Pharmacological coupling and functional role for CGRP receptors in the vasodilation of rat pial arterioles

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Hong, Ki Whan, Sung-Eun Yoo, Sung Suk Yu, Jung Yoon Lee, and Byung Yong Rhim. Pharmacological coupling and functional role for CGRP receptors in the vasodilation of rat pial arterioles. *Am. J. Physiol.* 270 (*Heart Circ. Physiol.* 39): H317–H323, 1996.—In this study, we investigated the signal transduction underlying the vasodilator action of calcitonin gene-related peptide (CGRP) in the rat pial arterioles. In an in vivo experiment, changes in pial arterial diameters (20.2 ± 1.9 μm) were observed under suffusion with mock cerebrospinal fluid containing CGRP (10^{-9}–10^{-7} M) directly through a closed cranial window. Changes in intracellular adenosine 3′,5′-cyclic monophosphate (cAMP) accumulation in response to CGRP and levcromakalim were measured in the pial arterioles in an in vitro experiment. CGRP-induced vasodilation and cAMP production were significantly inhibited by specific CGRP antibody serum and CGRP-(8—37) fragment, suggesting involvement of the $CGRP_1$ receptor subtype. Vasodilation and increase in cAMP production evoked by CGRP were inhibited not only by glibenclamide (ATP-sensitive K^+ channel blocker) but also by charybdotoxin (large-conductance Ca^{2+}-activated K^+ channel blocker), but this was not the case for the isoproterenol-induced vasodilation and cAMP production. These findings implicate the ATP-sensitive K^+ channels and the large-conductance Ca^{2+}-activated K^+ channels in the CGRP receptor-coupled cAMP production for vasodilation. Further study is required to identify whether the cAMP-dependent K^+ channel activation is related to CGRP-induced vasorelaxation of the rat pial arterioles.

calcitonin gene-related peptide; adenosine 3′,5′-cyclic monophosphate; potassium channels

A GROWING BODY OF EVIDENCE has demonstrated that calcitonin gene-related peptide (CGRP) exerts an extremely potent vasodilating effect on the cerebral artery in vitro (7, 29) and on the pial artery in situ (20, 34). In the cerebral vessels, CGRP-immunoreactive nerve fibers are demonstrated in all major arteries and cortical arterioles, including human pial arterioles (8). CGRP has been proposed as a candidate neurotransmitter involved in nonsympathetic neurogenic vasodilation of the cerebral vascular bed (1, 29).

It is widely known that activation of ATP-sensitive K^+ channels is an important mechanism of many vasodilators (24, 26). The vasodilator effect of CGRP is mediated in part via activation of ATP-sensitive K^+ channels (25) in contrast to other arteries (27). Recently, we reported that CGRP is implicated in cerebral autoregulation; that is, CGRP, which is reflexly released from perivascular sensory fibers in response to a transient hypotension, mediates the vasodilation of rat pial arterioles, and the vasodilatory effect of CGRP is associated with an activation of ATP-sensitive K^+ channels (14, 18). Recently, Kitazono et al. (16) reported that activation of ATP-sensitive K^+ channels in the rat basilar artery was mediated by an adenosine 3′,5′-cyclic monophosphate (cAMP)-dependent mechanism in the CGRP-induced vasodilation. On the other hand, the vasodilator response to CGRP has been correlated with increases in cAMP and guanosine 3′,5′-cyclic monophosphate (7, 17). However, the dependency of CGRP-induced vasodilation on the endothelium is reportedly not consistent among species and among organs (2, 7, 12).

In the present study, we investigate the important target of signal transduction mechanisms underlying the vasodilator action of CGRP in the rat pial arterioles. We have measured two parameters in the response to CGRP: *1*) the changes in the luminal diameter of pial arterioles in the in vivo experiment and *2*) the changes in cAMP production in the pial arterioles in the in vitro experiment in the absence and presence of K^+ channel blockers, because it has been documented that the relaxant effects of CGRP on the vascular smooth muscles are inhibited by glibenclamide (25). The results induced by CGRP were compared with those evoked by isoproterenol and levcromakalim. In particular, the biochemical action (activation of adenyl cyclase) of CGRP was correlated with its functional effect (vasodilation) in the rat pial arterioles.

MATERIALS AND METHODS

Preparation of Animals

Sprague-Dawley rats (250–300 g) were anesthetized with urethan (1 g/kg ip) and placed on a heating pad to maintain a constant body temperature. After a tracheostomy was performed, each rat was ventilated with a respirator (model 683, Harvard) with room air. The left femoral artery was cannulated with PE-50 polyethylene tubing for monitoring blood pressure (Statham P23D pressure transducer). Arterial blood was collected through the left carotid artery before and after installation of a cranial window for blood gas and pH determination (STAT Profile 3, Nova Biomedicals). The mean arterial blood gases and pH determined during experiments were as follows: pH, 7.37 ± 0.01; arterial P_{CO_2}, 31.3 ± 1.6 mmHg; arterial P_{O_2}, 98.0 ± 2.2 mmHg. Rectal temperature was monitored continuously and kept constant (37 ± 0.5°C) with a heating pad.

Measurement of Vessel Diameter

Pial microvessels were visualized through an implanted cranial window, as described previously (14). Briefly, the head

was fixed in the prone position with a stereotaxic apparatus (Stoelting), and a square (5 × 5-mm) craniotomy was made over the right parietal cortex. The dura was opened, and the burr hole was covered with warmed mineral oil during the operation. Pial precapillary microvessels (15–25 μm) were visualized through the implanted cranial window. Cerebral microvessels were allowed to equilibrate for 60 min after installation of the cranial window. The window field was suffused with mock cerebrospinal fluid (CSF) at 0.3 ml/min. The image of pial vessels was captured with a CCD videocamera (Sanyo, VDC 3900) through a stereoscope (model SMZ-2T, Nikon) and fed to a television monitor for direct observation, and the caliber was measured using a width analyzer (Hamamatsu) at ×480 magnification. The composition (mM) of the mock CSF was as follows: 125 NaCl, 3.5 KCl, 1.3 $CaCl_2$, 1.1 $MgCl_2$, and 25 $NaHCO_3$. The intracranial pressure was maintained constant at 5–6 mmHg throughout the experiment by adjusting the height of the free end of the plastic tubing, which was connected to the outlet of the window. In each rat, only one arteriole was observed under the window.

Protocols of In Vivo Experiment

1) We identified the normal autoregulatory response of the pial artery to a decline in arterial blood pressure by bleeding the blood into the reservoir and to a rise in blood pressure by infusing the blood under suffusion with mock CSF over the cerebral cortical surface. *2*) We observed the vasodilator responses of the resting pial vessels to CGRP suffused with the mock CSF. Each concentration of drug was suffused over the cortical surface for 3 min. *3*) The inhibitory effects of CGRP antibody serum (1:1,000) and CGRP-(8—37) fragment (10^{-8} M) on the CGRP-induced vasodilation were identified. The change in luminal diameter was monitored with a width analyzer every 4 s. *4*) Furthermore, to see the inhibitory effects of the K^+ channel blockers glibenclamide and charybdotoxin, they were applied from 30 min before suffusion of CGRP or other agonists.

Cyclic Nucleotide Determination

Rats (Sprague-Dawley, 250–300 g) were anesthetized with ether and killed by bleeding from carotid arteries. By direct observation under a stereoscope, the pial artery and its branches (20–30 μm diameter) were dissected from the surface of the cerebral cortex, the adhering extravascular tissue was removed, and the intraluminal cell components were cleaned by perfusion with mock CSF. Adenyl cyclase activity was measured on the pial arterioles, as described by Edwards et al. (9). The tissues were subjected to freezing and thawing twice in liquid nitrogen and finally stored overnight in liquid nitrogen. The tissues were incubated for 30 min in the working buffer consisting of (in mM) 100 tris(hydroxymethyl)aminomethane, 4.0 $MgCl_2$, 0.25 EDTA, 1.0 3-isobutyl-1-methylxanthine, 0.3 ATP, 0.1 guanosine 5′-triphosphate, and 20 phosphocreatine and 200 U/ml creatine kinase (pH 7.4 at 30°C) without and with drugs. The incubation was stopped by addition of 0.2 N HCl (50 μl) and freezing in liquid nitrogen. Thereafter, the pH of the buffer was readjusted by addition of 0.2 N NaOH and sodium acetate buffer. cAMP was measured with a radioimmunoassay kit purchased from Amersham Life Science Products. The activity of adenyl cyclase was expressed as femtomoles of cAMP per square millimeter of arteriole surface per 30 min.

Drugs

CGRP (Sigma Chemical), CGRP-(8—37) (Peninsula), and charybdotoxin (Peptide Institute) were dissolved in 0.1% bovine serum albumin to make a stock solution of 0.1 mM. Rabbit antiserum to rat CGRP (Cambridge Research Biochemicals) was diluted with mock CSF. Glibenclamide (Sigma Chemical) was sonicated in 1 ml of NaOH (0.1 N) and diluted with 5% glucose to make a stock solution of 10 mM. Isoproterenol HCl and forskolin were purchased from Sigma Chemical. Levcromakalim was donated by Korea Research Institute of Chemical Technology.

Statistics

Results are expressed as means ± SE. Statistical significance was determined by Student's *t*-test between two groups in the measurement of cAMP levels, and analysis of variance was used for comparisons of the results of vasodilators in the absence and presence of antagonists. $P < 0.05$ was considered to be statistically significant.

RESULTS

In control rats, mean arterial blood pressure was 115.7 ± 2.5 mmHg (n = 48) and the resting diameter of pial arteriole was 20.2 + 1.9 μm, which was constant throughout the experiment unless there was bleeding or an infusion of blood.

Table 1 compares effects of CGRP and levcromakalim on the changes in luminal diameter of pial arterioles. When cortical surface was suffused with mock CSF containing CGRP (10^{-9}–10^{-7} M) and levcromakalim (10^{-7} and 10^{-6} M), by increasing each concentration, the diameter of pial arterioles was remarkably increased in a concentration dependent manner (Fig. 1, Table 1). After 30 min of continuous suffusion with normal mock CSF, the luminal diameter returned almost to the original control value (21.5 ± 3.1 μm). The maximum responses occurred at 10^{-7} M CGRP and 10^{-6} M levcromakalim. The maximum diameters were 28.0 ± 2.2 (n = 15, 38.6%) and 27.4 ± 2.2 μm (n = 4, 38.4%), respectively.

Changes in Diameter in In Vivo Experiment

Effects of CGRP antibody serum and CGRP-(8—37). The CGRP-induced vasodilation was significantly inhibited under suffusion with mock CSF containing CGRP antibody serum (1:1,000) and CGRP-(8—37) fragment (10^{-8} M) from 30 min before the experiment (Fig. 2). Application of CGRP antibody serum or CGRP-(8—37)

Table 1. *Concentration-dependent increase in diameter of pial arterioles under suffusion with mock CSF containing CGRP and levcromakalim in rats*

Diameter	Control	n	Concentration, M 10^{-9}	10^{-8}	10^{-7}	10^{-6}
			CGRP			
μm	20.2 ± 1.9	15	19.9 ± 2.1	23.7 ± 2.1*	28.0 ± 2.2*	
%Δ			−1.5	17.3	38.6	
			Levcromakalim			
μm	19.8 ± 5.5	4			22.6 ± 6.1*	27.4 ± 2.2*
%Δ					14.1	38.4

Values are means ± SE; n, no. of experiments. CSF, cerebrospinal fluid; CGRP, calcitonin gene-related peptide. *$P < 0.05$ vs. control.

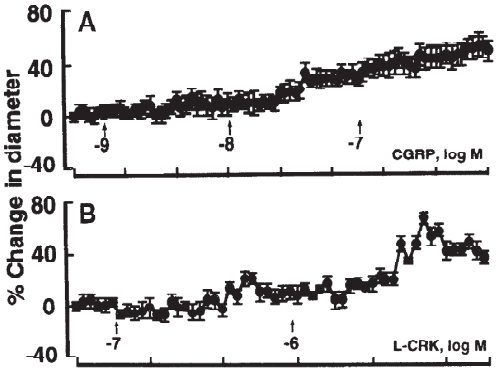

Fig. 1. Concentration-dependent increase in diameter of rat pial arterioles under suffusion with mock cerebrospinal fluid containing calcitonin gene-related peptide (CGRP, 10^{-9}–10^{-7} M, $n = 15$; *A*) and levcromakalim (L-CRK, 10^{-7} and 10^{-6} M, $n = 4$; *B*). Values are means ± SE.

fragment itself did not significantly affect the vessel diameter (Table 2).

Effect of K^+ channel antagonists on CGRP-induced vasodilation. The vasodilation induced by CGRP (10^{-9}–10^{-7} M) and levcromakalim (10^{-7} and 10^{-6} M), a K^+ channel opener, was significantly inhibited under previous suffusion with glibenclamide (10^{-5} M), an ATP-sensitive K^+ channel antagonist, or charybdotoxin (3×10^{-7} M), a large-conductance Ca^{2+}-activated K^+ channel antagonist, respectively (Figs. 3 and 4). Suffusion with mock CSF containing glibenclamide or charybdotoxin from 30 min before the experiment did not affect the resting diameter of pial arteries (Table 2). These results implicate the Ca^{2+}-activated K^+ channels and the ATP-sensitive K^+ channels in the vasodilation evoked by CGRP and levcromakalim.

Table 2. *Effects of glibenclamide and charybdotoxin, K^+ channel blockers, and CGRP-(8—37) and CGRP antibody serum, CGRP antagonists, on diameter of rat pial arterioles*

Antagonists	*n*	Control Diameter, μm	Change in Diameter, μm	%Change in Diameter
Glibenclamide (10^{-5} M)	8	21.1 ± 4.4	18.7 ± 3.2	−1.3 ± 1.4
Charybdotoxin (3×10^{-7} M)	9	20.9 ± 3.2	19.5 ± 2.2	−3.3 ± 4.7
CGRP-(8—37) (10^{-8} M)	5	17.4 ± 1.8	18.5 ± 3.1	0.3 ± 5.0
CGRP antibody serum (1:1,000)	4	21.8 ± 1.8	22.3 ± 2.3	2.0 ± 4.3

Values are means ± SE; *n*, no. of experiments.

Effect of K^+ channel antagonists on the vasodilation by isoproterenol. When the cortical surface was suffused with mock CSF containing isoproterenol (10^{-6} M), the luminal diameter was increased in a concentration-dependent manner. The vasodilation induced by isoproterenol (10^{-6} M), however, was not inhibited by glibenclamide (10^{-5} M) and charybdotoxin (3×10^{-7} M; Fig. 5).

Changes in cAMP Production in In Vitro Experiments

In another series of experiments, we compared the effects of CGRP (10^{-7} and 10^{-6} M) and levcromakalim (10^{-6} M) on the stimulation of adenyl cyclase. Significant stimulation ($P < 0.05$) was observed with 10^{-6} M CGRP but not with 10^{-6} M levcromakalim (Fig. 6).

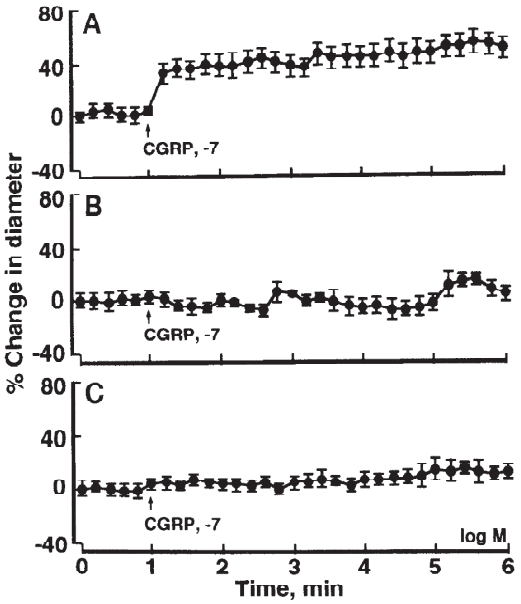

Fig. 2. Effect of suffusion with CGRP (10^{-7} M)-containing mock cerebrospinal fluid in absence (*A*) and presence of specific CGRP antibody serum (1:1,000; *B*) or CGRP-(8—37) (10^{-6} M) fragment (*C*). Values are means + SE from 5–6 experiments.

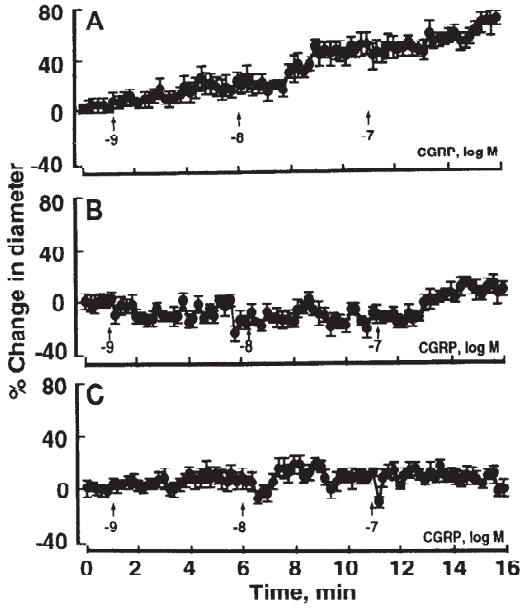

Fig. 3. Effect of suffusion with CGRP (10^{-9}, 10^{-8}, and 10^{-7} M)-containing mock cerebrospinal fluid in absence (*A*) and presence of glibenclamide (10^{-5} M; *B*) or charybdotoxin (3×10^{-7} M; *C*). Values are means + SE from 5 experiments.

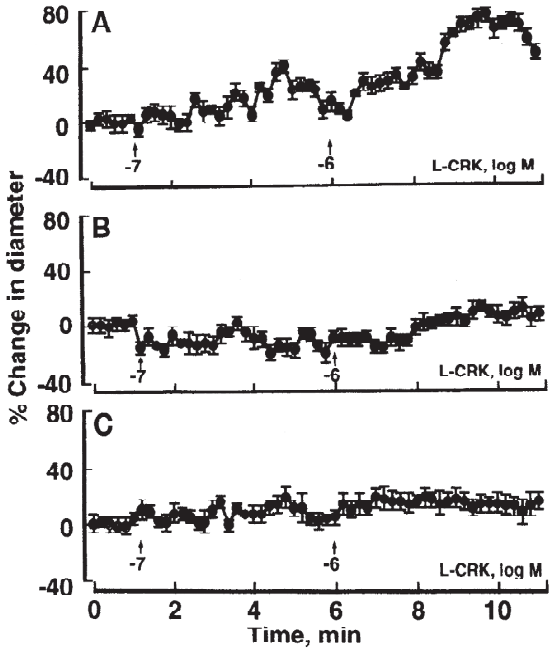

Fig. 4. Effect of suffusion with levcromakalim (L-CRK, 10^{-7} and 10^{-6} M)-containing mock cerebrospinal fluid in absence (*A*) and presence of glibenclamide (10^{-5} M; *B*) or charybdotoxin (3×10^{-7} M; *C*). Values are means ± SE from 4 experiments.

When the pial arteriole was incubated in the depolarizing physiological salt solution (60 mM K^+) containing 10^{-6} M CGRP, the CGRP-induced increase in cAMP production was not altered (data not shown).

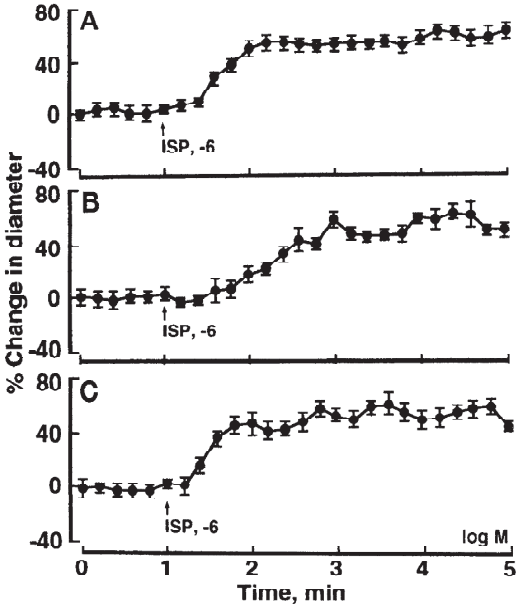

Fig. 5. Effect of suffusion with isoproterenol (ISP, 10^{-6} M) included in mock cerebrospinal fluid without (*A*) and with pretreatment with glibenclamide (10^{-5} M; *B*) or charybdotoxin (3×10^{-7} M; *C*). Values are means + SE from 7 experiments.

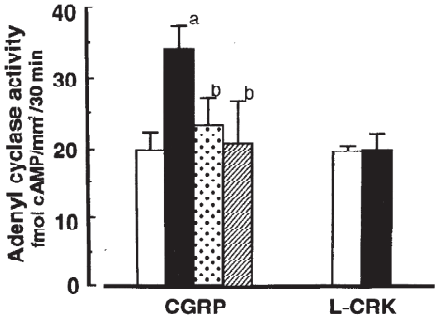

Fig. 6. Effects of CGRP (10^{-6} M, *left*) and levcromakalim (L-CRK, 10^{-6} M, *right*) on adenyl cyclase activity and inhibition by CGRP antibody serum (1:1,000) and CGRP-(8—37) fragment (10^{-6} M) of CGRP (10^{-6} M)-induced stimulation of cAMP production in rat pial arterioles. Open bars, control; filled bars, CGRP or L-CRK; stippled bars, +CGRP antiserum; hatched bars, +CGRP (8—37). Values are means ± SE from 4–5 experiments. $^aP < 0.05$ vs. control; $^bP < 0.05$ vs. CGRP alone.

Effects of CGRP antibody serum and CGRP-(8—37) fragment. CGRP (10^{-7} and 10^{-6} M) caused a significant increase in cAMP production in the pial arterioles from 19.9 ± 2.8 (basal level) to 29.5 ± 3.5 and 37.8 ± 5.1 fmol·mm^{-2}·30 min^{-1}, respectively ($P < 0.05$). The increase in cAMP production induced by CGRP (10^{-6} M) was significantly inhibited by pretreatment with CGRP antibody serum (1:1,000; $P < 0.05$) or CGRP-(8—37) fragment (10^{-6} M, $P < 0.05$), implicating cAMP in the CGRP-induced vasodilation of the pial arterioles (Fig. 6).

Effect of K^+ channel antagonists on cAMP production. The CGRP-induced increase in cAMP levels was significantly inhibited by charybdotoxin (3×10^{-7} M) as well as by glibenclamide (10^{-5} M; Fig. 7). However, the increase in cAMP production induced by isoproterenol (10^{-6} M) was not blocked by glibenclamide (10^{-5} M) or by charybdotoxin (3×10^{-7} M; Fig. 7).

DISCUSSION

The major findings of this study in the rat pial arterioles are as follows: *1*) the CGRP receptors mediating vasodilation and stimulation of cAMP accumula-

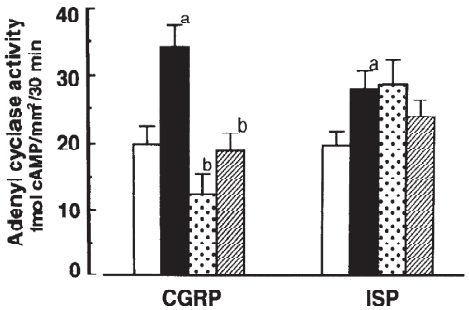

Fig. 7. Effects of K^+ channel blockers glibenclamide (10^{-5} M) and charybdotoxin (3×10^{-7} M) on CGRP (10^{-6} M, *left*)- and isoproterenol (ISP, 10^{-6} M, *right*)-induced stimulation of adenyl cyclase in rat pial arterioles. Open bars, control; filled bars, CGRP or ISP; stippled bars, + glibenclamide; hatched bars, +charybdotoxin. Values are means ± SE from 4–5 experiments. $^aP < 0.05$ vs. control; $^bP < 0.05$ vs. CGRP only.

tion in response to CGRP belonged to the $CGRP_1$ receptor subtype, *2*) vasodilation and accumulation of intracellular cAMP in response to CGRP were markedly inhibited by the K^+ channel blockers, and *3*) isoproterenol-induced stimulation of adenyl cyclase activity and vasodilation was not inhibited by the K^+ channel blockers. In these experiments, we employed glibenclamide (an ATP-sensitive K^+ channel blocker) (30) and charybdotoxin (a large-conductance Ca^{2+}-activated K^+ channel blocker) (11) to characterize a causative relationship between K^+ channel activation and cAMP accumulation in response to CGRP. In our experiments, to ensure that identical arterioles are sampled, the pial arterioles of the cerebral surface that were used for in vivo experiments were dissected and utilized.

Our results showed that arterial diameter and adenyl cyclase activity of the pial arterioles were increased by CGRP. These CGRP effects were significantly antagonized under suffusion with immunoreactive specific antibody serum for CGRP and a COOH-terminal fragment CGRP-(8—37) $CGRP_1$ receptor antagonist (6). These results indicate that the CGRP receptors that are present on the rat pial arterioles and mediate vasodilation and cAMP production appear to be of the $CGRP_1$ subtype.

Recently, much evidence suggests that activation of ATP-sensitive K^+ channels and Ca^{2+}-activated K^+ channels exerts an important role in vasodilation (24, 26). Nevertheless there is some controversy over whether the K^+ channel openers exert relaxation in the rat cerebral vasculature. McCarron et al. (19) and McPherson and Stork (21) reported that K^+ channel openers did not relax the small-resistance arteries from the rat cerebral vessels, whereas Nagao et al. (23) demonstrated cromakalim-induced relaxation of the rat posterior cerebellar artery. We have shown that levcromakalim exerted a strong vasodilator effect, which was markedly inhibited not only by glibenclamide but also by charybdotoxin, suggesting that the vasorelaxation to levcromakalim appears to result from the presence and activation of the ATP-sensitive K^+ channels and the Ca^{2+}-activated K^+ channels in the pial arterioles. Several different K^+ channels were demonstrated to be responsible for the actions of K^+ channel openers in various vascular beds (10, 15, 32). Furthermore it is known that, in vivo, the pressure drop is larger and the regulatory processes are more important in the microvasculature than in large cerebral arteries (22). Therefore the large regional difference in the responses of cerebral arteries might be very dependent on the situation of the tissues, for example, in vivo vs. in vitro or different preexisting conditions (e.g., depolarization or contracting state).

We have shown that the CGRP-induced vasodilation was inhibited by not only glibenclamide but also charybdotoxin, as was the levcromakalim-induced vasodilation. Glibenclamide and charybdotoxin showed no additive action on the CGRP-induced vasodilation. It is not known how ATP-sensitive K^+ channels and large-conductance Ca^{2+}-activated K^+ channels are activated by CGRP in the pial arterioles. Carl et al. (4) demonstrated that, in cell-attached patches from canine colon cells, levcromakalim increased the open probability of large-conductance Ca^{2+}-activated K^+ channels, which were prevented by glibenclamide and tetraethylammonium. Thus further study is required to identify electrophysiologically whether the K^+ channels activated by CGRP in the pial arteries share the properties of ATP-sensitive K^+ channels and Ca^{2+}-regulated K^+ channels. Recently, Trezise and Weston (33) compared the relaxant and hyperpolarizing actions of CGRP with those of BRL-38227 (levcromakalim) in the rabbit basilar arteries. They reported that CGRP consistently evoked a glibenclamide-inhibitable hyperpolarization, though it was less than that evoked by BRL-38227.

Vasorelaxation induced by CGRP has been proposed to be mediated by two interesting pharmacological actions: *1*) stimulation of adenyl cyclase activity with a subsequent accumulation of intracellular cAMP (7, 9) and *2*) activation of the K^+ channels and subsequent hyperpolarization (25, 35). The role of the K^+ channels was reported in the vascular response to several endogenous vasodilators (1, 3).

We have shown that CGRP significantly stimulated the adenyl cyclase activity with subsequent accumulation of intracellular cAMP in the pial arterioles. This CGRP effect on cAMP production was markedly inhibited by glibenclamide and charybdotoxin. These findings strongly support a role for the ATP-sensitive K^+ channels and the large-conductance Ca^{2+}-activated K^+ channels in the CGRP receptor-coupled cAMP production and vasorelaxation. In support of this conclusion is the recent report (31) that a hyperpolarization-activated K^+ conductance of the cell membrane of *Paramecium* directly stimulates adenyl cyclase activity as a carrier of the K^+ resting conductance. However, it has not been reported whether the K^+ conductance-coupled cAMP-producing system exists in the smooth muscle cells. We have shown that CGRP-induced stimulation of adenyl cyclase activity was not affected by levcromakalim, a hyperpolarizing agent, or by depolarizing physiological salt solution (60 mM K^+). It is likely that the activation of adenyl cyclase is not influenced by a change in membrane potential but is linked to an adjacent K^+ channel by an unknown mechanism. It is not clear how CGRP increases the K^+ conductance in the pial arterioles and whether the two K^+ channels act independently or cooperatively.

Recently, Nelson et al. (25) showed that CGRP activates an ATP-sensitive K^+ channel in single smooth muscle cells from rabbit mesenteric artery, and Edwards et al. (9) suggested that CGRP receptors in vascular smooth muscle are coupled to adenyl cyclase. Thus it is considered that activation of adenyl cyclase is closely linked to the K^+ channels in vascular smooth muscle cells. However, we do not know whether the K^+ channel blockers such as glibenclamide and charybdotoxin directly block the CGRP receptors. Additional in vitro studies are needed to identify a causative relationship between the inhibition of adenyl cyclase activity and CGRP receptors by these K^+ channel blockers,

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