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Cholinergic Inhibition of Adrenergic Neurosecretion in the Rabbit Iris-Ciliary Body

James E. Jumblatt and Ginnie T. North

The prejunctional effects of cholinergic agents on release of norepinephrine from sympathetic nerve endings were investigated in the isolated, superfused rabbit iris-ciliary body. Stimulation-evoked release of ^{3}H-norepinephrine was inhibited by the cholinergic agonists methacholine, oxotremorine, muscarine, carbamylcholine and acetylcholine (plus eserine), but was unmodified by pilocarpine or nicotine. Agonist-induced inhibition was antagonized selectively by atropine, indicating a muscarinic response. Atropine alone markedly enhanced norepinephrine release, revealing considerable tonic activation of prejunctional cholinergic receptors in this system. Prejunctional inhibition by carbamylcholine was found to completely override the facilitative action of forskolin or 8-bromo-cyclic AMP on neurotransmitter release. Cholinergic and alpha$_2$-adrenergic effects on neurosecretion were non-additive, suggesting that the underlying receptors coexist at neurotransmitter release sites. Invest Ophthalmol Vis Sci 29:615–620, 1988

Cholinomimetics have been in clinical use for over a century for treatment of glaucoma.[1] Muscarinic cholinergic agonists such as pilocarpine induce contraction of the ciliary muscle, resulting in facilitation of aqueous humor outflow.[1,2] Cholinomimetics have also been reported to alter aqueous humor formation[3–6] and permeability of the blood-aqueous barrier,[7] although the data are somewhat conflicting and the underlying mechanisms poorly resolved.[2]

Cholinergic nerves in the anterior segment of the eye consist mainly of postganglionic parasympathetic fibers that originate in the ciliary ganglia and terminate in the ciliary muscle and sphincter pupillae.[1] In addition, cholinergic nerves and/or receptors have been identified in structures with predominantly sympathetic input—eg, the dilator pupillae, ciliary processes and uveal blood vessels.[8–11] Recent evidence suggests that acetylcholine may have a modulatory influence on sympathetic neurotransmission at some of these sites.[11]

In vitro studies of neurotransmitter release have provided evidence that peripheral sympathetic nerve endings may contain prejunctional cholinergic receptors which, when activated by endogenous acetylcholine diffusing from adjacent parasympathetic terminals, inhibit the synaptic release of norepinephrine.[12,13] To investigate whether such a control mechanism exists at intraocular synapses, we have characterized the effects of cholinergic agonists and antagonists on the stimulation-evoked release of ^{3}H-norepinephrine in the isolated, superfused rabbit iris-ciliary body. In addition, we have examined the interactions between prejunctional cholinergic, alpha$_2$-adrenergic and cyclic AMP-mediated effects on norepinephrine secretion in this preparation.

From the Department of Ophthalmology, University of Louisville School of Medicine, Kentucky Lions Eye Research Institute, Louisville, Kentucky.

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Reprint requests: James E. Jumblatt, Department of Ophthalmology, University of Louisville School of Medicine, Kentucky Lions Eye Research Institute, 301 E. Muhammad Ali Boulevard, Louisville, KY 40202.

Materials and Methods

Animals

Adult albino rabbits (Pine Acres, Burlington, VT) weighing 2.5–3 kg were used for all experiments. Rabbits were sacrificed by injection of an overdose of sodium pentobarbital into the marginal vein of the ear. Maintenance and handling of animals were performed in accordance with NIH guidelines and the ARVO Resolution on the Use of Animals in Research.

Analysis of Neurosecretion

Field-stimulated secretion of ^{3}H-norepinephrine (^{3}H-NE) from isolated, superfused rabbit iris-ciliary bodies was measured as previously described.[14,15] In brief, freshly-dissected iris-ciliary bodies were incubated for 60 min at 37°C in a modified Krebs solution (composition: NaCl, 118 mM; KCl, 4.8 mM; $CaCl_2$, 1.3 mM; KH_2PO_4, 1.2 mM; $NaHCO_3$, 25 mM; dextrose, 10 mM; Na ascorbate, 0.1 mM; indomethacin, 0.003 mM; pH 7.3–7.4) containing 2.5

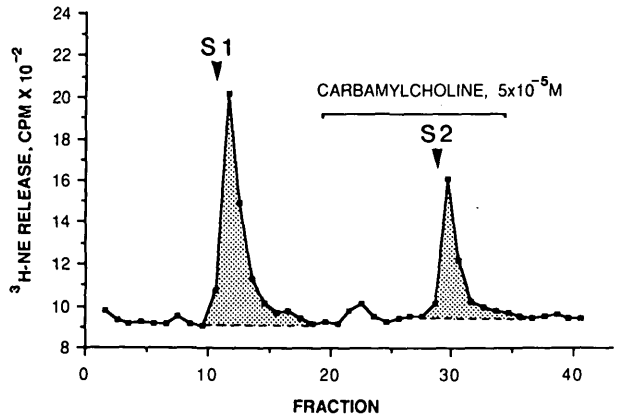

Fig. 1. Carbamylcholine-mediated inhibition of ^{3}H-norepinephrine release. One minute (2 ml) fractions of the superfusion medium were collected and analyzed for tritium overflow as described in **Methods.** Carbamylcholine (5×10^{-5} M) was added 10 min before the second train of field-stimulation (S2). Stimulation-dependent ^{3}H-NE release is indicated by the shaded peak areas above the extrapolated basal efflux (dotted lines).

μCi/ml ^{3}H-(-)-norepinephrine (New England Nuclear, Boston, MA; 33 Ci/mmol). The incubation medium was gassed continuously with 95% O_2/5% CO_2. The tissues were then rinsed, transferred to individual plexiglas perfusion chambers, and superfused at a rate of 2 ml/min with Krebs buffer containing 10^{-6} M cocaine hydrochloride to inhibit neuronal re-uptake of catecholamines. The superfusion medium was collected in 2 ml fractions which were combined with 14 ml of aqueous scintillation cocktail (Hydrofluor, National Diagnostics, Inc., Somerville, NJ) and analyzed for radioactivity by liquid scintillation spectrometry.

Release of ^{3}H-NE was elicited by consecutive trains of electrical field stimulation, each train consisting of 300 square wave pulses (10 Hz, 2 msec pulse duration, 12 V/cm interelectrode distance) delivered to the chamber electrodes with a Grass S48 stimulator (Grass Instruments, Quincy, MA). Stimulation-evoked release and overflow of tritium was estimated by subtraction of the extrapolated basal tritium efflux from the total tritium released during the 12 min period following the onset of stimulation. (See example in Fig. 1; shaded peak areas). Basal (unstimulated) tritium efflux was assumed to decline linearly between prestimulation and poststimulation fractions. Chromatographic analysis of the radioactive release products has revealed that most (>85%) of the tritiated material secreted in response to field-stimulation consists of unmetabolized ^{3}H-norepinephrine, whereas the spontaneously released material represents various norepinephrine metabolites and oxidation products.[14,16] Stimulus-dependent tritium efflux was thus designated as ^{3}H-NE release.

To measure the effects of exogenous drugs on ^{3}H-NE release, tissues received two stimulations (S1 and S2). Test agents were introduced 10 min before S2. Stimulation-dependent ^{3}H-NE release during S1 and S2 was determined graphically, and the ratio of the two peak areas (S2/S1) was calculated and compared to untreated control preparations in which the S2/S1 ratio was near unity (0.96 ± 0.03, n = 32). In some experiments, assays were repeated on the same tissue preparation following a 45 min washout for drug removal and tissue recovery. Results are expressed either the S2/S1 ratio (mean $\pm$ SEM, n = number of determinations) or as the percent change in this value relative to untreated control preparations. Significance of differences between experimental and control values was evaluated by the student t-test (two-tailed) for unpaired observations.

Materials

The following agents were purchased from Sigma Chemical Co. (St. Louis, MO): acetylcholine chloride, eserine salicylate, carbamylcholine chloride, epinephrine hydrochloride, indomethacin, 8-bromoadenosine 3',5' cyclic monophosphate, isobutylmethylxanthine, mecamylamine hydrochloride, atropine sulfate, methacholine chloride, oxotremorine sesquifumarate, muscarine hydrochloride, pilocarpine hydrochloride, nicotine. Forskolin was purchased from Calbiochem (Calbiochem/Behring, San Diego, CA). Cocaine hydrochloride was donated by Dr. L. Shuster, Tufts University School of Medicine, Boston.

Forskolin and indomethacin were prepared as concentrated stock solutions in ethanol and dimethylsulfoxide, respectively, and diluted to their appropriate final concentrations in Krebs medium. At the ultimate dilutions employed, (>2000-fold), neither solvent alone modified ^{3}H-NE release (North G, unpublished results). All other drugs were either dissolved directly in Krebs medium or diluted from concentrated stock solutions prepared in distilled water.

Results

Cholinergic Inhibition of ^{3}H-NE Release

The example in Figure 1 illustrates the effects of the nonselective cholinergic agonist carbamylcholine (5×10^{-5} M) on basal and field-stimulated ^{3}H-NE release. The small, transient increase in basal tritium efflux which coincided with the introduction of carbamylcholine (Fig. 1) was considered to be an artifact of miosis, since it did not occur in preparations in which pupillary constriction was prevented by transverse sectioning of the sphincter pupillae (not shown). Stimulation-dependent ^{3}H-NE release (shaded peak areas) was inhibited by carbamylcho-

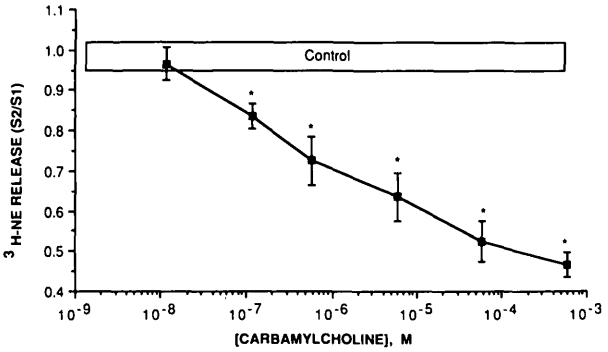

Fig. 2. Concentration-dependence of carbamylcholine-mediated inhibition of ^{3}H-NE release. The box indicates ^{3}H-NE release in control (untreated) preparations. Symbols represent ^{3}H-NE release (means ± SEM) in carbamylcholine-treated tissues: n = 4–12 determinations. *$P < 0.01$ relative to control.

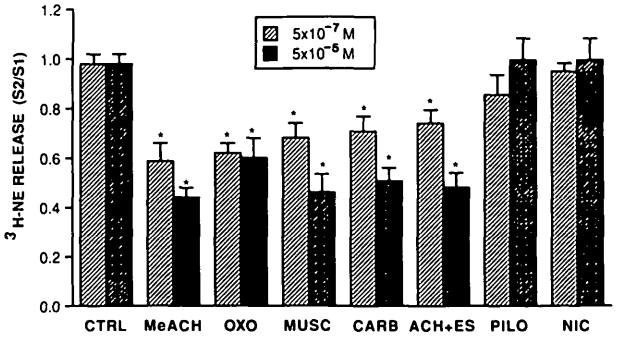

Fig. 3. Effects of cholinergic agonists on ^{3}H-NE release. CTRL = control (no drug); MeACH = methacholine; OXO = oxotremorine; MUSC = muscarine; CARB = carbamylcholine; ACh + ES = acetylcholine plus eserine (10^{-6} M); PILO = pilocarpine; NIC = nicotine. Vertical bars (and horizontal lines) represent means ± SEM; n = 4–12 determinations. *$P < 0.01$ relative to control.

line (Figs. 1, 2). The response was dosage-dependent, with an apparent threshold for inhibition near 10^{-7} M carbamylcholine (Fig. 2). The maximum inhibition obtained with 5×10^{-4} M carbamylcholine represented a 54% reduction in ^{3}H-NE release.

Figure 3 compares the prejunctional effects of several cholinergic agonists assayed at two concentrations: 5×10^{-7} M and 5×10^{-5} M. The selective muscarinic agonists mechacholine, muscarine and oxotremorine, as well as the nonselective agonists carbamylcholine and acetylcholine (plus eserine, 10^{-6} M) significantly depressed ^{3}H-NE release at both concentrations ($P < 0.01$), whereas nicotine and pilocarpine were inactive.

As shown in Figure 4, inhibition of ^{3}H-NE release by carbamylcholine was antagonized by the muscarinic antagonist atropine (10^{-7} M), but was unaffected by the selective nicotinic antagonist mecamylamine (10^{-6} M). Atropine not only reversed the effects of exogenous carbamylcholine, but alone markedly enhanced ^{3}H-NE secretion, thus revealing a high level of tonic cholinergic inhibition during field stimulation.

Interactions With Prejunctional Alpha$_2$-Adrenergic Receptors

Sympathetic terminals in the rabbit iris-ciliary body also contain prejunctional alpha$_2$- (but not alpha$_1$ or beta) adrenergic receptors which mediate inhibition of norepinephrine secretion.[15,17] As shown in Figure 5, the adrenergic agonist epinephrine (10^{-6} M) and the cholinergic agonist carbamylcholine (5×10^{-4} M) each inhibited ^{3}H-NE release to approximately 50% of control. When the two agonists were added simultaneously, no further inhibition was seen. Therefore, prejunctional muscarinic and alpha$_2$-adrenergic effects on neurosecretion are nonadditive in this system.

Interactions With Cyclic AMP

Forskolin and several other agents which elevate intracellular cAMP have been found to enhance ^{3}H-NE release in the rabbit iris-ciliary body.[14] This is illustrated by the results in Figure 6, in which forskolin (5×10^{-6} M) and 8-bromo cAMP (0.5 mM) increased stimulation-evoked ^{3}H-NE release by 44% and 76%, respectively. Neither of these agents, however, modified carbamylcholine-mediated inhibition of ^{3}H-NE release (Fig. 6). In contrast, the inhibitory response to carbamylcholine was partially antagonized by the cyclic nucleotide phosphodiesterase inhibitor isobutylmethylxanthine (IBMX, 0.5 mM) which, alone, did not significantly affect release.

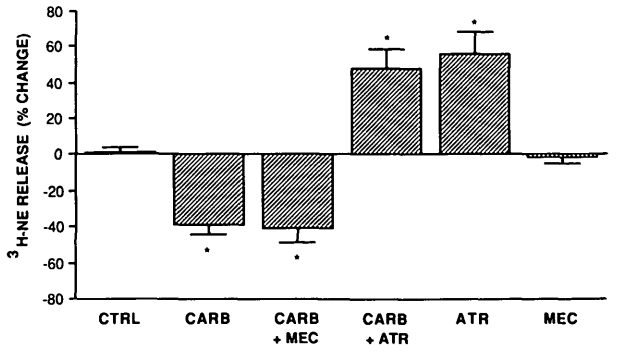

Fig. 4. Selective antagonism by atropine of carbamylcholine-mediated inhibition. CTRL = control (no drug); CARB = carbamylcholine, 5×10^{-5} M; MEC = mecamylamine, 10^{-6} M; ATR = atropine, 10^{-7} M; Results are expressed as % change (positive or negative) in field-stimulated ^{3}H-NE release relative to untreated control. Vertical bars (and horizontal lines) represent means ± SEM, n = 6–12 determinations. *$P < 0.01$ in comparison to control.

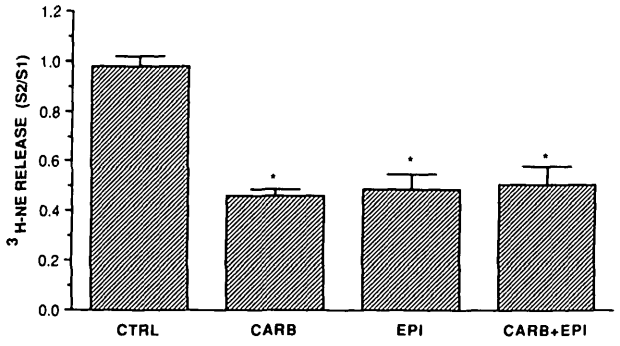

Fig. 5. Non-additivity of prejunctional cholinergic and alpha$_2$-adrenergic effects on ^{3}H-NE release. CTRL = control (no drug); CARB = carbamylcholine, 5×10^{-4} M; EPI = epinephrine, 10^{-6} M. Vertical bars (and horizontal lines) represent means ± SEM; n = 6–12 determinations. *$P < 0.01$ relative to control.

Discussion

Over the past decade, in vitro studies of neurotransmitter release have provided evidence that the quantity of norepinephrine secreted at peripheral neuroeffector junctions is subject to local regulation by neurotransmitters, hormones and tissue autacoids acting at prejunctional receptors.[12,13] The results of this study demonstrate that sympathetic terminals in the rabbit iris-ciliary body contain prejunctional cholinergic receptors which, upon activation by exogenous cholinomimetics or endogenous acetylcholine, depress the synaptic release of norepinephrine. Stimulation-evoked secretion of ^{3}H-NE was inhibited by several cholinergic agonists with muscarinic activity and was enhanced selectively by atropine, indicating a muscarinic cholinergic response. These findings are compatible with histological evidence for close physical proximity between catecholaminergic and cholinergic fibers in areas of the rabbit dilator pupillae.[8,9,18] Cholinergic inhibition of adrenergic neurosecretion in the iris provides another dimension to the well-known physiological antagonism between sympathetic and parasympathetic function in this structure.

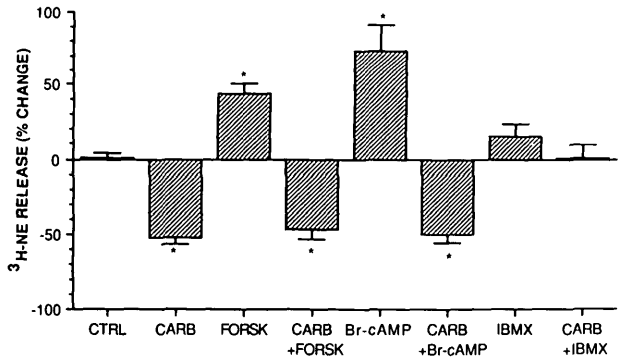

Fig. 6. Effects of forskolin and 8-bromo cyclic AMP on cholinergic inhibition of ^{3}H-NE release. Results are expressed as explained in Figure 4, legend. CTRL = control (no drug); CARB = carbamylcholine, 5×10^{-4} M; Br-cAMP = 8-bromo cyclic AMP, 0.5 mM; IBMX = isobutylmethylxanthine, 0.5 mM. Vertical bars (and horizontal lines) represent means ± SEM; n = 4–12 determinations. *$P < 0.01$ relative to control.

Maximum stimulation of prejunctional muscarinic receptors by exogenous carbamylcholine inhibited ^{3}H-NE release by approximately 50% (Figs. 2, 5). This response is superimposed on considerable tonic cholinergic inhibition mediated, presumably, by endogenously secreted acetylcholine. In support of this interpretation, field-stimulation of the rabbit iris-ciliary body prelabeled with ^{3}H-choline was found to elicit the secretion and overflow of ^{3}H-acetylcholine (Jumblatt J and O'Connor L, unpublished results). To investigate additivity between prejunctional cholinergic and alpha$_2$-adrenergic effects on ^{3}H-NE release, we compared the individual and combined responses to epinephrine and carbamylcholine at optimal concentrations (Fig 5). Complete or partial additivity would be predicted if: (1) the two receptor types were located on separate populations of nerve endings; or (2) were on the same terminals but operate independently to modulate neurosecretion. No additivity was observed, however, suggesting that prejunctional muscarinic and alpha$_2$-adrenergic mechanisms coexist at norepinephrine release sites and possibly share a common pathway for inhibition of neurosecretion.

The signal transduction and effector mechanisms used by prejunctional muscarinic cholinergic receptors are unknown. Stimulation of muscarinic receptors in the rabbit iris results in increased phosphoinositide metabolism and the release of arachadonic acid.[19,20] Possibly, one or more of the numerous reaction products generated in this cascade might function as an intracellular second messenger to modify some step in neurosecretion. Alternatively, prejunctional muscarinic receptors might be coupled in more direct fashion to membrane ion channels, as recently described for postjunctional muscarinic receptors in atrial muscle.[21] Other biochemical responses associated with muscarinic receptor activation in neural tissues include: (1) elevation of cyclic GMP; (2) inhibition of adenylate cyclase; and (3) activation of cyclic nucleotide phosphodiesterase.[21–23] Cyclic GMP elevation seems an unlikely mechanism for inhibition of neurosecretion, since 8-bromo cGMP was observed to enhance rather then inhibit ^{3}H-NE release in this system.[14] Mechanism (2)—inhibition of adenylate cyclase—is difficult to reconcile with the failure of either forskolin or 8-bromo cAMP to antagonize muscarinic inhibition of ^{3}H-NE release (Fig. 6). If the reduction in neurotransmitter release were the

direct result of decreased cAMP biosynthesis, replacement of intracellular cAMP by the cell-permeant 8-bromo derivative would be expected to attenuate the muscarinic response. Mechanism (3)—activation of phosphodiesterase leading to cAMP (and/or cGMP) breakdown—remains a viable possibility. Such a mechanism would explain not only the ability of carbamylcholine to override the effects of forskolin and 8-bromo cAMP, but also the antagonism of the muscarinic response by IBMX. Parallel biochemical and electrophysiological studies of isolated sympathetic neurons are needed to evaluate these and other possible mechanisms and to identify the molecular targets for regulation.

The failure of the muscarinic agonist pilocarpine to inhibit ^{3}H-NE release in the rabbit iris-ciliary body was somewhat surprising, considering the potency of this drug in other systems[24-26] and its longstanding clinical efficacy as a miotic agent and glaucoma medication. This apparent discrepancy may reflect a pharmacological peculiarity of the rabbit muscarinic receptor. Pilocarpine has been reported to lack potency at both prejunctional and postjunctional muscarinic receptors in the rabbit heart,[26] and has been characterized as a mixed agonist/antagonist in the isolated rabbit sphincter pupillae.[27] It has been speculated, moreover, that prejunctional inhibition of sympathetic neurotransmission might contribute to the relatively weak miotic response to pilocarpine in this species.[27] Although the present results do not support such an interpretation, they do not exclude the possibility that pilocarpine may have significant prejunctional effects on adrenergic neurosecretion in the eyes of other species, including humans.

The biological significance of prejunctional muscarinic receptors in the iris and/or ciliary body remains to be established. Presumably, cholinergic inhibition of norepinephrine secretion in the dilator pupillae would serve to augment the miotic response to parasympathetic stimulation. The beneficial effects of pilocarpine and other cholinomimetic agents in glaucoma therapy are attributed primarily to contraction of the ciliary muscle with subsequent enhancement of aqueous humor drainage.[2] The ciliary muscle has been reported to contain adrenergic receptors (mainly beta) which mediate relaxation.[28-30] Conceivably, prejunctional inhibition of norepinephrine secretion might contribute to the cholinergic responsiveness of this muscle as well. Results of other studies suggest that cholinergic drugs may alter aqueous humor formation,[3-6] although the nature and significance of these effects are controversial.[2] Other agents which act prejunctionally to inhibit adrenergic neurosecretion in ocular tissues include alpha$_2$-adrenergic agonists,[15,16] prostaglandins[16] and dopaminergic agonists.[31] In view of the effectiveness of some of these agents for reducing intraocular pressure in rabbits and other species, further consideration of prejunctional muscarinic receptors as potential targets for ocular hypotensive drugs seems warranted.

Key words: prejunctional, cholinergic, adrenergic, neurosecretion, iris

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