Role of K⁺ channels in adrenal catecholamine secretion in anesthetized dogs

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Nagayama, Takahiro, Kimiya Masada, Makoto Yoshida, Mizue Suzuki-Kusaba, Hiroaki Hisa, Tomohiko Kimura, and Susumu Satoh. Role of K⁺ channels in adrenal catecholamine secretion in anesthetized dogs. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R1125–R1130, 1998.—We examined the role of K⁺ channels in the secretion of adrenal catecholamine (CA) in response to splanchnic nerve stimulation (SNS), acetylcholine (ACh), 1,1-dimethyl-4-phenyl-piperazinium (DMPP), and muscarine in anesthetized dogs. K⁺ channel blockers and the cholinergic agonists were infused and injected, respectively, into the adrenal gland. The voltage-dependent K⁺ channel (Kᵥ type) blocker mast cell degranulating (MCD) peptide infusion (10–100 ng/min) enhanced increases in CA output induced by SNS (1–3 Hz), but it did not affect increases in CA output induced by ACh (0.75–3 µg), DMPP (0.1–0.4 µg), or muscarine (0.5–2 µg). The small-conductance Ca²⁺-activated K⁺ (SKCa) channel blocker scyllatoxin infusion (10–100 ng/min) enhanced the ACh-, DMPP-, and muscarine-induced increases in CA output, but it did not affect the SNS-induced increases in CA output. These results suggest that Kᵥ channels may play an inhibitory role in the regulation of adrenal CA secretion in response to SNS and that SKCa channels may play the same role in the secretion in response to exogenously applied cholinergic agonists.

adrenal gland; mast cell degranulating peptide; scyllatoxin; voltage-dependent potassium channels; small-conductance calcium-activated potassium channels

THE CATECHOLAMINE (CA) secretion from the adrenal medulla is controlled by splanchnic nerve-innervating chromaffin cells. Activation of the splanchnic nerve causes the release of acetylcholine (ACh) from its terminal into the intrasynaptic cleft, which subsequently activates nicotinic receptors of the adrenal medullary chromaffin cells. Stimulation of nicotinic receptors depolarizes the chromaffin cell membrane, and the resulting depolarization causes Ca²⁺ influx through the opening of voltage-dependent Ca²⁺ channels (5, 6). The elevation of intracellular Ca²⁺ triggers the exocytotic secretion of adrenal CA (8). The membrane depolarization may activate voltage-dependent K⁺ channels, leading to the facilitation of repolarization, and the elevation of intracellular Ca²⁺ may activate Ca²⁺-activated K⁺ channels, leading to hyperpolarization. The facilitation of repolarization or hyperpolarization may cause the inhibition of further influx of Ca²⁺. Therefore, blockade of K⁺ channels is thought to facilitate the depolarizing phase and results in the enhancement of adrenal CA secretion through the increase in Ca²⁺ influx.

Materials and Methods

Animal preparation. Mongrel dogs of either sex, weighing 8–12 kg, were anesthetized intravenously with 30 mg/kg of pentobarbital sodium, and a constant level of anesthesia was then maintained by an intravenous infusion of pentobarbital sodium at a rate of 6 mg·kg⁻¹·h⁻¹ with an infusion pump (201B; Atom, Tokyo, Japan). Artificial respiration was performed by means of a respiration pump (model 607; Harvard Apparatus, Millis, MA), with room air being administered at 18 strokes/min (20 ml/kg tidal volume). The surgical procedure used in the present study was described previously (14). The left adrenal gland was exposed by a retroperitoneal flank incision, and a polyethylene cannula was inserted into the left adrenolumbar vein for collection of the venous effluent blood from the adrenal gland. A thread was placed around the juncture of the adrenolumbar vein and the abdominal vena cava. Adrenal blood samples were obtained by pulling the thread, thus occluding the adrenolumbar vein and causing a retrograde flow of blood to ensue. The 1- or 2-ml blood samples were collected in chilled test tubes containing disodium EDTA. When it was not being sampled, adrenal venous blood was returned directly to the vena cava. Coagulation of

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blood was prevented by an initial intravenous injection of sodium heparin (500 U/kg) and hourly intravenous injections of 100 U/kg. Systemic blood pressure and heart rate were measured by a pressure transducer (MPU-0.5, Nihon Kohden, Tokyo, Japan) and a carotidocatheter (RT-5, Nihon Kohden), respectively, and were recorded on a heat-writing oscillograph (R) G-4128, Nihon Kohden).

A peripheral infusion of drugs was performed during the study period of SNS. The left splanchnic nerves were dissected free from surrounding tissue and cut. A bipolar platinum electrode was placed in contact with the distal end of the splanchnic nerves. The splanchnic nerves were stimulated with rectangular pulses of 1 ms and 10 V (supramaximal voltage) delivered by an electronic stimulator (SEN-1101, Nihon Kohden) and an isolation unit (SS-101J, Nihon Kohden). Stimuli were applied at 1 Hz for 2 min and subsequently at 2 Hz for 2 min and 3 Hz for 2 min during a 6-min stimulus period.

Experimental protocol. The dogs were divided into eight groups (groups 1-4 and groups 5-8, MCD peptide and scyllatoxin experiments, respectively). In group 1 (n = 6), the effect of MCD peptide on the SNS-induced increase in CA output was examined. SNS was repeated at 30 min intervals. The first SNS trial during the infusion of 0.9% saline solution into the adrenal gland was regarded as a control. MCD peptide infusions (10, 30, and 100 ng/min) were started 5 min before the start of the second, third, and fourth SNS, respectively. In group 2 (n = 6), the effect of MCD peptide on the ACh-induced increase in CA output was examined. A set of ACh injections (0.75, 1.5, and 3 µg) into the adrenal gland was repeated at 40-min intervals. The first set of ACh injections during the infusion of 0.9% saline solution was regarded as a control. MCD peptide infusion was started 5 min before the second, third, and fourth set of ACh injections, respectively. In groups 3 (n = 6) and 4 (n = 6), the effects of MCD peptide on increases in CA output induced by DMPP (0.1, 0.2, and 0.4 µg) and muscarine (0.5, 1, and 2 µg) were examined, respectively, with the same protocol as used in group 2. The effects of scyllatoxin (10, 30, and 100 ng/min) on increases in CA output induced by SNS (group 5, n = 9), ACh (group 6, n = 7), DMPP (group 7, n = 7), and muscarine (group 8, n = 7) were examined with the same protocol used in the MCD peptide experiments.

Previously, we reported that the SNS-induced increases in CA output were reproducible during repetitive SNS periods (14), and in preliminary experiments we confirmed that repeated injections of ACh, DMPP, and muscarine produced increases in CA output to almost the same extent (within 5% difference) as in the first trial.

Blood sampling and determination of adrenal CA output. Adrenal venous blood was sampled before and during SNS and injections of ACh, DMPP, and muscarine to determine basal CA output and stimul-i-induced increases in CA output, respectively. The sampling during basal state (during saline, MCD peptide, or scyllatoxin infusion) was performed 2 min before SNS or sets of cholinergic agonist injections. The time required to collect 1 ml (during basal state or SNS) or 2 ml (during cholinergic agonist injections) of blood served to estimate adrenal venous flow rate.

Adrenal blood samples were centrifuged to obtain plasma samples. CA was extracted from plasma by alumina adsorption method, and plasma epinephrine and norepinephrine concentrations were determined by high-performance liquid chromatography with electrochemical detection (LC-304, Bioanalytical Systems, West Lafayette, IN), as described previously (14). Epinephrine and norepinephrine output (ng/min) were calculated by multiplying plasma concentration (ng/ml) by adrenal plasma flow rate (ml/min), and total output of epinephrine and norepinephrine were expressed as CA output. Adrenal CA flow rate was calculated by multiplying adrenal venous blood flow by 1 − hematocrit. The basal CA output was determined from samples collected before SNS or injections of the cholinergic agonists. The SNS- and ACh-, DMPP-, or muscarine-induced changes in CA output were calculated by subtracting the basal CA output from that obtained during the stimulus state.

Analysis of data. The results were expressed as means ± SE throughout the study. Analysis of variance and Dunnett’s test were used for statistical analysis of multiple comparisons of data. P values <0.05 were considered to be statistically significant.

Drugs. The drugs used were MCD peptide, scyllatoxin (Peptide Institute, Osaka, J apan), ACh chloride (Daichi Sankyo, Tokyo, J apan), DMPP iodide (Aldrich, Milwauk ee, WI), and muscarine chloride (Sigma, St. Louis, MO). All drugs were dissolved in 0.9% saline solution.

RESULTS

Increases in CA output in response to SNS, ACh, DMPP, and muscarine. SNS (1, 2, and 3 Hz) or intra-arterial injections of ACh (0.75, 1.5, and 3 µg), DMPP (0.1, 0.2, and 0.4 µg), and muscarine (0.5, 1, and 2 µg) into the adrenal gland produced frequency- and dose-dependent increases in adrenal venous plasma CA concentration (data not shown). The ACh- and muscarine-induced increases in CA concentration were accompanied by increases in adrenal plasma flow rate (Tables 1 and 2). The SNS- and DMPP-induced increases in CA concentration were accompanied by no or slight increases in adrenal plasma flow rate. CA output, calculated by CA concentration and adrenal plasma flow rate, was increased by SNS, ACh, DMPP, and muscarine. The increases in CA output induced by SNS (3 Hz), ACh (3 µg), DMPP (0.4 µg), and muscarine (2 µg) during the control stimulation periods were 448 ± 71 (n = 15), 653 ± 141 (n = 13), 928 ± 151 (n = 13), and 474 ± 114 ng/min (n = 13), respectively, in groups 1-8, in which basal CA output during the resting state was 1.3 ± 0.2 ng/min (n = 54).

SNS produced small pressor and bradycardic responses. The increase in blood pressure produced by 3-Hz SNS was 9 ± 3 mmHg (n = 15), and the decrease in heart rate was 9 ± 3 beats/min (n = 15), and the changes were statistically significant (P < 0.01). Both ACh and muscarine decreased blood pressure, and they did not modify heart rate. The decreases in blood pressure produced by 3 µg ACh and 2 µg muscarine were 14 ± 2 mmHg (n = 13) and 31 ± 4 mmHg (n = 13), respectively, and the changes were statistically signifi-
and injections of ACh, DMPP, and muscarine plasma flow during basal state and during SNS

Table 1. Effects of MCD peptide infusion on adrenal plasma flow during basal state and during SNS and injections of ACh, DMPP, and muscarine

<table>
<thead>
<tr>
<th>MCD peptide infusion, ng/min</th>
<th>Control</th>
<th>10</th>
<th>30</th>
<th>100</th>
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</thead>
<tbody>
<tr>
<td>Adrenal Plasma Flow Rate, ml/min</td>
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<tr>
<td>SNS Group 1 (n = 6)</td>
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<tr>
<td>Basal state</td>
<td>1.6 ± 0.3</td>
<td>1.5 ± 0.3</td>
<td>1.3 ± 0.3†</td>
<td>1.2 ± 0.3†</td>
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<tr>
<td>1 Hz</td>
<td>1.5 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>1.3 ± 0.3†</td>
<td>1.2 ± 0.2†</td>
</tr>
<tr>
<td>2 Hz</td>
<td>1.7 ± 0.3</td>
<td>1.6 ± 0.3</td>
<td>1.5 ± 0.3*</td>
<td>1.5 ± 0.3†</td>
</tr>
<tr>
<td>3 Hz</td>
<td>1.9 ± 0.4</td>
<td>1.8 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>1.7 ± 0.3†</td>
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<tr>
<td>Group 2 (n = 6)</td>
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<tr>
<td>ACh</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
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<tr>
<td>0.75 µg</td>
<td>2.8 ± 0.4</td>
<td>2.8 ± 0.3</td>
<td>2.7 ± 0.4</td>
<td>2.7 ± 0.3</td>
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<tr>
<td>1.5 µg</td>
<td>3.0 ± 0.3</td>
<td>2.9 ± 0.4</td>
<td>2.8 ± 0.4</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>3 µg</td>
<td>3.1 ± 0.4</td>
<td>3.0 ± 0.4</td>
<td>3.0 ± 0.4</td>
<td>3.1 ± 0.3</td>
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<tr>
<td>Group 3 (n = 6)</td>
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<tr>
<td>DMPP</td>
<td>1.8 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>1.7 ± 0.3</td>
<td>1.5 ± 0.2†</td>
</tr>
<tr>
<td>0.5 µg</td>
<td>3.2 ± 0.5</td>
<td>3.1 ± 0.5</td>
<td>3.0 ± 0.5†</td>
<td>2.9 ± 0.5†</td>
</tr>
<tr>
<td>1 µg</td>
<td>3.3 ± 0.5</td>
<td>3.2 ± 0.5</td>
<td>3.2 ± 0.6</td>
<td>3.0 ± 0.6</td>
</tr>
<tr>
<td>2 µg</td>
<td>3.6 ± 0.5</td>
<td>3.5 ± 0.6</td>
<td>3.5 ± 0.6</td>
<td>3.3 ± 0.6*</td>
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<tr>
<td>Group 4 (n = 6)</td>
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<tr>
<td>Muscarine</td>
<td>2.2 ± 0.2</td>
<td>2.1 ± 0.2</td>
<td>2.0 ± 0.2*</td>
<td>1.9 ± 0.2†</td>
</tr>
<tr>
<td>1 Hz</td>
<td>2.0 ± 0.3</td>
<td>1.9 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>2 Hz</td>
<td>2.1 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>2.0 ± 0.2</td>
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<tr>
<td>3 Hz</td>
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<td>2.2 ± 0.2</td>
<td>2.3 ± 0.3</td>
<td>2.2 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE. MCD, mast cell degranulating; SNS, splanchnic nerve stimulation; ACh, acetylcholine; DMPP, 1,1-dimethyl-4-phenyl-piperazinium. *P < 0.05, †P < 0.01 compared with corresponding control values; ‡P < 0.05, §P < 0.01 compared with values during basal state under control conditions.

Effects of MCD peptide on the SNS-, ACh-, DMPP-, and muscarine-induced increases in CA output. Infusion of MCD peptide (10, 30, and 100 ng/min) into the adrenal gland enhanced the SNS-induced increase in CA output (Fig. 1A). The enhancements were small, but they were dose dependent and statistically significant. Percentage of enhancement by the highest dose (100 ng/min) of MCD peptide of increases in CA output induced by 1, 2, and 3 Hz of SNS were 38 ± 6, 37 ± 11, and 50 ± 21%, respectively. The ACh-, DMPP-, and muscarine-induced increases in CA output were not affected even by the highest dose (100 ng/min) of MCD peptide (Fig. 1B–D).

Basal CA output was not affected by MCD peptide. In groups 1-4 (n = 24), basal CA output before and during 10, 30, and 100 ng/min MCD peptide infusion was 0.8 ± 0.2, 1.1 ± 0.2, 1.0 ± 0.2, and 1.0 ± 0.2 ng/min, respectively. MCD peptide decreased adrenal plasma flow rate slightly with or without statistical significance (Table 1). MCD peptide did not affect blood pressure (mean pressure 134 ± 3 mmHg) or heart rate (123 ± 4 beats/min) in groups 1-4 (n = 24).

Effects of scyllatoxin. Infusion of scyllatoxin (10, 30, and 100 ng/min) into the adrenal gland enhanced the ACh-, DMPP-, and muscarine-induced increases in CA output (Fig. 2, B–D). The enhancements were dose dependent with or without significance. Percentages of enhancement by the highest dose (100 ng/min) of scyllatoxin were 150 ± 72, 108 ± 54, and 77 ± 51% at 0.75, 1.5, and 3 µg of ACh, respectively; 171 ± 87, 160 ± 58, and 100 ± 37% at 0.1, 0.2, and 0.4 µg of DMPP, respectively; and 103 ± 27, 73 ± 19, and 52 ± 19% at 0.5, 1, and 2 µg of muscarine, respectively. The SNS-induced increase in CA output was not affected even by the highest dose (100 ng/min) of scyllatoxin (Fig. 2A).

Scyllatoxin did not affect basal CA output. In groups 5-8 (n = 30), basal CA output before and during 10, 30, and 100 ng/min scyllatoxin infusion was 1.7 ± 0.3, 1.5 ± 0.3, 1.4 ± 0.2, and 1.4 ± 0.2 ng/min, respectively. Scyllatoxin decreased adrenal plasma flow rate slightly with or without statistical significance (Table 2). Scyllatoxin did not affect blood pressure (mean pressure 120 ± 4 mmHg) or heart rate (124 ± 5 beats/min) in groups 5-8 (n = 30).

DISCUSSION

Intra-arterial injections of ACh, DMPP, and muscarine into the adrenal gland produced marked increases in adrenomedullary secretion.
in CA output. The highest dose of ACh (3 µg) or muscarine (2 µg) caused a transient depressor response. However, it is unlikely that the baroreflex-mediated CA secretion is involved in the CA response to both agonists, because the adrenal gland was decentralized by cutting the splanchnic nerves and because adrenal venous blood sampling was completed before the pressure change. The intra-arterial administration method made it possible to examine the direct action of MCD peptide and scyllatoxin on adrenal CA secretion in response to SNS and cholinergic agonists under in vivo conditions.

MCD peptide, a 22-amino acid peptide isolated from the venom of the bee *Apis mellifera* (11), has been reported to suppress K_A channels in sensory ganglion cells (27) and brain membranes (17). MCD peptide infused into the adrenal gland enhanced the SNS-induced increase in CA output in a dose-dependent manner without affecting the basal CA output. This indicates that MCD peptide influences the secretion process induced by SNS but does not stimulate the secretion process by itself. Previously, we demonstrated under the same experimental conditions as in this study that the SNS-induced CA secretion is mainly mediated by nicotinic receptors (15, 26). Therefore, the enhancing effect of MCD peptide on the SNS-induced secretion of CA is explained by its facilitatory action on the nicotinic receptor-mediated pathway. However, MCD peptide did not affect increases in CA output in response to ACh, DMPP, or muscarine. We demonstrated also that exogenous ACh causes the secretion of CA by activating both nicotinic and muscarinic receptors (15). Here, the question arises as to why MCD peptide influences the nicotinic receptor-mediated secretion of CA differently, causing a facilitation in the case of SNS and no effect in the case of injections of ACh and DMPP. Two explanations might be possible to understand this discrepant effect of MCD peptide.

One possibility is that K_A channels located presynaptically in the splanchnic nerve terminals may play an
inhibitory role in the release of ACh and other neurotransmitters. It has been suggested that the secretion of CA is stimulated by neuropeptides, such as opioid peptides and vasoactive intestinal peptide, coreleased with ACh from splanchnic nerves in rat (19) and dog adrenal glands (9, 31). If the membrane depolarization of the terminals evoked by SNS activates K_A channels that are capable of facilitating repolarization, it would be expected that activated K_A channels attenuate the release of neurotransmitters by diminishing the depolarizing phase. MCD peptide might produce the facilitation of the neurotransmitter release by blocking the K_A channel-mediated negative control. Consequently, the secretion of CA in response to SNS may be facilitated. The finding might support the possible involvement of presynaptic K_A channels capable of inhibiting neurotransmitter release.

Another explanation is that intrasynaptic K_A channels in the adrenal medullary cells may play an inhibitory role in the secretion of CA. Activation of nicotinic receptors promotes Na^+ and Ca^{2+} influx through receptor-linked ion channels, and the resulting depolarization produces Ca^{2+} influx through voltage-dependent Ca^{2+} channels (5, 8). Simultaneously, the depolarization may activate K_A channels, and activated K_A channels increase K^+ efflux, and the resulting facilitation of repolarization may lead to inhibition of further Ca^{2+} influx. As a result, the secretion of CA may be inhibited. Therefore, it is probable that MCD peptide enhances the CA secretion mediated by nicotinic receptors by blocking the K_A channel-mediated inhibition of Ca^{2+} influx. Endogenous ACh released from the splanchnic nerves would predominantly activate nicotinic receptors located intrasynthetically. Exogenous ACh and DMPP delivered through the arterial supply could diffuse into extrasynaptic regions and would predominantly activate nicotinic receptors located extrasynthetically. If K_A channels are primarily concentrated in intrasynaptic zones but not in extrasynaptic regions, they could affect the depolarization due to the activation of intrasynaptic nicotinic receptors but could not affect the depolarization due to the activation of extrasynaptic nicotinic receptors. Recently, it was reported that K_A channels are particularly concentrated at the site of synaptic contacts on postsynaptic membranes in rat supraoptic nucleus neurons (3). This finding might support our hypothesis, although no report is available suggesting synaptic localization of K_A channels in chromaffin cells.

Scyllatoxin infused into the adrenal gland enhanced the adrenal CA secretion in response to ACh, DMPP, and muscarine in a dose-dependent manner without affecting the basal CA output. These results are consistent with the observation with apamin, a SK_{Ca} channel blocker in the dog (23), indicating that scyllatoxin facilitates the secretion of CA by affecting pathways mediated by both nicotinic and muscarinic receptors but that it does not stimulate the secretion process by itself. From these results, it is suggested that SK_{Ca} channels play an inhibitory role in the adrenal CA secretion mediated by both nicotinic and muscarinic receptors, as suggested in the perfused cat adrenal gland (22, 28, 29) and in bovine adrenal chromaffin cells (18).

The elevation of intracellular Ca^{2+} resulting from the activation of nicotinic receptors triggers the secretion of CA and simultaneously may activate SK_{Ca} channels. Increases of K^+ efflux caused by the activation of SK_{Ca} channels results in hyperpolarization, which leads to inhibition of further Ca^{2+} influx, and the secretion of CA may be inhibited. Therefore, it seems probable that scyllatoxin enhances the secretion of CA mediated by nicotinic receptors by blocking the SK_{Ca} channel-mediated inhibition of Ca^{2+} influx. On the other hand, the elevation of intracellular Ca^{2+} mobilized from intracellular storage sites is thought to contribute to the muscarinic receptor-mediated secretion of adrenal CA (12, 21, 24). Furthermore, it has been shown that muscarinic receptor activation depolarizes the adrenal chromaffin cells of chickens (16), rats (2), and guinea pigs (13) and that the secretion of CA induced by methacholine, a pure muscarinic agonist, is potentiated by apamin, but, in the presence of furnidipine, an L-type Ca^{2+} channel blocker, its potentiation disappears (28). Therefore, the facilitatory effect of scyllatoxin on the muscarinic receptor-mediated secretion of CA can be explained in the same manner as for the nicotinic receptor-mediated secretion.

Scyllatoxin did not affect the SNS-induced increase in CA output. This result indicates that SK_{Ca} channels have no role in the nicotinic receptor-mediated secretion in response to endogenous ACh and that they contribute differently to the secretion between endogenous and exogenous ACh. The differential effects of scyllatoxin on the secretion between endogenous and exogenous ACh may be explained by differential distribution of SK_{Ca} channels on the medullary cell membrane in intrasynaptic and extrasynaptic regions, although regional localization of SK_{Ca} channels in chromaffin cells has not yet been proven. If SK_{Ca} channels are primarily concentrated in extrasynaptic regions but not in synaptic zones, they could affect the elevation of Ca^{2+} due to the activation of extrasynaptic nicotinic and muscarinic receptors but could not affect the elevation of Ca^{2+} due to the activation of intrasynaptic nicotinic receptors. However, the secretion of CA under physiological conditions is caused by activation of the splanchnic nerves. Therefore, the physiological role of extrasynaptic SK_{Ca} channels remains to be resolved.

In conclusion, this study demonstrates that MCD peptide facilitates adrenal CA secretion in response to SNS but not to ACh, DMPP, or muscarine and that scyllatoxin facilitates the secretion in response to ACh, DMPP, and muscarine but not to SNS. These results suggest that K_A channels may play an inhibitory role in the regulation of adrenal CA secretion in response to SNS and that SK_{Ca} channels may play the same role.
the secretion in response to exogenously applied cholinergic agonists.

Perspectives

From the results of this study, it is suggested that $K_a$ channels may play an inhibitory role in the regulation of adrenal CA secretion through an intrasynaptic mechanism, a presynaptic inhibition of neurotransmitter release, or a postsynaptic inhibition of the nicotinic receptor-mediated CA secretion and that $SK_{Ca}$ channels may play the same role in the control of secretion mediated by extrasynaptic nicotinic and muscarinic receptors. To understand this hypothesis, localization mediated by extrasynaptic nicotinic and muscarinic receptors may play the same role in the control of secretion and adrenal chromaffin cells will need to be clarified.

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