Modulation of Cardiac Sodium Channels by cAMP Receptors on the Myocyte Surface

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The phosphorylation of the cardiac sodium channel by adenosine 3′,5′-monophosphate (cAMP)–dependent protein kinase A leads to its inactivation. It was shown that extracellular cAMP can also modulate the sodium channel of rat, guinea pig, and frog ventricular myocytes in a rapid (less than 50 milliseconds), reversible, and dose-dependent manner. The decrease in the sodium current was accompanied by a 10- to 15-millivolt shift in the steady-state availability of the sodium channel toward more negative potentials and was inhibited by guanosine-5′-O-(2-thiodiphosphate) or pertussis toxin, suggesting that the extracellular modulation of the sodium channel by cAMP is mediated by a membrane-delimited mechanism that includes a pertussis toxin–sensitive G protein.

THE SODIUM CHANNEL IS ESSENTIAL for the excitability of heart muscle (*1, 2*). Although its physiological regulation is not well understood, the Na^+ channel can be modulated by several hormones (*3, 4*). β-Adrenergic agonists, for instance, suppress the Na^+ channel by shifting the voltage dependence of its inactivation toward more negative potentials (*5, 6*). This inhibition appears to be caused by the phosphorylation of the α subunit of the Na^+ channel by intracellular cAMP (7). Extracellular cAMP functions as a chemoattractant in the slime mold *Dictyostelium discoideum* by binding to surface receptors for cAMP and inducing transient phosphorylation of a regulatory G protein, Gα2 (*8, 9*). We now present evidence for the existence of cAMP receptors that regulate the Na^+ channel on the surface membrane of cardiac myocytes.

Isolated myocytes (*10*) in a whole-cell voltage-clamped configuration (*11*) were dialyzed with a solution containing EGTA (*12*) and rapidly (<20 ms) exposed to cAMP by means of an electronically controlled concentration-clamp technique (*13, 14*). cAMP (100 μM) decreased the Na^+ current (I_{Na}) reversibly by about 55% (Fig. 1A and Table 1). To measure I_{Na} accurately, the extracellular Na^+ concentration was lowered to 10 mM, and the Ca^{2+} current (I_{Ca}) was blocked by nitrendipine (1 to 10 μM) or Cd^{2+} (50 μM) or by lowering of the extracellular Ca^{2+} concentration to 100 μM. In a frog myocyte (Fig. 1, A and C), cAMP suppressed I_{Na} equally effectively in low or high extracellular Na^+ concentrations (Table 1). The suppression by extracellular cAMP varied somewhat from cell to cell but was generally complete within 50 ms in a rat ventricular myocyte (Fig. 1B). In frog ventricular myocytes, the suppressive effect of cAMP was sustained and repeatable for the duration of its application, and recovery of I_{Na} was rapid and complete on removal of cAMP (Fig. 1C). Mammalian atrial and ventricular myocytes responded similarly to brief exposures of cAMP, but prolonged exposures resulted in slow and complete recovery of I_{Na} in the presence of 100 μM cAMP. Such myocytes were often partially or completely insensitive to second or third applications of cAMP, suggesting possible desensitization of the response. The effect of cAMP was dose-dependent, such that 10 μM cAMP suppressed I_{Na} much less than did 100 μM, and 1 μM cAMP did not significantly suppress I_{Na} (Table 1). cAMP was equally effective in suppressing I_{Na} in high (100 mM) or low (10 mM) extracellular Na^+ concentrations and also when Ca^{2+} was absent from the bathing solution. This finding suggests that cAMP suppression of the Na^+ channel was not mediated by alteration of the channel selectivity (*4*).

Because cAMP does not easily permeate the cell membrane, because its suppressive effect on I_{Na} is almost complete within 50 ms, and because the effect is rapidly (<5 s) reversible even after 2 to 3 min of continuous exposure, it is likely that this effect is mediated by a surface membrane–limited mechanism. To further differentiate between the extracellular and possible intracellular effects of cAMP on I_{Na}, we used the ability

Table 1. Suppression of I_{Na} (mean ± SEM) by different concentrations of cAMP in rat, guinea pig, and frog ventricular (V) or atrial (A) myocytes bathed in solutions containing normal and reduced concentrations of Na^+. Holding potentials were −80 to −100 mV for ventricular myocytes and −120 mV for atrial myocytes. The Na^+ current was measured at depolarizing pulses to −40, −30, or −20 mV. I_{Ca} was blocked by 50 μM Cd^{2+} or 1 μM nitrendipine or was suppressed by 100 μM extracellular Ca^{2+}. In rat ventricular myocytes, the current density of I_{Na}, in the absence of extracellular cAMP, decreased from −120 ± 45 pA/pF to −16 ± 3 pA/pF when extracellular Na^+ was reduced from 137 to 10 mM. In frog ventricular myocytes, I_{Na} density similarly decreased from −65 ± 12 pA/pF in 103 mM Na^+ to −8.7 ± 0.8 pA/pF in 10 mM Na^+. Standard mammalian and amphibian internal solutions were used to dialyze the cells (*12*).

Source of cells	Extracellular Na^+ (mM)	Suppression of I_{Na} (%)		
		100 μM cAMP (*n*)	10 μM cAMP (*n*)	1 μM cAMP (*n*)
Rat (V)	137	62.4 ± 8.2 (6)	18.9 ± 7.6 (3)	
Frog (V)	103	54.0 ± 5.1 (10)	21.0 ± 3.4 (4)	
Rat (A)	80	55.1 ± 3.9 (10)		
Rat (V)	20	58.7 ± 5.2 (11)		4.8 ± 1.5 (5)
Guinea pig (V)	20	68.1 ± 5.3 (4)		
Rat (V)	10	55.8 ± 6.8 (13)	12.3 ± 1.8 (2)	
Guinea pig (V)	10	44.8 ± 2.7 (12)		
Frog (V)	10	55.0 ± 4.2 (22)		

Table 2. Suppression of I_{Na} (mean ± SEM) in frog ventricular myocytes in control cells, cells dialyzed with cAMP or G protein substrates, and cells incubated with PTX. External and internal Na^+ concentrations were 10 mM. I_{Ca} was blocked by 50 μM Cd^{2+} or 1 μM nitrendipine or was suppressed by 100 μM extracellular Ca^{2+}; *n*, number of cells; V_h, holding potential; V_T, test potential.

Treatment (*n*)	I_{Na}		V_h (mV)	V_T (mV)
	Control (pA/pF)	100 μM cAMP (pA/pF)		
Control (22)	−8.7 ± 0.7	−4.2 ± 0.6	−90 or −100	−20 or −30
50 μM cAMP (8)	−8.0 ± 0.7	−7.4 ± 0.7	−90 or −100	−20 or −30
50 μM GTPγS (8)	−6.1 ± 0.7	−3.5 ± 0.5	−90 or −100	−20 or −30
1 mM GDPβS (7)	−11.6 ± 1.5	−11.1 ± 1.6	−80 or −90	−20 or −30
PTX (0.5 μg/ml) for 5 hours (4)	−14.4 ± 1.6	−12.9 ± 2.0	−90	−30

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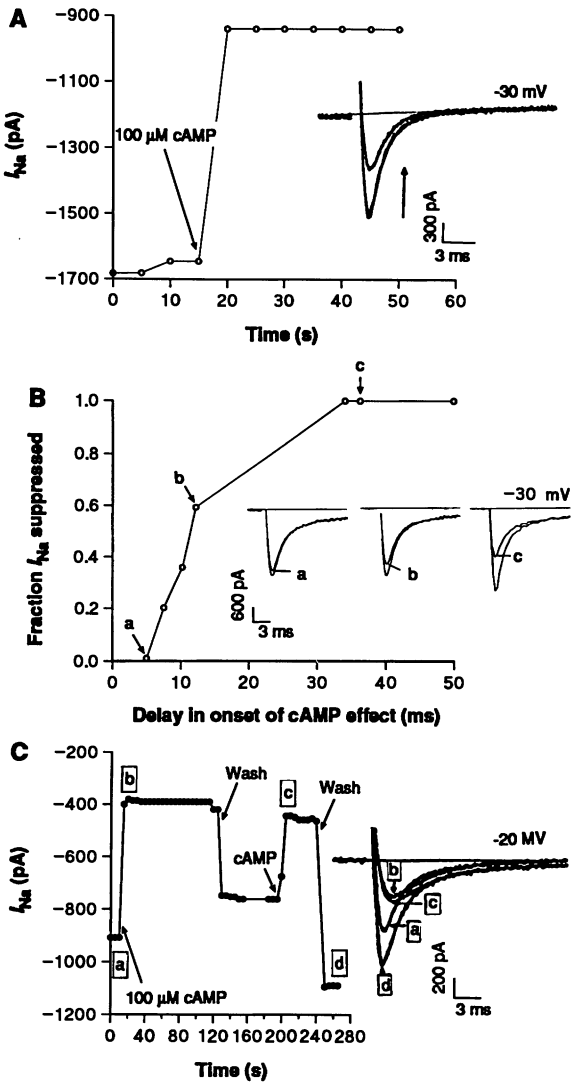

Fig. 1. Effect of extracellular cAMP on the Na^+ current in frog and rat ventricular myocytes. (**A**) Time course of suppression of I_{Na} in a frog myocyte by 100 μM cAMP in 10 mM extracellular Na^+. (**Inset**) Superimposed recordings of I_{Na} in control and cAMP-containing solutions activated by 30-ms depolarizing pulses to −30 mV at 5-s intervals from a holding potential of −100 mV (direction of arrow indicates reduction of I_{Na}). (**B**) Time course, in milliseconds, of the delay in onset of the suppression of I_{Na} in response to 100 μM cAMP in a rat ventricular myocyte, extracellular sodium concentration ($[Na^+]_o$) = 10 mM. (**Inset**) Superimposed tracings of I_{Na} activated by 20-ms depolarizing pulses to −30 mV at 5-s intervals from a holding potential of −70 mV at 5 ms (a), 12.19 ms (b), and 36.29 ms (c). (**C**) Time course of suppression of I_{Na} by repeated applications of 100 μM cAMP, $[Na^+]_o$ = 10 mM. (**Inset**) Superimposed tracings of I_{Na} activated by 30-ms depolarizing pulses to −20 mV from a holding potential of −90 mV: control I_{Na} (a); I_{Na} in the presence of 100 μM cAMP (b); I_{Na} after the second application of cAMP (c); I_{Na} after the second removal of cAMP (d). Atrial and ventricular myocytes from rat and ventricular myocytes from guinea pig and frog (*Rana pipiens*) were enzymatically isolated (*10*). The myocytes were placed in a fibronectin-coated chamber to stabilize the cells mechanically and allow rapid exchange (<50 ms) of the bathing solutions around individual cells with an electronically controlled, multibarreled concentration-clamp system (*4, 12*). Pipettes of resistance 1 to 2 megohms were used to whole-cell clamp (*11*) the mammalian myocytes (cell capacitances, 80 to 190 pF). The amphibian myocytes were smaller (cell capacitances, 45 to 100 pF) and were clamped with pipettes of resistance 3 to 5 megohms. K^+ was omitted from all solutions and was replaced by Cs^+. Amphibian external and internal solutions had lower osmolarities than mammalian solutions but otherwise were similar in composition (*12*). All experiments were carried out at room temperature. Composition of bathing and internal pipette solutions: (A) The amphibian external solution contained 10 mM NaCl, 100 μM $CaCl_2$, and 2 mM $MgCl_2$; the cell was dialyzed with standard internal solution (*12*); the cell capacitance was 92 pF. (B) Standard mammalian external (*12*) containing 10 mM NaCl and standard internal solutions were used; the cell capacitance was 345.02 pF. (C) External solution was the standard 10 mM NaCl solution; the internal solution contained no cAMP; the cell capacitance was 79 pF.

of intracellular cAMP to enhance I_{Ca} as an assay for the intracellular presence of cAMP by measuring the effect of extracellular application of cAMP on I_{Na} and I_{Ca} simultaneously with a double-pulse procedure. Although cAMP consistently and reversibly suppressed I_{Na}, it had no significant effect on I_{Ca} (Fig. 2A). The increase in intracellular cAMP concentrations occurring secondary to the application of isoproterenol, on the other hand, increased I_{Ca} over a period of a few minutes (Fig. 2C). If cAMP suppressed I_{Na} by diffusing into the cell, then it should have also produced comparable increases in I_{Ca} in Fig. 2, A and B. These findings support the idea that the rapid effect of extracellular cAMP is mediated by a membrane-delimited pathway.

To ensure that cAMP was acting through a surface receptor and was not gaining access to the inside of the myocyte, 10 μM H-7 (a protein kinase inhibitor) was included in the internal dialysate to prevent possible intracellular phosphorylation of the Na^+ channel. H-7 increased I_{Na} density in rat ventricular myocytes from −7.00 ± 1.1 to −18.11 ± 2.5 pA/pF (mean ± SEM, n = 7) and decreased I_{Ca} density from −11.88 ± 1.4 to −3.29 ± .76 pA/pF (mean ± SEM, n = 13), consistent with a suppressed protein kinase A system. In such cells, even though isoproterenol was ineffective in enhancing the Ca^{2+} channel, extracellular cAMP continued to suppress I_{Na} by 47.57 ± 4.8% (mean ± SEM, n = 7). Incubation of mammalian myocytes with the phosphodiesterase inhibitor theophylline (1 to 2 mM) or inclusion of 10 μM theophylline inside the patch pipette did not modify the effect of 1 μM extracellular cAMP on I_{Na}. These results further confirm that cAMP may suppress I_{Na} through a surface membrane mechanism.

In frog and mammalian myocytes, cAMP suppressed I_{Na} uniformly at all membrane potentials (Fig. 3A). In frog ventricular myocytes, the suppressive effect of cAMP was accompanied by a 10- to 15-mV shift in the voltage dependence of the steady-state availability of I_{Na} toward more negative potentials (n = 15) (Fig. 3B). The shift in the steady-state inactivation of I_{Na} with frog myocytes cannot account for all the suppressive effect of cAMP because cAMP continued to suppress the current even at a potential more negative than −120 mV where there is a plateau in the I_{Na} availability curve. In mammalian myocytes, the shifts in the inactivation parameters of I_{Na} were often small (~5 mV in rat atrium), insignificant (rat ventricle), or even in the wrong direction (~8 mV in guinea pig ventricle) to account for strong I_{Na}-suppressive effects of cAMP. After removal of cAMP, I_{Na} not only recovered fully, but was often enhanced (Figs. 1C and 3, B and C). This time-dependent enhancement of I_{Na}, observed consistently even in control cells, or prolonged dialysis (*6*) may result in an underestimation of the cAMP-induced suppressive effect.

Possible involvement of regulatory G proteins in mediating the I_{Na} response to extracellular cAMP was tested by inclusion of nonhydrolyzable substrates of G proteins (*14*) in the dialysis solution of the patch pipette or by preincubation of the myocytes with pertussis toxin (PTX). Inclusion of 1 mM guanosine-5′-*O*-(2-thiodiphosphate) (GDPβS) in the intracellular dialysis solution almost completely eliminated the suppressive effect of extracellular cAMP on I_{Na} (Fig. 4 and Table 2). In frog ventricular myocytes incubated with PTX (0.5 μg/ml for 5 hours at room temperature), 100 μM cAMP also had no significant effect on I_{Na} (Table 2). As in the frog myocytes (Table 1), suppressive effect of cAMP on the I_{Na} could be inhibited in rat ventricular myocytes by treatment of the cells with PTX (0.5 μg/ml for 5 hours at room temperature; n = 4). Thus, the extracellular effect of cAMP on I_{Na} may not be mediated through an α_s G protein previously shown for the β-adrenergic response, but through a G_i or novel

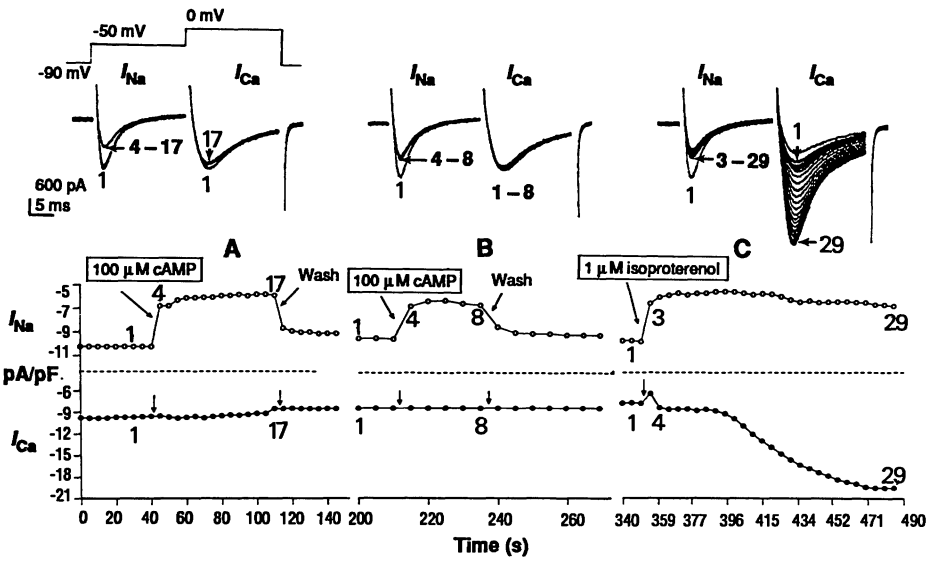

Fig. 2. The effect of extracellular application of cAMP (100 μM) on I_{Na} and I_{Ca}, measured simultaneously in a rat ventricular myocyte. Na^+ and Ca^{2+} currents were activated sequentially by depolarization of the cell first to −50 mV and then to 0 mV from a holding potential of −90 mV. (**A**) Top, superimposed traces of I_{Na} and I_{Ca} before and after cAMP treatment at points indicated in the lower panel by numbers. Bottom, time course of the effect of cAMP on I_{Na} and I_{Ca}. (**B**) Top, superimposed traces of I_{Na} and I_{Ca} after 2 s of application of cAMP [same cell as in (A)] at points indicated by arrows in the lower panel. Bottom, time course of suppressive effect of cAMP after a second application. (**C**) Top, superimposed traces of I_{Na} and I_{Ca} [same cell as in (A) and (B)] after treatment with 1 μM isoproterenol at points indicated in the lower panel. Bottom, time course of I_{Na} and I_{Ca} after addition of isoproterenol. The external solution (*12*) contained 10 mM NaCl. The internal solution (*12*) contained no cAMP and contained, in addition, 20 mM tetraethylammonium.

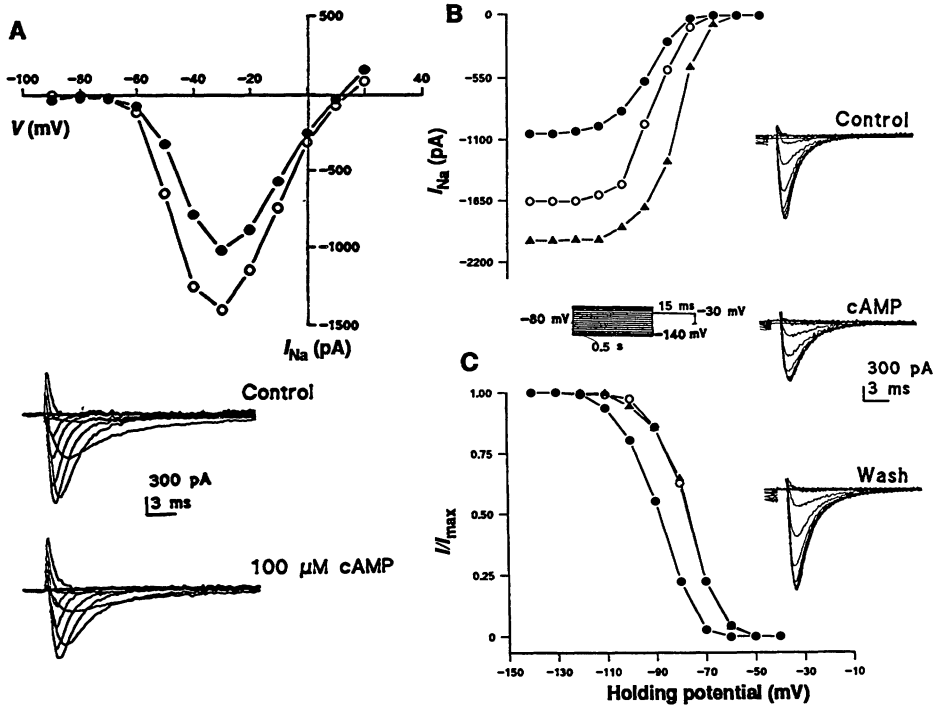

Fig. 3. Effect of cAMP on the voltage dependence and the steady-state availability of I_{Na} in a frog ventricular myocyte. (**A**) Top, voltage-dependence of I_{Na} from which the leak and capacitance currents have been subtracted in the presence (●) and absence (○) of 100 μM cAMP. Depolarizing clamp pulses of 30-ms duration were applied at 5-s intervals. Bottom, tracings of membrane currents, activated from −100 mV to +20 mV in control solutions and 100 μM cAMP. (**B**) Voltage dependence of the steady-state inactivation of I_{Na} in the presence (●) and absence (○, ▲) of 100 μM cAMP. (**Inset**) Superimposed tracings of membrane currents activated by conditioning pulses of 0.5-s duration from −140 mV to −40 mV with a 15-ms test pulse to −30 mV. (**C**) Normalized steady-state inactivation curves of I_{Na}. The standard external solution (*12*) was modified by reducing the Na^+ concentration to 10 mM and the Ca^{2+} concentration to 100 μM while increasing Mg^{2+} from 1 to 3 mM. The internal solution (*12*) contained no cAMP. Cell capacitance was 92 pF.

PTX-sensitive G protein. Inclusion of 50 μM guanosine-5′-*O*-(3-thiotriphosphate) (GTPγS) in the patch pipette, on the other hand, failed to alter the suppressive effect of cAMP on I_{Na} (Fig. 4 and Table 2), suggesting multiplicity of GTPγS effects, including those mediated through the arachidonic acid pathway (*15*). Thus, similar to the action of catecholamines on the Na^+ channel (*6*), cAMP may bind directly to an extracellular receptor site that is coupled to a regulatory G protein, causing inactivation of the Na^+ channel in a membrane-delimited fashion, or cAMP may phosphorylate the channel intracellularly and inactivate it.

To differentiate between mechanisms by which cAMP may suppress I_{Na} in the ventricular myocytes, we examined the effect of external cAMP in the presence of different intracellular concentrations of cAMP. When the internal concentration of cAMP was increased from 10 to 50 or 100 μM, the extracellular suppressive effect of cAMP on I_{Na} was often reduced or completely eliminated. Although I_{Na} was suppressed by about 60% when myocytes were dialyzed with solutions containing no cAMP, I_{Na} was not significantly altered by extracellular application of cAMP if intracellular cAMP was 50 to 100 μM (Fig. 4 and Table 2). Because intracellular elevation of cAMP also alters the gating parameters of I_{Na} by shifting the steady-state inactivation of I_{Na} toward more negative potentials (*6*), the extracellular and intracellular regulatory pathways may be mediated by a common mechanism that leads to phosphorylation of I_{Na}.

Surface receptors other than the purinergic receptors may mediate the effects of cAMP on the Na^+ channel because cAMP continued to suppress I_{Na} in the presence of adenosine, and adenosine triphosphate continued to suppress I_{Na} even when I_{Na} had recovered in the presence of cAMP. Slow recovery of I_{Na} during prolonged exposure to extracellular cAMP in mammalian myocytes may suggest desensitization of the putative cAMP receptor. Inclusion of GTP (200 μM) or GTPγS (50 μM) in the internal dialyzing solution did not alter the transient nature of the suppressive effect of cAMP on I_{Na}. In this respect, recovery from desensitization was often slow and incomplete, suggesting slow (8 to 10 min) turnover of the receptors or possible internalization of the receptor protein. In terms of its transient nature, the effect of cAMP in mammalian myocytes appears to be similar to the effects of cAMP on *Dictyostelium*, in which the activity of Gα2 returns to baseline values after 15 min of exposure to cAMP and where the second application of cAMP is ineffective in altering the activity of Gα2 (*9*).

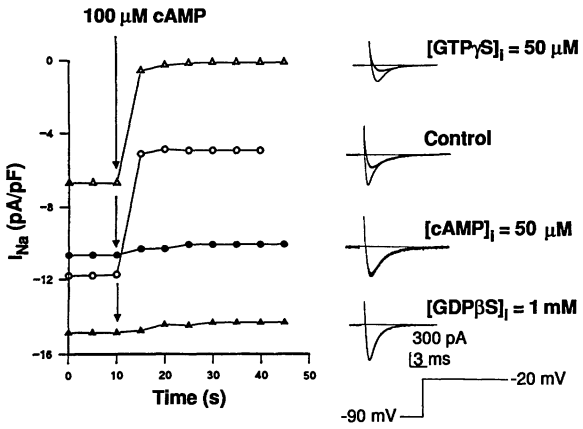

Fig. 4. The effect of extracellular cAMP on I_{Na} in frog ventricular myocytes dialyzed with cAMP, GTPγS, or GDPβS. Left, time course of suppression of I_{Na} by 100 μM cAMP applied 1 to 2 s after the third control measurement in cells dialyzed with the following: 50 μM GTPγS (△), control solutions with no intracellular cAMP (○), 50 μM intracellular cAMP (●), or 1 mM GDPβS (▲). Right, superimposed tracings of I_{Na} in the four indicated conditions activated by 15-ms depolarizing pulses to −20 mV from a holding potential of −90 mV. Solutions used in myocytes dialyzed with control (○) or 50 μM cAMP (●): all external solutions (*12*) contained 10 mM NaCl and, in the case of GTPγS and GDPβS, 1 μM nitrendipine. The internal solution (*12*) was standard except for the changes in the concentration of cAMP or replacement of cAMP with GTPγS or GDPβS. Cell capacitances were 79 to 99 pF.

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12. Mammalian external solutions consisted of 137 mM NaCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 10 mM glucose, and 10 mM Hepes buffer titrated to pH 7.4. Mammalian internal solutions contained 110 mM CsCl, 10 mM NaCl, 5 mM magnesium adenosine triphosphate (MgATP), 14 mM EGTA, 0 to 10 μM cAMP, and 20 mM Hepes buffer at pH 7.2. Amphibian external solution contained 103 mM NaCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, and 10 mM Hepes buffer at pH 7.4. Amphibian internal solutions contained 77.5 mM CsCl, 10 mM NaCl, 5 mM MgATP, 10 mM EGTA, 0 to 10 μM cAMP, and 10 mM Hepes buffer at pH 7.2. We adjusted the pH by adding the hydroxide of the major cation (Cs^+ or Na^+). Extracellular Na^+ concentrations were lowered by substitution of equimolar CsCl for NaCl.
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Autoassociation and Novelty Detection by Neuromechanics

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Many biomechanical systems contain ball joints with several elastic actuators (muscles) obliquely attached to the links. The problem of calculating the optimum actuator commands to achieve a desired link orientation is a difficult one for any control system; however, the elasticity of the actuators may be part of the solution. Mechanoreceptors such as those found in muscles and tendons are capable of performing operations that can be regarded as autoassociation and novelty detection, respectively, by minimization of potential energy. The information provided by such sensors may then be exploited for optimization of muscle coordination.

JOINTS IN BIOMECHANICAL SYSTEMS are usually moved by muscles attached to the links. Such muscles are elastic, so a given motor command does not result in a unique muscle length or torque. The arrangement of muscles in space is oblique, so the direction of movement generated by one muscle is affected by the activation of another muscle, and the number of muscles is always greater than the number of degrees of freedom of the joint, so there is a continuum and hence an infinite number of possible motor commands for achieving a given movement of a link. As a result, it seems difficult to find a procedure that yields an optimal pattern of motor commands for any desired orientation of the link. The information provided by sensors located in the elastic actuators can help to solve this coordination problem, if the system incorporates operations similar to autoassociation and novelty detection.

Autoassociation has been shown to exist in multiunit systems that allow for "multilateral" or long-range interactions, such as simulated neural networks interacting through synapses (*1*), spin glasses interacting through electromagnetic fields (*2*), electronic circuits interacting through connections (*3*), or optical systems interacting through photons (*4*). I will show that the interactions between elastic actuators, such as muscles, acting on a common rigid body, combined with suitable receptors, such as mechanoreceptors, provide the basis for autoassociation and novelty detection. Among vertebrate muscle systems, the muscles rotating the eyeball expose these properties particularly clearly: there are six springlike muscles attached to a common rigid body, each muscle richly endowed with muscle receptors (*5*) and tendon receptors (*6*) that increase their activity upon mechanical stretch of the "parent" muscle.

To keep the treatment as simple as possible and to arrive at a linear characterization of the mappings, I used a first-order approximation (*7*) of the system behavior in the vicinity of a particular operating point. Thus an orientation change of the rigid body can be represented by a three-dimensional (3-D) vector δe, the direction of which is the axis of rotation and the length of which is a measure of the angle of rotation (*8*). The angular elongations δp_i of the n individual muscles are obtained from the scalar product of the direction of orientation change δe with the unit directions of muscle action, and they may be written

$$\delta p = -M^T \delta e \qquad (1)$$

where M is a $3 \times n$ matrix, the columns of which are formed by the n unit directions of rotations that could be caused by individual muscles, and the superscript T denotes the

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