tive field center, the alternating stimulus was moved by small increments (1 mm = 4.3′ of arc) to either side of the null position, and the responses were measured. In Fig. 1, the maximum firing rate is plotted as a function of eccentricity from the null position. Lower firing rates exhibited by Siamese units support the behavioral findings of Blake and Antoinetti (*12*) that Siamese cats exhibit reduced overall contrast sensitivity.

The decreased Y/X ratio we found is not easily explained, but it conflicts with the hypothesis that the "visual system of the Siamese cat is composed predominantly of Y-cells" (*12*, p. 110). The significance of this ratio and visual acuity in Siamese and normal cats has not yet been established, although several studies have suggested a possible relationship between X-cell properties and visual acuity in ordinary cats (*13, 14*). Since Siamese retinal ganglion cells reveal no reduction in the percentage of X-cells, compared with ordinary cats, the data are consistent with an earlier finding (*11*) that the two kinds of cats have similar acuity. It is not clear, however, whether the Y/X ratio can account for the lower spatial contrast sensitivity found behaviorally in Siamese cats, or whether this phenomenon is simply a function of the lower firing rates exhibited by the Siamese retinal ganglion cells in response to contrast.

The lack of pigment in the retinal epithelium in Siamese cats is well known (*17*). Our results indicate that the retinal neurophysiology of these animals may also differ from that of ordinary cats. The ultimate source of this difference probably lies distal to the ganglion cells.

YUZO M. CHINO
MICHAEL S. SHANSKY
Division of Visual Science, Illinois College of Optometry, Chicago 60616
D. I. HAMASAKI
Bascom Palmer Eye Institute, William L. McKnight Vision Research Center, University of Miami, Miami, Florida 33136

References and Notes

1. The optic-nerve fibers that originate primarily from a vertical strip of retina about 20° to 25° in width lying just temporal to the area centralis are misrouted in the optic chiasm so that they project to the LGN of the contralateral side of the brain. As a result of this misrouting, the sequential representation of the visual field within lamina A1 of the LGN is not only disrupted, but the visual field representation by the abnormal segment of lamina A1 is reversed.
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12. The animals of R. Blake and D. Antoinetti [*Science* **194**, 109 (1976)] exhibited (i) a lower overall spatial contrast sensitivity, (ii) a lower high-frequency cutoff point, and (iii) less falloff in sensitivity at low spatial frequencies.
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15. Those cells which showed a null position (linear spatial summation) in the receptive field were classified as X-cells according to the designation of Enroth-Cugell and Robson (*13*); those cells which failed to show a null position (nonlinear spatial summation) were classified as Y-cells. However, because most units do not show perfect linear spatial summation, a more objective method had been used to segregate cells. From the responses obtained with the stimulus at the null or equal response position, the firing rate at the time of the maximal response was compared with the firing rate 300 msec later. When the distribution of the ratios of the two firing rates was plotted for all cells, two groups of cells were found; those with high ratios ($\bar{X} = 0.68$) were classified as X-cells by their histograms, and those with low ratios ($\bar{X} = 0.04$) were classified as Y-cells (two-tailed t-test, $P < .001$). The two groups of cells can be shown to arise from two populations (D. I. Hamasaki and V. Sutija, in preparation). For surgical details, see R. N. Winters and D. I. Hamasaki [*Vision Res.* **16**, 36 (1976)].
16. Nine percent (3/35) of misrouted fibers compared to 8 percent (8/101) of normally routed fibers were classified as Y-units. In addition, the Siamese cats in these experiments all exhibited a convergent strabismus (optic disk separations of 16.2°, 21.6°, and 24°) when compared with a control group of ten normal cats (optic disk separations ranging from 33.5° to 48.2°) (Y. M. Chino, M. S. Shansky, and D. I. Hamasaki, in preparation).
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Efflux of Cyclic Nucleotides from Rat Pineal: Release of Guanosine 3′, 5′-Monophosphate from Sympathetic Nerve Endings

Abstract. *Potassium and norepinephrine stimulate the efflux of adenosine 3′,5′-monophosphate (cyclic AMP) and guanosine 3′,5′-monophosphate (cyclic GMP) from intact pineal glands. The postsynaptic β-adrenergic receptor mediates the efflux of cyclic AMP. In contrast, the efflux of cyclic GMP requires calcium and intact nerve endings. It appears that sympathetic nerve endings may release cyclic GMP into the synaptic space.*

Adenosine 3′,5′-monophosphate (cyclic AMP) has been shown to act intracellularly as a second messenger in the action of several hormones (*1*). In addition, the release of cyclic AMP into perfusates or culture media by a variety of tissues (*2*) and cells (*3*), including brain (*4*), has been described. Although extracellular cyclic AMP plays an important role in intercellular communication in slime molds (*5*), its roles in mammalian systems have not been elucidated.

Guanosine 3′,5′-monophosphate (cyclic GMP) has been shown to increase in response to neurotransmitters and depolarizing agents in several tissues (*6*), including brain (*7*). It has been proposed that cyclic GMP may act intracellularly to elicit effects which oppose, or differ from, those of cyclic AMP (*8*). Extracellular cyclic GMP has been shown to increase in plasma in response to norepinephrine (*9*). Recently, Kapoor and Krishna demonstrated the secretagogue-stimulated elevation of both intracellular and extracellular cyclic GMP in the exocrine pancreas (*10*).

In the rat pineal gland, cyclic AMP mediates the postsynaptic effects of the neurotransmitter norepinephrine (*11*). The gland is innervated exclusively by noradrenergic nerves whose cell bodies lie in the superior cervical ganglia (*12*). Stimulation of the β-adrenergic receptors leads to the induction of serotonin *N*-acetyltransferase and ultimately to the synthesis and secretion of the hormone melatonin (*11*). In addition, norepinephrine and depolarizing agents increase the concentration of cyclic GMP in the pineal gland (*13*). A major component of the effect on cyclic GMP concentrations depends on the presence of intact nerve endings in the gland (*13*). We therefore examined the possibility that cyclic nucleotides might be released by the rat pineal, and, in particular, by the sympathetic nerve endings which it contains. Our results indicate that the efflux of both cyclic nucleotides can be elicited from intact glands. However, the release of cyclic AMP differs from that of cyclic GMP. Cyclic AMP appears to be released from postsynaptic sites on paren-

chymal cells whereas cyclic GMP appears to be released from presynaptic sites on the sympathetic nerve endings.

Male Sprague-Dawley rats (150 to 175 g; Zivic-Miller Laboratories) were housed in our facilities for at least 6 days under diurnal lighting conditions before each experiment. Rats were killed by decapitation and their pineal glands (approximately 1 mg of tissue) were immediately removed and placed into a modified Krebs-Ringer-glucose (KRG) solution (*14*). In some experiments glands were exposed to ^{3}H-labeled norepinephrine (*15*) for 30 minutes. In all experiments, after prior incubation and washing, the glands were exposed to drugs or modified KRG. The medium was aspirated and portions were assayed for cyclic nucleotides. Cyclic AMP was determined by the radioisotope dilution assay of Brown *et al.* (*16*). Cyclic GMP was determined, after acetylation of samples, by radioimmunoassay (*17*). Tritiated catecholamine was determined by liquid scintillation counting.

Intact pineal glands that were exposed to high concentrations of potassium for 15 minutes released both cyclic AMP and cyclic GMP into the medium (Table 1). The amounts released were often 15 times greater than controls. However, these ratios varied severalfold among experiments over a 6-month period. *l*-Norepinephrine also caused the efflux of both cyclic nucleotides. The amount of each cyclic nucleotide released by high concentrations of potassium *l*-norepinephrine was comparable to the amounts in the tissue (*18*).

The effect of norepinephrine on both cyclic nucleotides is stereospecific (Table 1). *d*-Norepinephrine did not increase the efflux of either cyclic nucleotide above control levels. This makes a nonspecific effect of norepinephrine unlikely, *l*-Isoproterenol, a potent β-adrenergic agonist, increased the release of cyclic AMP but not of cyclic GMP. These data suggest that the efflux of cyclic AMP, but not cyclic GMP, may be secondary to stimulation of the β-adrenergic receptor.

The effect of extracellular calcium also distinguishes the two cyclic nucleotides (Table 1). Potassium-stimulated efflux of cyclic AMP is calcium-dependent. However, the effect of norepinephrine on cyclic AMP is not. Thus, the action of high potassium concentrations may be secondary to the resulting calcium-dependent stimulation of the release of norepinephrine from the sympathetic nerve endings in the tissue. The norepinephrine in the synaptic space would then increase cyclic AMP synthesis and release

Table 1. Efflux of cyclic nucleotides from rat pineal glands. Pineal glands from rats which had been exposed to light for 24 hours were incubated for 15 minutes in oxygenated KRG (*14*) at 37°C. They were washed three times in KRG and individual glands were incubated for an additional 5 minutes. Individual pineals were then incubated in 0.5 ml of KRG media, modified as indicated, for 15 minutes. All experimental media contained 0.5 m*M* IBMX. Calcium-free media contained 1 m*M* EGTA. Glands incubated in calcium-free media were also incubated for 5 minutes in calcium-free KRG. In media containing 100 m*M* KCl this compound was substituted for an equivalent amount of NaCl. Portions of medium were assayed for cyclic AMP (*16*) and cyclic GMP (*17*), respectively. Each value represents the mean ± standard error for the number of glands indicated in parentheses.

Medium	Nucleotide [pmole gland^{-1} (15 min)$^{-1}$]	
	Cyclic AMP	Cyclic GMP
Control	3 ± 0.7 (6)	1.4 ± 0.3 (6)
High K^+ (100 m*M*)	54 ± 10 (6)	20 ± 5 (6)
l-Norepinephrine (10 μM)	74 ± 10 (5)	21 ± 3.7 (5)
d-Norepinephrine (10 μM)	4.5 ± 1.4 (6)	0.8 ± 0.2 (6)
l-Isoproterenol (0.1 μM)	45 ± 3 (6)	2.5 ± 0.5 (6)
High K^+ minus Ca^{2+}	4.9 ± 1.5 (6)	1.7 ± 0.2 (5)
l-Norepinephrine minus Ca^{2+}	78 ± 9 (5)	6 ± 0.4 (5)

Table 2. Effect of denervation on the efflux of cyclic nucleotides from rat pineal glands. Rats with denervated pineal glands were prepared by bilateral superior cervical ganglionectomy at least 1 month prior to use. Efflux of cyclic nucleotides from denervated glands and from glands removed from sham-operated controls was assessed under the conditions described in Table 1. Each value represents the mean ± standard error for the number of glands indicated in parentheses.

Medium	Nucleotide [pmole gland^{-1} (15 min)$^{-1}$]			
	Cyclic AMP		Cyclic GMP	
	Sham	Denervated	Sham	Denervated
Control	1.5 ± 0.8 (6)	0.1 ± 0.2 (6)	2.6 ± 0.4 (5)	0.7 ± 0.1 (6)
High K^+ (100 m*M*)	95 ± 13 (6)	4.3 ± 5 (6)	16 ± 3 (6)	1.3 ± 0.5 (6)
l-Norepinephrine (10 μM)	81 ± 11 (6)	82 ± 9 (6)	43 ± 10 (6)	1.2 ± 0.2 (6)

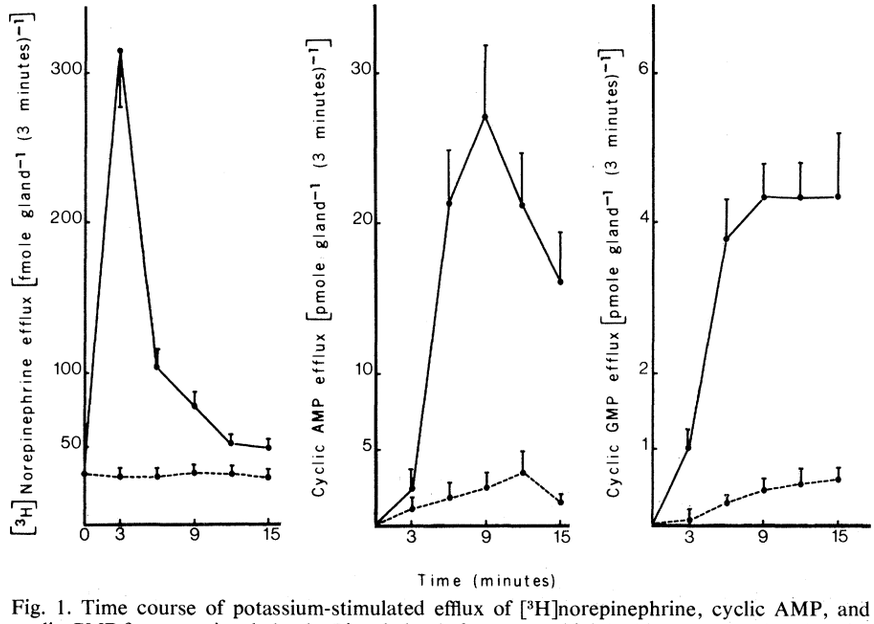

Fig. 1. Time course of potassium-stimulated efflux of [^{3}H]norepinephrine, cyclic AMP, and cyclic GMP from rat pineal glands. Pineal glands from rats which had been exposed to light for 24 hours were first incubated for 15 minutes in KRG (*14*). Groups of four pineals were exposed to 0.225 μM [^{3}H]norepinephrine (*15*) (2 μc/ml) for 30 minutes (*19*). The radioactive medium was removed and the glands were washed three times in KRG containing 10 μM desmethylimipramine (DMI). After another incubation period and wash, individual glands were exposed to either 0.5 ml of KRG containing DMI and 0.5 m*M* 3-isobutyl-l-methylxanthine (IBMX) (•-----•) or to a similar solution in which 100 m*M* KCl was substituted for an equivalent amount of NaCl (•——•). Medium was removed and replaced at 3-minute intervals. Portions were counted for tritium efflux. Other portions were assayed for cyclic AMP (*16*) and cyclic GMP (*17*), respectively. Each point represents the mean ± standard error of eight glands.

by its stimulation of the postsynaptic β-adrenergic receptor. This latter action does not require calcium. In contrast, both the potassium- and norepinephrine-stimulated efflux of cyclic GMP require calcium. Extracellular norepinephrine alone is not sufficient to stimulate fully the synthesis and release of cyclic GMP.

Experiments with denervated glands further distinguish the release of cyclic AMP from that of cyclic GMP (Table 2). The presence of intact nerve endings is required for the release of cyclic AMP by high potassium concentrations. However, norepinephrine remains effective in stimulating the efflux of cyclic AMP in the absence of nerve endings. Thus, the action of high concentrations of potassium on cyclic AMP appears to be secondary to the ability of potassium to release norepinephrine from nerve endings. In contrast, both high potassium concentrations and norepinephrine fail to stimulate the release of cyclic GMP from the denervated glands. Thus, the release of cyclic GMP, unlike that of cyclic AMP, requires the presence of extracellular calcium and of intact nerve endings in the pineal gland.

The temporal relations among the efflux of norepinephrine, cyclic AMP, and cyclic GMP were examined by comparing the kinetics of release of each compound (Fig. 1). Efflux of norepinephrine was monitored by measuring the release of tritium from glands which had taken up [^{3}H]norepinephrine (*19*). The effect of high potassium concentrations on norepinephrine release was greatest in the first 3 minutes and diminished rapidly thereafter. The efflux of cyclic AMP increased for the first 9 minutes and then diminished, being significantly reduced after 15 minutes. The efflux of cyclic GMP also increased initially but did not show the clear reduction in rate seen with cyclic AMP. Comparison of the curves for [^{3}H]norepinephrine and cyclic GMP indicates that the stimulation of the efflux of cyclic GMP by high potassium concentrations is not directly coupled to the exocytotic release of norepinephrine. It is not clear whether the effect of the potassium on the release of cyclic GMP depends on the action of the norepinephrine which is released into the synaptic cleft.

In all of the experiments described above, 0.5 m*M* 3-isobutyl-1-methylxanthine (IBMX) was included in the final incubation medium. The presence of the phosphodiesterase inhibitor markedly enhanced the release of cyclic nucleotides (*20*). In some types of cells the addition of IBMX inhibits the efflux of cyclic AMP (*3*). Thus, interpretation of the effects of IBMX must be approached with caution. However, in the pineal gland, the effect of IBMX is consistent with an increased recovery of cyclic nucleotides in the medium resulting from the inhibition of their destruction by phosphodiesterase.

It is not clear from our studies whether phosphodiesterase acts on extracellular as well as intracellular cyclic nucleotides. However, the ability of phosphodiesterase to destroy extracellular cyclic AMP has been demonstrated in other tissues (*21*). Furthermore, histochemical studies have revealed that phosphodiesterase is associated with the plasma membrane, and, in particular, with postsynaptic sites (*22*). Thus, in addition to mechanisms for the release of cyclic nucleotides into the synaptic space, there appears to be a mechanism for their local destruction. Cyclic nucleotides in the synaptic space, or their metabolites (*23*), may have actions on the external surface of presynaptic or postsynaptic membranes. These extracellular compounds may participate in the functions of cyclic nucleotides in nervous tissue (*24*).

Our results clearly distinguish between factors regulating the efflux of cyclic AMP and cyclic GMP from the rat pineal gland. Efflux of cyclic AMP appears to accompany its increased synthesis and accumulation in response to postsynaptic β-adrenergic stimulation. In contrast, the efflux of cyclic GMP is calcium-dependent and requires the presence of intact nerve endings. Thus, cyclic GMP may be released into the synaptic space by sympathetic nerve endings.

MARTIN ZATZ
ROBERT F. O'DEA
Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland 20014

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15. The *l*-[7-^{3}H]norepinephrine (8.9 c/mmole) was purchased from Amersham/Searle. After purification by alumina column chromatography, stock solutions were lyophilized and stored in 0.01*N* HCl.
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18. The amounts of cyclic AMP in the tissue (picomoles per gland, $N = 6$) after 15 minutes were: control (IBMX), 9.1 ± 2.4; high potassium, 110 ± 19; *l*-norepinephrine, 140 ± 15. The amounts of cyclic GMP in the tissue (picomoles per gland, $N = 6$) after 15 minutes were: control (IBMX), 2.7 ± 0.4; high potassium, 11 ± 5; *l*-norepinephrine, 16 ± 3.
19. Control glands took up 1.70 ± 0.07 pmole per gland, $N = 16$. The uptake of [^{3}H]norepinephrine was inhibited 80 percent by 10 μ*M* desmethylimipramine. These results are consistent with those of R. W. Holz, T. Deguchi, and J. Axelrod [*J. Neurochem.* **22**, 205 (1974)]. Control gland⁻ {IBMX) released 0.08 ± 0.01 pmole/10 min ($N = 12$). High concentrations of potassium released 0.62 ± 0.08 pmole/10 min ($N = 6$). In the absence of calcium, the release by high potassium concentrations was inhibited at least 80 percent.
20. In the absence of IBMX, the amounts of cyclic AMP released (picomoles per gland, $N = 6$) in 15 minutes were: control 1.5 ± 2; high potassium, 11 ± 7.5; *l*-norepinephrine, 17 ± 7. The amounts of cyclic GMP released (picomoles per gland, $N = 6$) in 15 minutes were: control, 0.2 ± 0.2; high potassium, 0.9 ± 0.4; *l*-norepinephrine, 0.6 ± 0.3. The amounts of cyclic AMP in the tissues (picomoles per gland, $N = 6$) after 10 minutes were: control, 12 ± 2.5; high potassium, 28 ± 11; *l*-norepinephrine, 69 ± 11; and of cyclic GMP; control, 0.2 ± 0.05; high potassium, 2.5 ± 0.8; *l*-norepinephrine, 0.8 ± 0.2
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