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Medical Intelligence

Cyclic Nucleotides

*Richard A. Wiklund, M.D.**

IN THE 1950's, Sutherland and Rall discovered the intracellular mediator of the glycogenolytic effect of epinephrine and subsequently identified this mediator as cyclic 3',5'-adenosine monophosphate[1] (fig. 1). This knowledge has led to new understanding in many areas of endocrinology, including the adrenergic and cholinergic mechanisms so important in the care of anesthetized patients. Alterations of the adrenergic and cholinergic systems represent a significant aspect of the toxicity of the inhalational anesthetics; drugs affecting these systems are commonly used before, during and after anesthesia. Research in cyclic nucleotides has progressed to a point where it is useful to review established principles and to speculate on expected advances.

Information Transfer and Messenger Hormones

Since early in the twentieth century, catecholamines have been known to produce elevations in blood glucose and free fatty acids. Sutherland, Rall, and co-workers[2-5] described the means by which these *extracellular* hormones produce metabolic changes *within cells*. Epinephrine activates the phosphorylase required for the conversion of glycogen to glucose. Activation of the enzyme results from its phosphorylation, a process requiring ATP. When liver was homogenized and separated into particulate and supernatant fractions by centrifugation, Rall *et al.*[5] found that an initial interaction between epinephrine and the particulate fraction was essential for activation of phosphorylase. Following this interaction, a heat-stable factor that could activate phosphorylase activity of liver homogenates in the absence of epinephrine was isolated. Lipkin *et al.*,[6-7] in collaboration with Sutherland's group, aided in the identification of the heat-stable mediator of epinephrine-induced phosphorylase activation as cAMP.

Sutherland's work supports a broad concept, originally propounded by Huxley,[8] that hormones and other chemical transmitters such as epinephrine are "information transferring molecules." Epinephrine stimulates a receptor in the membrane of sensitive cells influencing the conversion of ATP to cAMP. Robison, Butcher, and Sutherland[9] have called such chemical transmitters "messenger hormones," and cAMP, as the intracellular mediator of hormone stimulation, the "second messenger." The messenger hormones have the ability to elicit a rapid response from target cells, with the extent degree of response related to the concentration of hormone present. There are many messenger hormones with widely different "messages" or information for transfer. In common, their message is mediated by alterations of intracellular levels of cyclic nucleotides. It is apparent that there are other classes of hormones that are not mediated by cyclic nucleotides, *e.g.*, growth hormone, thyroid hormone, and the glucocorticoids.

While its exact mechanism is not understood, the adenylate cyclase system represents a sensitive and effective means of information transfer from extracellular substances to

ABBREVIATIONS

AMP = 3',5'-adenosine monophosphate
cAMP = cyclic 3',5'-adenosine monophosphate
ATP = adenosine triphosphate
CN-PDE = cyclic nucleotide phosphodiesterases
GMP = 3',5'-guanosine monophosphate
DB-cAMP = N^6-2'0-dibutyryl-cAMP
MB-cAMP = N^6-monobutyryl-cAMP

* Assistant Professor of Anesthesiology, Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, Virginia 22901.

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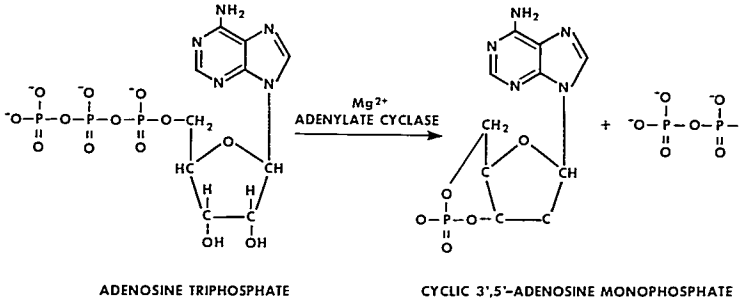

FIG. 1. The enzymatic production of cyclic 3',5'-adenosine monophosphate. Enzymatic activity is limited to particulate fractions of cell homogenates. Since intracellular pyrophosphatases limit the availability of inorganic pyrophosphate, the reverse reaction is of no biologic significance.

effect control of basic cellular processes such as glycogen metabolism, membrane permeability, and cellular contractility. Robison *et al.*[10] proposed a two component model of this system (fig. 2). An analogy was drawn to the established relationship of the regulatory and catalytic subunits of enzymes. The "regulatory subunit," or hormone receptor, faces the extracellular fluid and gives the adenylate cyclase system a degree of specificity in hormone binding. In an undetermined manner, receptor binding of hormones activates a "catalytic subunit" which is oriented toward the inside of the cell. This catalytic site has access to substrate (ATP) for conversion to cAMP. Depending on the tissue studied, the "regulatory subunit" may contain a variety of receptors for different hormones, all of which seem to be linked to a single catalytic site. Thus, epinephrine and glucagon are bound to different receptors on the liver cell membrane but activate the same catalytic site to produce an increase in cAMP content with subsequent activation of phosphorylase activity.

Formation and Disposition of Cyclic AMP

Cyclic AMP is a purine nucleotide derived enzymatically from ATP (fig. 1).[11-12] While the equilibrium constant of the reaction favors the formation of ATP, ubiquitous intracellular pyrophosphatases limit the availability of inorganic pyrophosphate. Thus, reversal of the adenylate cyclase reaction has not been demonstrated in intact cells, and is probably of no significance.

The free energy of hydrolysis of the diester bond of cAMP is −11,900 calories per mole.[13] However, in the biologic role of cAMP as a mediator of hormone action, this energy is not released, since activation of receptor subunits of intracellular enzymes does not involve the formation of a covalent bond with the nucleotide. Thus, activation of enzymes by cAMP is readily reversed.

While catalytic activity remains intact, hormone sensitivity is lost when adenylate cyclase is solubilized from particulate fractions of cell or tissue homogenates.[11,14-16] Bacterial sources, such as *Brevibacterium liquifaciens*, contain soluble adenylate cyclase with high specific activity.[17] Although homogenization produces a decreased affinity of receptors for hormones, broken cell preparations provide a suitable means of examining hormonal effects on the catalytic activity of adenylate cyclase.

Adenylate cyclase is unique among enzymes in that it is stimulated by inorganic fluoride at millimolar concentrations.[11] The nature of such stimulation appears to be a change in the maximum velocity of reaction with no change in the affinity of the enzyme for its substrate, ATP. Speculatively, it has been sug-

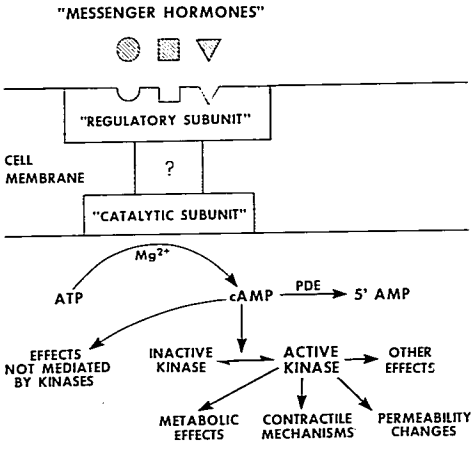

FIG. 2. Two-component model of adenylate cyclase proposed by Robison *et al.*[10] The "regulatory subunit" represents the receptors for various hormones most likely to be linked to a common catalytic site. The means by which the subunits are linked is undetermined. The "catalytic subunit" represents the membrane-bound enzyme, adenylate cyclase. Cellular mechanisms are altered by kinases, which are activated by cyclic AMP, the "second messenger" of hormone action.

gested that fluoride activation of adenylate cyclase may involve dephosphorylation of a phosphorylated and inactive catalytic site.[18]

Cyclic AMP is hydrolyzed to 5' AMP (figs. 2 and 3) by intracellular cyclic nucleotide phosphodiesterases (CN-PDE).[19] Brooker *et al.*[20] were the first to establish the existence of different forms of phosphodiesterase. Preparations from rat brain contained enzymes with high and low affinities for cAMP ($K_m = 1 \times 10^{-6}$ M and 1.3×10^{-4} M). Since then, kinetic as well as other characteristics of high- and low-affinity CN-PDE in many tissues have been described.[21] Both forms exist in most tissues. Cyclic AMP is the specific substrate for the high-affinity enzyme,[20] which is generally contained in the particulate fraction of cell homogenates.[21] Both cAMP and a second naturally occurring cyclic nucleotide, cyclic 3',5'-guanosine monophosphate (GMP), are suitable substrates for the low-affinity form of CN-PDE, a soluble enzyme.[20]

Magnesium is necessary for the catalytic hydrolysis of cyclic nucleotides.[19] High-molecular-weight, heat-stable activators of phosphodiesterase activity have been demonstrated in many tissues.[22–24] One such factor facilitates calcium-induced activation of phosphodiesterase activity in brain tissue.[24]

The phosphodiesterases are a likely target for pharmacologic intervention, or possibly, endocrine control. The methylxanthines, including caffeine, theophylline, and methylisobutylxanthine, are competitive inhibitors of phosphodiesterase activity[19] and are used experimentally to demonstrate potentiation of hormone response as well as low levels of adenylate cyclase activity.[9] Certain therapeutic effects seen with inhibitors of phosphodiesterase activity probably result from increases in intracellular levels of cAMP. For instance, the bronchiolar dilation observed with theophylline and the arteriolar dilation produced by papaverine probably result from smooth muscle relaxation associated with altered metabolism of cAMP.[25–26] Papaverine is a potent inhibitor of CN-PDE derived from vascular smooth muscle. Studies aimed at seeking new and selective inhibitors of CN-PDE offer the potential of providing a suitable means of treatment for a number of endocrinopathies.

Since cAMP penetrates cell membranes poorly and is rapidly metabolized, exogenous cAMP does not effectively mimic hormonal effects.[27] However, a variety of substituted derivatives of cyclic AMP may penetrate cell membranes, are not rapidly metabolized, and

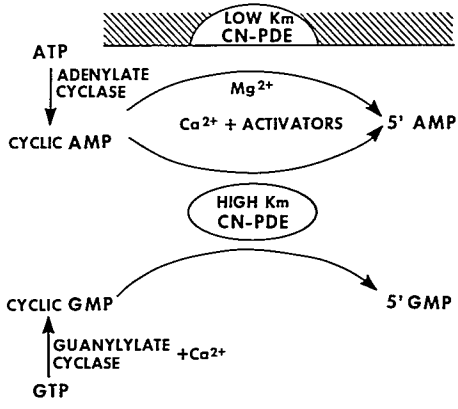

FIG. 3. The enzymatic degradation of cyclic nucleotides. Cyclic nucleotides are hydrolyzed to respective 5' monophosphates by cyclic nucleotide phosphodiesterases (CN-PDE). High-affinity (low K_m) CN-PDE is membrane bound and specific in substrate requirement for cyclic AMP. Low-affinity (high K_m) CN-PDE is soluble and capable of hydrolyzing both cyclic AMP and cyclic GMP. Enzymic activity is controlled by calcium ions and protein activators.

more accurately mimic hormones.[28] Such a compound is N^6-2'0-dibutyryl-cAMP (DB-cAMP). The oxygen at the 2' position must be free for biologic activity. DB-cAMP is converted to N^6-monobutyryl-cyclic AMP (MB-cAMP), which has approximately 80 per cent of the physiologic activity of cAMP ($K_a = 10^{-7}$ M for protein kinase of brain and heart[29]). At concentrations far higher than needed for physiologic effect, both DB-cAMP and MB-cAMP are effective inhibitors ($K_I = 10^{-5}$ to 10^{-3} M) of the high-affinity form of CN-PDE. Further, both compounds are poor substrates for the enzyme.

Site and Mechanism of Action of Cyclic AMP

In 1968, Walsh *et al.*[30] described the isolation of a cAMP-dependent protein kinase from skeletal muscle. Cyclic AMP bound to protein kinase, and binding was associated with activation of the kinase. In general, a kinase is a phosphorylating enzyme that uses ATP as a substrate. Phosphorylation of other enzymes by kinases may produce changes in activity of the enzyme. In liver and muscle, a cAMP-dependent protein kinase serves to phosphorylate and activate phosphorylase kinase.[31]

Several investigators[30–33] have studied the mechanism of cAMP activation of the protein kinases from liver and muscle in detail (fig. 4). They have shown that protein kinase is an enzyme composed of two subunits: a regulatory subunit and a catalytic subunit. As a complex of the two subunits, protein kinase has no catalytic activity. Cyclic AMP causes a dissociation of the holoenzyme. The free catalytic subunit has kinase activity and is able to activate inactive phosphorylase kinase. When cAMP is removed, reversal occurs, with loss of kinase activity.

We may now offer an explanation of the metabolic actions of epinephrine on glucose metabolism in the liver. Epinephrine stimulates beta-adrenergic specific receptors in hepatocytes, leading to increased levels of cAMP. Cyclic AMP interacts with the inactive protein kinase to yield an active protein kinase. This kinase phosphorylates phosphorylase kinase, which in turn converts inactive phosphorylase to active phosphorylase. Finally, active phosphorylase cleaves a glucose subunit from glycogen by phosphorylating it to glucose-6-phosphate.

Kuo and Greengard[34] have proposed a unifying hypothesis suggesting that all effects mediated by cAMP result from activation of protein kinases. Activated protein kinases then phosphorylate functional proteins, producing

alterations of metabolism, membrane permeability, contractility, or other basic cellular mechanisms (fig. 2). ATP is utilized by the protein kinases in the phosphorylation of these functional proteins. Phosphatases, on the other hand, dephosphorylate and reverse the altered activity of the functional proteins. In some systems, however, the need for protein kinase has been questioned.[35]

Adrenergic Mechanisms and the Cyclic AMP System

The criteria necessary to establish a relationship between a hormonal effect and the mediation of the cAMP system have been summarized by Sutherland. 1) the hormone should stimulate adenylate cyclase in broken cell preparations; 2) hormone stimulation in intact cells should produce a rise in cAMP levels coincident with or preceding the physiologic response; 3) inhibitors of cyclic nucleotide phosphodiesterase should potentiate the hormonal effect; 4) cAMP or substituted derivatives such as DB-cAMP and MB-cAMP should mimic the hormonal effect. All beta-adrenergic mechanisms are mediated by elevations of intracellular levels of cAMP.[9] These criteria are used below to show how cAMP is involved in the adrenergic pharmacology of interest to the anesthesiologist.

Murad *et al.*[14] prepared from canine cardiac muscle and liver membranous particles that were sensitive in their formation of cAMP to stimulation by adrenergic agents. Micromolar concentrations of epinephrine produced half-maximal activation which was competitively antagonized by dichloroisoproterenol. In the heart, partial antagonism was observed with cholinergic agents, but this could be blocked with atropine. They established a relative order of potencies for various agonists that paralleled those required for beta-adrenergic physiologic effects.

Robison *et al.*[36] correlated the relative contractile forces induced by beta-adrenergic agents with rises in cAMP content of perfused hearts. Beta-adrenergic blocking agents were capable of blocking the rise in cAMP content as well as the changes in inotropism. Initially, some doubt about the association of changes in cAMP content and increased inotropism existed, because the activation of phosphorylase seen with hormonal stimulation lagged behind augmented contractility.[37] It is now known that cAMP-activated protein kinases produce effects other than activation of phosphorylase, so this objection is no longer valid.

Rall and West[38] showed that the inotropic response to catecholamines was enhanced by theophylline, a known inhibitor of phosphodiesterase. Butcher and Sutherland[19] described the properties of cyclic nucleotide phosphodiesterase derived from cardiac muscle and showed that its activity was competitively inhibited by the methylxanthines, especially theophylline. Kukovetz[39] studied the effect of DB-cAMP in increasing the rate and force of contraction in guinea pig and rat hearts.

Skelton *et al.*[40] produced a dose-related change in the inotropism of electrically paced papillary muscles with DB-cAMP. Force–velocity curves shifted upward and to the right, indicating augmentation of contractility of the muscle. While propranolol was capable of blocking the response of catecholamines, it had no effect on the increased inotropism produced by DB-cAMP. Augmented contractility was not due to the hydrolytic release of butyrate, since responses were not altered by butyric acid alone at concentrations as high as 10^{-2}M. In cultured and beating isolated rat heart cells, Wollenberger[41] showed that the rhythmic and arrhythmic activity was increased by adrenergic hormones and DB-cAMP.

Ventricular muscle thus responds to cAMP by augmented contractility. How does this occur? Bailey and Villar-Palasi[42] have shown that a cAMP-dependent protein kinase derived from heart muscle controls the phosphorylation of troponin II. This fraction of the troponin–tropomyosin complex inhibits the ATP-ase activity of cardiac muscle actomyosin. Beta-adrenergic modification of cardiac muscle inotropism may well be mediated by phosphorylation of this component.

Alternatively, cAMP may influence myocardial contractility by exerting control over the flux of free calcium in the myoplasm. Cyclic AMP has been shown to activate protein kinase derived from cardiac sarcoplasmic reticulum and thus increase calcium transport.[43]

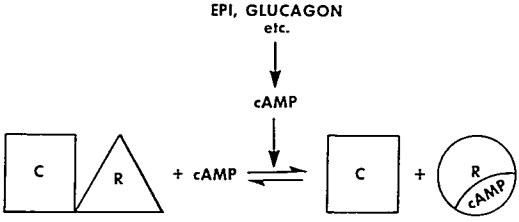

FIG. 4. Mechanism of cyclic AMP activity. Protein kinase is a holoenzyme that is dissociated in the presence of cyclic AMP into a regulatory (R) and a catalytic subunit (C). When dissociated, the kinase catalytic subunit is able to phosphorylate substrate. When cyclic AMP is withdrawn, the two subunits reassociate and the kinase becomes inactive.

Cyclic AMP is involved in the beta-adrenergic contractile response of smooth muscle. In contradistinction to cardiac muscle, the response is one of relaxation. Beta-adrenergic agonists produce marked relaxation in intestinal smooth muscle,[44] uterine muscle,[26] tracheal strips,[25] and aortic strips,[26] all of which can be prevented by beta antagonists. Relaxation occurs coincident with increases in cAMP content. Both are potentiated by methylxanthines. DB-cAMP produces similar relaxation. Szentivanyi[45] has suggested that bronchial asthma may represent a defect in adrenergic sensitivity of bronchiolar smooth muscle. Bernstein *et al.*[46] have reported that asthmatic patients have decreased urinary excretion of cAMP in response to administered epinephrine compared with normal controls.

The mechanism by which beta-adrenergic stimulation produces relaxation is not clear because of the confusing issues of alpha-adrenergic contraction or relaxation, cholinergic innervation, and the role of calcium in controlling smooth muscle tone. Andersson *et al.*[44] have proposed a negative-feedback mechanism involving cAMP and free calcium in the myoplasm. Cyclic AMP stimulates calcium binding and promotes muscle relaxation.

Calcium can be an activator or an inhibitor of phosphodiesterase activity.[22-24,44] In intestinal smooth muscle, calcium binding may allow unmasking of phosphodiesterase activity, with subsequent hydrolysis of cAMP. The picture is further confused by the presence of alpha-adrenergic and cholinergic receptors in intestinal smooth muscle. The mechanism of alpha-adrenergic-mediated intestinal smooth muscle relaxation is not understood, but does not appear to involve alterations of cAMP levels.[47] Cholinergic stimulation of intestinal smooth muscle contractility is related to the presence of a second naturally occurring cyclic nucleotide, cyclic 3',5'-guanosine monophosphate (cyclic GMP) and its associated catalytic enzyme, guanylylate cyclase.[48] Calcium appears to be essential for intracellular synthesis of cyclic GMP. Thus, in intestinal smooth muscle there is an elaborate balance between adrenergic and cholinergic mechanisms and the intracellular cyclic nucleotides with free calcium, possibly controlling phosphodiesterase activity on one hand and cyclic GMP synthesis on the other (see below).

In adipose tissue, catecholamines control lipolysis in a fashion similar to hepatic glycogenolysis.[49-50] Again, catecholamines interact with a receptor to increase intracellular cAMP content. An inactive protein kinase is activated and controls the conversion of an inactive lipase to an active form, with subsequent hydrolysis of triglycerides and release of free fatty acids. However, epinephrine is capable of activating both alpha- and beta-adrenergic receptors in human adipocytes. The overall result is an elevation of cAMP levels which is blocked by beta-adrenergic antagonists. Alpha-adrenergic antagonists potentiate the epinephrine-induced rise in cAMP, suggesting that, in adipose tissue, alpha-adrenergic mechanisms antagonize beta-adrenergic activation of adenylate cyclase.

Cyclic AMP and Adrenergic Neural Transmission

Certain neurotransmitters, including the three naturally occurring catecholamines,

have been identified in various regions of the central and autonomic nervous system. At some adrenergic sites, a hormone-specific receptor with adenylate cyclase activity has been demonstrated.[51-53] Adenylate cyclase activity is high in subcellular fractions associated with synaptic transmission.[53] CN-PDE has been shown by histochemical techniques to be associated with the postsynaptic membrane.[54]

Noradrenergic and dopaminergic neurons at certain sites in the central nervous system function mainly as inhibitory neurons. Siggins *et al.*[55-56] combined several complex techniques to show that noradrenergic neurons had inhibitory synaptic connections with Purkinje cells in the rat cerebellum, and that these inhibitory effects were mediated by cAMP, producing hyperpolarization of the postsynaptic membrane and decreased membrane conductance. Kebabian *et al.*[52] isolated a dopamine-sensitive adenylate cyclase from the caudate nucleus. These cells are part of the nigrostriatal tracts that exert an inhibitory influence on extrapyramidal motor neurons. The phenothiazines and butyrophenones (haloperidol and droperidol) are selective antagonists of dopamine receptors linked to adenylate cyclase derived from this region. For this reason, Wiklund and Ngai[57] have advised against the use of these tranquilizers for parkinsonian patients supported on L-DOPA therapy.

Bjorklund *et al.*[58] demonstrated concentrations of small, intensely fluorescent cells, believed to contain dopamine, in sympathetic ganglia (fig. 5). Libet and Tosaka[59] showed that dopamine produced hyperpolarization of the postsynaptic membrane which modulated nicotinic transmission. Kebabian and Greengard[51] have demonstrated dopamine-specific adenylate cyclase in the cervical sympathetic ganglia and believe it is the receptor for dopamine released from small interneurons. The interneurons receive their innervation (muscarinic synapse) from the same preganglionic fibers that synapse with the postganglionic cells (nicotinic synapse).

At the neuromuscular junction, catecholamines play a facilitative role that is not understood. Goldberg and Singer[60] showed increases in frequency of miniature end-plate potentials (MEPP) and neurotransmitter quantal content when DB-cAMP in high concentrations was added to the organ bath. This effect was potentiated by theophylline. They suggest that cAMP may limit the availability of calcium and thus facilitate neurotransmitter release.

Cyclic GMP

Cyclic GMP is of interest as a possible mediator of cholinergic transmission in some areas. Studies of the mediating role of cyclic GMP have not been as extensive as those with cAMP for several reasons. Goldberg *et al.*,[61] in their review, draw attention to the fact that cyclic GMP was demonstrated in tissues several years prior to any suggestion of its biologic role. Further, cyclic GMP is present in tissues in concentrations an order of magnitude less than cyclic AMP, and the synthetic enzyme, guanylylate cyclase, appears to be, at least in part, soluble.

Krause *et al.*[62] have shown that cyclic GMP produces slowing of spontaneously beating cultured heart cells. George *et al.*[63] showed that cholinergic stimulation of perfused hearts led to increases in cyclic GMP content. Lee, Kuo and Greengard[48] have shown similar effects in cerebral cortex, cardiac ventricle, and ileum. The increases in cyclic GMP content were blocked by atropine but not hexamethonium, suggesting that stimulation of guanylylate cyclase activity is associated with activation of muscarinic receptors. Goldberg *et al.*[61] suggest that calcium may be an obligatory participant in hormone-activated synthesis of cyclic GMP. Such an additional controlling component is not seen with adenylate cyclase. In those tissues with dual innervation, such as intestinal smooth muscle, this additional component may control the balance between adrenergic and cholinergic mechanisms.

Anesthetic Implications

There is evidence that anesthetics may alter relationships in cAMP systems, and that these alterations may be related to some aspects of the toxicity of the volatile anesthetics. In the early years after the introduction of

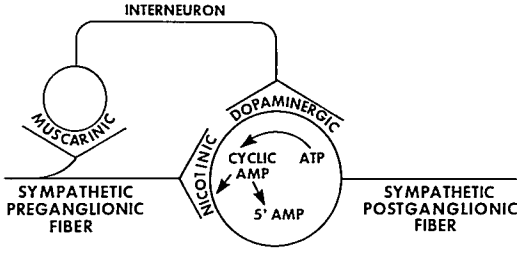

FIG. 5. Cyclic AMP modulation of synaptic transmission in sympathetic ganglia. Preganglionic stimulation leads to muscarinic stimulation of small interneurons. Release of dopamine from the terminals of the interneurons leads to activation of adenylate cyclase in the postganglionic neuron. Interneuronal cyclic AMP produces hyperpolarization of the postsynaptic membrane and thus modulates nicotinic depolarization.

chloroform into clinical use, Levy and Lewis[64] described the occurrence of ventricular arrhythmias associated with its use. Since then, it has been appreciated that the volatile and gaseous anesthetics produce variable "sensitization" of the myocardium and other tissues to endogenously released or exogenously administered catecholamines. The anesthetist recognizes many factors that favor the occurrence of arrhythmias in the presence of the "sensitizing" anesthetics: anesthetic dose coupled with ventilatory depression,[65] reflex stimulation,[66] excessive use of locally administered vasoconstrictors,[67] as well as others. While the precise mechanisms are poorly understood, these factors evoke beta-adrenergic stimulation as a common mechanism.[68]

In the presence of a "sensitizing" anesthetic, the amount of exogenously administered catecholamine required to produce ventricular arrhythmias is a fraction of that in the unanesthetized individual.[69] It should be noted that the increased blood levels of catecholamines observed in patients anesthetized with diethyl ether and cyclopropane are below predicted arrhythmogenic thresholds.[69] Studies of catecholamine turnover in the presence of "sensitizing" anesthetics have shown no alteration of release or reuptake of norepinephrine to explain this phenomenon.[70–73]

Yang *et al.*[71] have studied the role of halothane in potentiating the uterine relaxation produced by epinephrine. Halothane potentiated the effect of epinephrine and produced increases in the catalytic activity of adenylate cyclase and cyclic nucleotide phosphodiesterase. Detailed information about cellular concentrations of cAMP is needed.

Sprague and Ngai[75] showed that cyclopropane produced alpha-adrenergic potentiation in vascular smooth muscle associated with decreased incorporation of ^{14}C-adenine into cAMP. In a similar study, halothane and isoflurane produced inhibition of alpha-adrenergic-induced contraction of aortic strips and led to increased incorporation of labelled precursor into cAMP.[76] Adenylate cyclase activity was not measured directly in either of these studies, and the relationships between alpha- and beta-adrenergic systems in vascular smooth muscle are poorly understood. Despite these objections, it remains a likely hypothesis that anesthetic sensitization of adrenergically innervated tissue may be related to an effect of the anesthetics on cAMP metabolism and/or action.

Other Effects of Cyclic AMP

Cyclic AMP is the mediator or "second messenger" of many other hormones, including parathyroid hormone, thyrocalcitonin, gastrin, hypothalamic releasing factors, pituitary trophic hormones, and the prostaglandins.[9] The concepts and mechanisms observed in the cAMP-mediated systems discussed here apply to other hormones as well. Cyclic AMP is involved in areas of genetic control, especially gene expression.[35] Similarly, it is involved in the control of cell

differentiation, and loss of such control may be involved in malignant transformation.[77]

Summary

Cyclic nucleotides have been shown to be the intracellular mediators or "second messengers" of a wide variety of hormones. Cyclic AMP is produced by an enzyme, adenylate cyclase, which is an integral part of the cell membrane and is activated through undetermined means by an interaction of hormone with a receptor subunit on the surface of the plasma membrane.

Cyclic AMP appears to alter some aspects of cell function by producing structural alteration of a protein kinase within the cell. Interaction of cAMP with the receptor subunit of the protein kinase frees a catalytic subunit which, then, is able to phosphorylate functional proteins. Phosphorylation of these functional proteins may lead to changes in cell permeability, contractility, or metabolism. Cyclic nucleotide phosphodiesterases which hydrolyze the 3′5′ diester bond of the cyclic nucleotide play a limiting role in hormonally induced changes of cAMP levels.

Beta-adrenergic stimulation in all sensitive tissues studied produces activation of adenylate cyclase and elevation of tissue levels of cAMP. Effects of volatile anesthetics on adenylate cyclase and cyclic nucleotide phosphodiesterase activity may account for the phenomenon of anesthetic sensitization of adrenergic receptors in a variety of tissues.

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