holmgaard in the porcine retina could be related to the type of preconstrictor agonist used, we were unable to directly test this in rat retinal whole mounts, as arterioles in these preparations failed to display significant vasoconstrictor responses in the presence of U66619 and the NMDA receptor antagonist DL-APV. They might, however, simply reflect species differences in the mechanisms underlying GABAergic neurovascular signaling between the rat and the porcine retina. Such differences highlight the need for a detailed analysis of the role of GABA in the regulation of arteriolar diameter in the human retina as well as in other species.

One obvious question that arises from the current study is how does the activation of GABAA and/or GABAB receptors in the retinal neuropile result in both vasodilator and vasoconstrictor effects in rat retinal arterioles? Although further studies are clearly needed to fully address this question, our data suggest that Müller cells could potentially be involved. Müller cells have end-feet processes that surround retinal arterioles, and recent studies have shown that these cells can induce either vasodilator or vasoconstrictor responses in rat retinal arterioles in response to the same stimuli. Consistent with the idea that Müller cells could contribute to GABA-evoked changes in retinal arteriolar diameter, we have demonstrated immunoreactivity for both GABAA and GABAB receptors on isolated rat retinal Müller cells. GABAA and GABAB receptor expression levels have previously been reported in Müller cells from several species, although to the best of our knowledge, the present study represents the first report of their expression in rat retinal Müller cells. It is worth stressing, however, that Müller cells may not be the only cell type involved in mediating GABA-induced vasomotor responses in the rat retina. Many types of neurons in the retina express GABAA and GABAB receptors, and GABA could potentially exert its vascular effects through modulation of retinal neuronal activity. Also, in both the brain and the retina, astrocytes and their end-feet processes envelop blood vessels and have been implicated in vascular tone regulation. Nonetheless, although GABA receptors have been reported on astrocytes in the brain, there is currently little evidence for the presence of these receptors on retinal astrocytes, with the exception of those situated on the vitreal surface of the rabbit visual streak.

The physiological relevance of the GABA-evoked changes in retinal arteriolar diameter observed in the present study requires further clarification. It is notable that high concentrations of GABA were necessary to elicit vasoactive effects, indicating perhaps that this vasoregulatory pathway may be of more importance during pathophysiological rather than physiological processes in the retina. Under hypoxic or ischemic conditions, for example, GABA release from retinal neurons is increased and GABA accumulates both extracellularly and in retinal Müller cells. At the present time, however, we cannot fully rule out the possibility that the requirement for high GABA concentrations may have resulted from diffusion barriers between the tissue bath and possible sites of action inside the retinal tissue. In studies designed to examine the role of endogenous GABA in the control of retinal arteriolar diameter, GABAA and GABAB receptor antagonists failed to elicit significant vascular responses in all but a very small proportion of vessels (Fig. 8). These findings suggest that endogenous GABA is unlikely to be an important regulator of resting vascular diameter and blood flow in the retina, at least under basal physiological conditions. It should be noted, however, that in the absence of Et-1, rat retinal arterioles appear fully dilated in whole-mount preparations. Because further dilation from a fully dilated state is impossible, in these experiments we were limited to the assessment of vasoconstrictor responses to GABA antagonists and thus vasodilator effects of endogenous GABA. For this reason, using this preparation, we are at present unable to completely exclude a possible vasoconstrictor contribution of endogenous GABA to the regulation of the resting state of rat retinal arterioles.

In summary, our data suggest that GABA is capable of eliciting both vasodilator and vasoconstrictor responses in the retina. These responses appear to be mediated primarily by GABAB receptors in the perivascular retinal tissue but do not exclude some contribution by GABAA receptors. While the exact cells involved in mediating the effects of GABA on retinal arteriolar diameter remain uncertain, we have demonstrated that rat retinal Müller cells express both GABAA and GABAB receptors. Given their well-established role in mediating neurovascular signaling in the retina, these cells represent possible candidates for initiating the GABA-evoked vascular reactions observed in this study. Defining the functional significance of GABAergic modulation of retinal arteriolar diameter remains an important challenge for the future, but such studies could lead to a much better understanding of the mechanisms underlying blood flow regulation in the retina under both health and disease conditions.

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