posefully grooved and highly polished specimens of magnetic minerals are of particular interest. It would also be useful for the archeologist excavating Olmec burials and offerings to carefully note their alignments and consider them in a geomantic context.

In addition to the discovery of supporting artifacts, establishment of Olmec primacy of the lodestone compass depends on the acquisition of the archeomagnetic data for the Early Formative period. I appeal to archeologists who find good archeomagnetic samples (burned hearths and postholes) from the Formative periods to convey this information to R. DuBois of the University of Oklahoma. In a few years, the archeomagnetic data should be available for the last three millennia and the possibilities are very exciting.

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33. R. L. DuBois, personal communication.

34. I give special thanks to Michael Coe for permitting me to examine the San Lorenzo artifact and for much helpful encouragement and enthusiasm, B. J. Evans for his warm offer of help and expertise in providing the Mössbauer spectral data and analysis, and Robert DuBois and his students for the very useful discussions of the archeomagnetic record and the spinner magnetometer analysis. I also thank Kent Flannery, Robert Fuson, David Grove, David Joralemon, and Mary Buchwald for stimulating discussions and ideas and Anthony Aveni for introducing me to the fantastic civilizations of the pre-Columbian New World.

The Metabolic Code

Biological symbolism and the origin of intercellular communication is discussed.

Gordon M. Tomkins

This article presents a model for the evolution of biological regulation and the origin of hormone-mediated intercellular communication. Because of certain similarities with the processes of genetic coding, the present hypothesis is termed the "metabolic code." The formulations are almost entirely speculative and should therefore be regarded, at least for the moment, primarily as a pedagogical device for organizing a number of facts about cellular control. However, since analogies are drawn between regulation in unicellular prokaryotes and in multicellular eukaryotes, the ideas put forward might also prove useful for suggesting new experimental approaches to understanding sophisticated control mechanisms in complicated higher organisms.

Because of the ubiquity of cyclic adenosine monophosphate (cyclic AMP) in biological regulation, considerable attention is directed toward its function and possible evolution. Nevertheless, as treated in the present context it may represent only a model for other as yet undiscovered intracellular effectors which also operate according to the principles outlined below.

Cyclic AMP, originally discovered during studies on the mechanism of epinephrine action (*1*), has subsequently been shown to mediate the intracellular actions of almost all those hormones that interact with the cell membrane (*2*). Cyclic AMP also controls the "catabolite repression"

mechanism in bacteria (*3*) and other microorganisms (*4*), and more recently—together with the related nucleotide cyclic GMP (cyclic guanosine monophosphate) has been implicated in the modulation of growth and development of a large number of cell types in both prokaryotic and eukaryotic organisms. For example, it has been suggested that these molecules play important roles in the immune response (*5*), the nervous system (*6*), and the process of malignant transformation (*7*).

Such ubiquity implies one of two explanations. The cyclic nucleotides, by virtue of some intrinsic chemical or physical properties, could be absolute requirements for the living state. This seems unlikely, however, in view of the viability of mutant organisms lacking adenylate cyclase, the enzyme that catalyzes the formation of cyclic AMP (*8, 9*). Alternatively, once the cyclic nucleotides had formed (as the result of a biosynthetic accident), their universality derived from the adaptive advantages conferred upon descendants of the organisms in which they first appeared.

In this article I adopt the latter point of view which, together with other assumptions about the evolutionary origins of biological control, suggests a model for the organization and strategy of regulatory mechanisms in modern unicellular organisms as well as indicating the principles which underlie intercellular communication in metazoa.

Simple and Complex Regulation and the Metabolic Code

Even the most ancient molecular assemblies possessing recognizable cellular properties must have been capable of self-duplication, implying the prior existence of DNA and the machinery necessary for its replication. Obviously, these organisms also contained mechanisms for the expression of genetic information. Since both nucleic acid and protein synthesis are endergonic reactions, primordial cells were almost certainly endowed with the capacity to capture the necessary energy from the environment and to transform it into usable form, presumably ATP (adenosine triphosphate).

The biosynthetic capabilities of primitive cells were, however, probably quite limited. Changes in the environment which diminished the supply either of the monomeric units required for polymer synthesis, or compromised the formation of ATP might have easily proven lethal. Survival would therefore have required the evolution of regulatory mechanisms that could maintain a relatively constant intracellular environment in the face of changes in external conditions.

In this discussion, I shall define two modes of regulation, "simple" and "complex," both present in modern organisms, which differ from each other in their relative sophistication as well as, most likely, the order in which they evolved.

The essential feature of simple regulation is a direct chemical relationship between the regulatory effector molecules and their effects. Thus, substrates or end products affect their own metabolism, independent of the biochemical mechanism employed. Simple regulation may be positive, as in enzyme induction, or negative, as in feedback inhibition of enzyme activity and repression of enzyme biosynthesis.

If regulation were limited only to simple mechanisms, survival might be tenuous, since the regulatory effector molecules are themselves important metabolic intermediates. Dramatic changes in the intracellular environment could therefore follow rapid depletion or replenishment of essential nutrients. However, present-day organisms also display more sophisticated regulatory behavior, presumably of later evolutionary origin than the simple mechanisms, which confer greater stability on the internal environment. I define these as "complex" control mechanisms.

Complex regulation is characterized by two entities not operating in simple mechanisms: metabolic "symbols" and their "domains." The term "symbol" refers to a specific intracellular effector molecule which accumulates when a cell is exposed to a particular environment (*10*). For example, cyclic AMP in most microorganisms acts as a symbol for carbon-source starvation, and ppGpp (guanosine 5′-diphosphate 3′-diphosphate) (*11*), a symbol for nitrogen or amino acid deficiency.

Metabolic symbols need bear no structural relationship to the molecules which promote their accumulation in a nutritional or metabolic crisis (that is, cyclic AMP is not a chemical analog of glucose). Another important propety of intracellular symbols is metabolic lability, which allows their concentrations to fluctuate quickly in response to environmental change. For instance, cyclic AMP and ppGpp are both rapidly formed and inactivated by specific enzymic reactions (*12, 13*).

Since a particular environmental condition is correlated with a corresponding intracellular symbol, the relationship between the extra- and intracellular events may be considered as a "metabolic code" in which a specific symbol represents a unique state of the environment.

A second essential concept in complex regulation is that of the "domain" of a symbol, defined as all the metabolic processes controlled by the symbol. For instance, the responses of a glucose-starved *Escherichia coli* constitute the domain of cyclic AMP in this organism, and the reactions of the "stringent response" (*14*) of amino acid–deprived bacteria form the domain of ppGpp. A comparison of these responses illustrates that the biochemical reactions included in the domain of a symbol are related by their biological effects rather than their chemical mechanisms. Thus, ppGpp may interact with a variety of cellular macromolecules to coordinate the reactions involved in the stringent response; these reactions include gene transcription (*15*), membrane transport (*16*), and a variety of enzyme-catalyzed metabolic interconversions (*17*). Cyclic AMP, on the other hand, may interact with only a single bacterial receptor protein (CRP) which, in turn, associates with specific DNA sequences regulating the transcription of genes under catabolite repression control (*18*).

In *E. coli*, flagellin synthesis requires cyclic AMP (*19*). As a result, bacteria become motile, presumably as an adaptation to nutritional stress. The catabolite repression domain therefore contains elements that affect gross aspects of bacterial behavior as well as metabolism. Furthermore, a given process may be included in a particular domain under only special circumstances. For instance, the transcription of an inducible, catabolite-repressible operon will take place only in the presence both of its specific inducer as well as of cyclic AMP. Moreover, a given process might be part of several different domains. These considerations indicate that the symbol-domain relationship endows a cell with considerable regulatory sophistication, allowing a relatively simple environmental change to bring about a complex coordinated cellular response.

Evolution and Universality of the Metabolic Code

To explore these ideas further, and in particular to extend them to intercellular communication, it is useful to speculate about the evolutionary basis of complex regulation. Despite the virtual impossibility of obtaining relevant experimental data about historical origins, an examination of present-day biochemical reactions suggests reasonable possibilities. For example, ppGpp is made from GTP (guanosine triphosphate) during the "idling" of protein synthesis (*20*), while the ribosome-messenger complex is temporarily deprived of the

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amino acid specified by a particular codon (*21*). This mechanism also suggests the evolutionary origin of ppGpp. Since GTP is used extensively in protein synthesis, inhibition of this process by amino acid starvation of a primitive organism could have led to the formation of ppGpp, which for accidental (but genetically determined) reasons had favorable regulatory consequences for the organism in question and its progeny.

Similarly, cyclic AMP might have become associated with carbon-source starvation as a result of the "idling" of a primordial kinase which normally catalyzed the phosphorylation of glucose with ATP. In the absence of glucose, ATP might have been converted to the cyclic phosphate, again with favorable evolutionary consequences for the descendants of the organism in which it originally occurred.

The origins of the domains are equally obscure. However, one might assume that when cyclic AMP or ppGpp first appeared in evolution, nucleotide binding sites on proteins (*22*) already existed. As analogs of the nucleoside triphosphates, the regulatory molecules would thus have had a number of potential enzyme binding sites, interaction with which might have simultaneously influenced a number of biochemical reactions. The aggregate of those modulations that proved adaptively useful would ultimately have evolved into the complex regulatory domains.

By whatever means, complex domains probably evolved initially by the gradual accretion of new elements. Having once attained a certain level of complexity, however, they may have undergone significant changes in the rate and manner of their evolution. As illustrated by the universality of the genetic code (*23*), biological networks that interconnect a number of important cellular processes tend to attain evolutionary stability (*24*). This arises because mutations damaging one element of a system have pleiotropic effects that might imperil the entire organism. If this reasoning is applied to the symbol-domain relationship of the metabolic code, then once a domain has reached a certain degree of complexity at least some of its regulatory interactions would become constant with respect to evolutionary change.

This stability might be one of the explanations not only for the ubiquity of the cyclic nucleotides but also for an apparent generality of the metabolic code. For instance, cyclic AMP symbolizes carbon-source starvation in *E. coli*, whereas glucagon and epinephrine, hormones which stimulate cyclic AMP production in vertebrates, mobilize metabolic stores such as glycogen (*2*) and triglycerides (*25*) as if these organisms were also subjected to acute starvation. These aspects of the mammalian and bacterial responses to cyclic AMP seem quite similar. This and other apparent similarities between prokaryotic and eukaryotic regulation (*26*) indeed suggest a sort of universality in metabolic coding.

Intercellular Transfer of Metabolic Information: Origin of Hormones

According to the ideas already presented, the overall functional state of any cell is determined by the activities of the reactions in the various domains. In a colony of unicellular organisms, each individual cell responds independently to the environment by generating appropriate intracellular metabolic symbols. In most multicellular organisms, however, only certain cells are stimulated directly by the environment. These in turn secrete specific effector molecules, the hormones, which signal other cells (perhaps insulated from the environment) to respond metabolically to the initial stimulus. In higher organisms, such a chain of cellular communication may involve many intermediate steps. For example, in vertebrates, many environmental conditions are processed as nerve impulses impinging on the hypothalamus, from which hormones travel to the pituitary. From there, other hormones are transmitted to a variety of different cells, many of which manufacture specific products in response to the initial stimulus originating in the nervous system. Here I propose a mechanism by which metabolic coding in unicellular organisms might have evolved into the endocrine system of the metazoa.

Dictyostelium discoidium, a cellular slime mold, serves as an excellent model for how the transition might have come about. Given sufficient nutrients, this organism exists as independent myxamoebas. Upon starvation, they generate cyclic AMP and release it into the surrounding medium (*27*). This substance serves as a chemical attractant that causes the aggregation of a large number of myxamoebas (*28*) to form a multicellular "slug." In this case, as in *E. coli*, cyclic AMP acts as an intracellular symbol of carbon-source starvation. In addition, however, the cyclic nucleotide is released from the *Dictyostelium* cells in which it is formed and diffuses to other nearby cells, promoting the aggregation response. Cyclic AMP thus acts in these organisms both as an intracellular symbol of starvation and as a hormone which carries this metabolic information from one cell to another.

These phenomena raise the question of why the cyclic nucleotides do not commonly play extracellular, hormonal roles in organisms more complex than the slime mold. Although it has been suggested (*29*) that these compounds mediate some short-range intercellular transactions, their locus of action is largely intracellular, while long-range chemical communication between cells is effected by other types of molecules. One reason for the predominantly intracellular action of the cyclic nucleotides may be their metabolic lability. It was pointed out above that the rapid turnover of intracellular symbols is advantageous for adaptation in unicellular organisms. Because of their sensitivity to hydrolysis the extracellular lifetime of the cyclic nucleotides is probably not long enough to allow them to travel the relatively long distances required for intercellular communication in large metazoa. It has been argued (*30*) that an increase in the size of organisms is favored by evolution. If this be the case, metabolic information must be transmissible over longer and longer distances (up to several meters in large vertebrates). Because of the unsuitability of intracellular symbols for this purpose, I propose that the hormones, which are more metabolically stable, took on this role.

These substances carry information from "sensor" cells in direct contact with environmental signals, to more sequestered responder cells. Specifically, the metabolic state of a sensor cell, represented by the levels of its intracellular symbols, is "encoded" by the synthesis and secretion of corresponding levels of hormones. When the hormones reach responder cells, the metabolic message is "decoded" into corresponding primary intracellular symbols. Thus, hormones apprise responder cells of the concentrations of intracellular symbols in the sensor cells, allowing relatively protected internal organs to respond coordinately to external perturbations.

These reactions are clearly illustrated in the vertebrate endocrine system. Pituitary cells generate intracellular cyclic AMP in response to the polypeptide "releasing factors" from the hypothalamus (*31*). The cyclic AMP, in turn, stimulates the pituitary cells to release specific trophic hormones such as ACTH (adrenocorticotrophic hormone) or TSH (thyroid-stimulating hormone) (*32*). These diffuse to their target cells (adrenal or thyroid, for instance) where, after interaction with specific membrane receptor proteins, they stimulate the production of cyclic AMP. Depending on the nature of the target cell, the stimulation may cause the release of yet other hormones (steroids or thyroxin). In this way, endocrine cells act as both sensors

and responders, that is, intermediates in the transmission of metabolic information from primary sensor cells to the tissues in which the final chemical responses take place.

Neural Transmitters as Hormones

In many organisms the nervous and endocrine systems are intimately connected, and hormone release is often activated by neural stimulation. Moreover, intercellular communication within the nervous system is mediated by hormones, the neurotransmitters, that operate over very short distances. In view of the previous discussion, it is interesting to speculate on the possible metabolic origins and significance of the transmitters. Some of these substances, such as acetylcholine, occur in organisms under circumstances where they serve no apparent neural function (*33*). This suggests that the evolutionary appearance of the transmitters preceded that of the nervous system. Their hormonal function in modern organisms implies that they might have arisen as regulatory molecules—perhaps metabolic symbols, in the sense defined here. A possible clue to the biochemical origins of the neurotransmitters is provided by the fact that all the compounds currently accepted as transmitters are either amino acid metabolites—for example, the catecholamines, serotonin, γ-aminobutyric acid, acetylcholine—or are themselves amino acids (for example, glycine). Thus, perhaps the transmitters acted in primitive cells as intracellular symbols representing changes in environmental amino acid concentration. Eventually, these primordial nerve cells might have utilized the symbols in short-range intercellular (hormonal) roles, originally concerned with transducing information related to amino acid accumulation, and gradually with many other aspects of the environment.

Conclusions

Quite obviously, the formulations presented in this article are largely speculative. They represent an attempt to understand regulation in complicated multicellular organisms in terms of the evolution and function of seemingly comparable processes which occur in much simpler systems. Clearly, a number of gaps remain in the scheme. Nowhere have I dealt, for example, with the origins and significance of the steroids or thyroxin.

These molecules act as hormones in the sense that they transmit information about cyclic AMP levels from the sensor cells where they are produced to specific responder cells. Nevertheless, the effectors themselves appear to function primarily as direct intracellular modulators of gene activity in responder cells (*34, 35*). Thus, like cyclic AMP in *D. discoidium*, steroids and thyroxin act as both hormone and intracellular symbols. Their effects tend to be more protracted than those of the membrane-bound hormones which regulate cyclic AMP concentrations, perhaps because of relatively slow breakdown in the responder cells. Clearly, further work is required to begin to understand the evolutionary and metabolic significance of the thyroid hormones and the steroids.

A further difficulty relates to the fact that, although I have frequently referred to "symbols" in the plural, the only substances that might legitimately be so termed in eukaryotic cells at the present are the cyclic nucleotides. Nevertheless, there are increasing indications that other substances including certain ions (Ca^{2+}, Na^{+}, and K^{+}) might also function in this way (*36*).

Despite these evident deficiencies, it seems to me that there are significant advantages in presenting a general hypothesis at this time. One is that a great deal of heretofore unrelated information is unified for pedagogical reasons. Another is based on the likelihood that both the molecular mechanisms and overall strategy of regulation will be understood first in simple organisms. If this is the case, then the general scheme outlined here might suggest new experimental approaches to the study of intercellular communication in more complex organisms.

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