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Reaction Rates of a Muscle Model with Nucleotides

We have previously reported (*1*) that UTP (uridine triphosphate) might replace ATP (adenosine triphosphate), mole for mole, in eliciting the contractile response that is characteristic of the glycerol-extracted muscle fiber model. The present report (*2*) is an extension of this work to include an analysis of the rates of response of the model to ATP, UTP, and CTP (cytidine triphosphate). In addition, some indirect evidence is exhibited to support the hypothesis that the reaction of these nucleotides with the contractile protein may be a direct one that need not be mediated by a high-energy phosphate group transfer system such as the nucleoside diphosphokinase system identified by Krebs and Hems (*3*) and recently purified by Berg and Joklik (*4*).

The methods were essentially the same as those used in earlier experiments (*5*). Dog or rabbit psoas muscle fiber bundles were extracted at rest length in 2.9*M* glycerol at −15°C. A fiber bundle of about 0.1-mm² cross-sectional area was isolated and divided to provide a pair of shorter duplicate preparations, one of which was induced to contract with ATP, and the other of which was contracted in the presence of either CTP or UTP (*6*). The medium in which contraction was induced was phosphate-buffered $5 \times 10^{-2}M$ KCl containing $5 \times 10^{-3}M$ $MgCl_2$, at *p*H 7.8 and ionic strength 0.11 at 25°C. Nucleotides, as sodium salts, were added to the system to make their concentrations 4, 6, or $8 \times 10^{-4}M$. The latter value approximates the minimum amount of nucleotide necessary to induce maximal contraction (*5*). The tension developed by the model in the first minute following nucleotide addition was used as the criterion of the rate of the contractile response.

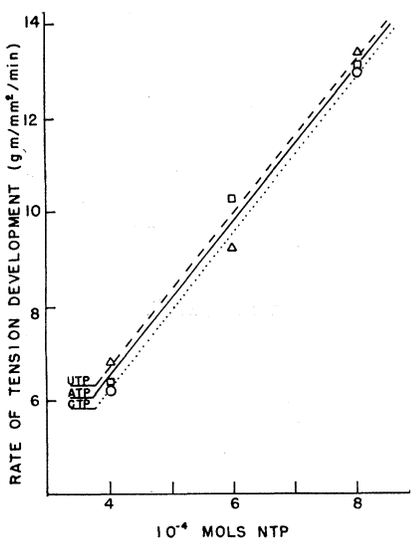

Fig. 1. Rate of tension development of the muscle model system when either ATP, CTP, or UTP was used as the stimulating nucleotide. Each point is the mean response of three or more fiber preparations. ATP, △——△; CTP, ○·····○; UTP, □ - - - - - □. The abbreviation NTP stands for any one of the three nucleotides tested.

The rates of tension development in a rabbit psoas model system are shown in Fig. 1. As nucleotide concentrations were increased toward the value necessary for maximal contraction, the rate of contraction increased linearly. It would appear that there was no significant difference in the model responses to either ATP, CTP, or UTP. Through accident the data for CTP at $6 \times 10^{-4}M$ were useless. Limited amounts of this material prevented complete repetition of the experiment, but a second comparison at this concentration alone showed no significant difference in the rates of tension development when either ATP, CTP, or UTP was used to stimulate contraction of the model system.

It is of interest that preliminary experiments employing guanosine triphosphate or adenosine tetraphosphate (*7*) as the nucleotide in this model system showed greatly reduced rates of tension development when they were compared with ATP-stimulated responses. Confirmation of these observations would indicate that a certain degree of specificity exists in the nucleotide-actomyosin reaction that might be related to nucleotide structure.

In order to elucidate further the similarities of the reaction of these nucleotides with the contractile proteins, the rates of tension development were diminished by employing several nonspecific inhibitors of the contractile response. Table 1 shows the similarity in degree of inhibition of the ATP or UTP response achieved by (i) aging the fibers 21 days at −15°C; (ii) partial sulfhydryl-group blockade with *p*-chloromercuribenzoate; and (iii) two intensities of trypsin digestion. These data have been interpreted as indicating that even when some essential sulfhydryl groups were blocked or when partial denaturation was achieved either by aging or by digestion, no significant differentiation in the model response to these two nucleotides was effected.

In certain energy-transfer systems (*4*), only one of the purine or pyrimidine nucleotides reacts directly with its acceptor substance. We must conclude from the present evidence, however, that for the muscle model system utilized in this investigation, three constituents of the "nucleotide pool," ATP, CTP, and UTP, may be equally available for direct and independent reaction with actomyosin to effect the molecular rearrangement that is the essence of muscular contraction.

Table 1. Nonspecific inhibition of the model response to ATP or UTP addition. (Dog psoas fibers extracted for 7 days were treated with each inhibitor and the rates of contraction of duplicate fibers were measured when either $10^{-3}M$ ATP or $10^{-3}M$ UTP was used to stimulate tension development)

Treatment	Percentage inhibition	
	ATP	UTP
Fibers aged 21 days at −15°C	58	62
p-Chloromercuribenzoate ($10^{-4}M$)	46	59
Tryptic digestion (trypsin concentrate, 2μg/ml, 5 min at 25°C)	34	50
Tryptic digestion (trypsin concentrate, 2μg/ml, 10 min at 25°C)	73	72

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North-South Asymmetry of the Pleistocene Ice Sheet

Geologists have long considered the great continental ice sheets of Pleistocene time to have been more or less symmetrical. An examination of the meteorology involved, however, does not lead to such a conclusion.

The cold winds that sweep across the Northern Hemisphere land masses may be described as polar air moving south-

ward. The cold air that chills the United States between October and April acquires its chief characteristics in Canada, Alaska, the northern Pacific, or, less commonly, in the northern Atlantic or in the northern mountain states. Such winds are called "northers" in many parts of the country because of the obvious source. The moisture that accompanies such winds is not, however, derived from the same source.

An outbreak, to the south, of polar air is generally accompanied by a southward displacement of the polar front, a more-or-less continuous east-and-west boundary zone between colder air to the north and warmer air to the south. In the winter, the polar front commonly lies across the United States. On the polar front are developed local eddies (these are 300 miles across, more or less). In each eddy, the polar front may be bent northward toward an apex at the center of the eddy. The left, or west, limb is a cold front, and the right, or east, limb is a warm front. (Mirror image relationships exist between the Northern and Southern Hemispheres.)

The cold air mass, the polar front, and hence the cold and warm fronts move southward, generally from Canada. The precipitation that accompanies the cold and warm fronts, however, is derived from the south. Warm, moist Gulf of Mexico or Atlantic air, lifted by the outbreaking polar air mass, is forced 20,000 feet or more above the ground surface; in the ascent it loses part of its moisture. The cold air, then, moves from the north, but the moisture has its source to the south. The material reviewed in the preceding paragraphs can be confirmed in almost any introductory textbook on meteorology.

It should be reasonably obvious that an outbreak of polar air is not necessary to precipitation of moisture from Gulf or Atlantic air. Should saturated tropical maritime air flow northward across the continent, topographic irregularities would result in a lift similar to that associated with the cold and warm fronts. Such "orographic" rain is in part responsible for the excess precipitation that coastal-plain and foothills areas receive over midwestern states. Under otherwise constant conditions, rainfall is a function of altitude. Nor should it matter a great deal whether the topographic irregularities are composed of rocks or ice.

Many North American geologists have presented the idea that the ice sheet was about 2 miles thick (*1*). Revelle, Sverdrup, and Munk (*2*) have recently suggested that either heat flow from the rocks beneath or plastic flow within the icecap will impose a thickness limit of between 1 and 6 kilometers. If their calculations are accepted, and isotasy is considered, the ice sheet may be treated as an orographic barrier that grew to heights between 5000 and 15,000 feet above undisturbed ground level. Such an orographic barrier, extending in an east-west line across the northern tier of states (or southern Canada), would be nourished by moisture derived from the south and, to a lesser extent, from the east. The northern and northwestern slopes would receive much less precipitation.

The Himalaya Mountains constitute an east-west orographic barrier with a regional altitude at least as great as that given in the preceding paragraph. North of the mountains, annual precipitation is in general less than 25 centimeters, and at all points it is less than 50 centimeters. South of the mountains, annual precipitation falls between a low of 100 centimeters over most of the plain of the Ganges River and a high in excess of 200 centimeters in the foothills and along the southern mountain slopes.

From this description, it may be reasoned that an ice sheet, initiated southeast or south of Hudson Bay, should grow southeastward or southward. Further, the higher it grows, the faster it should grow, until it reaches certain natural limits, such as those suggested by Revelle, Sverdrup, and Munk (*2*), or that imposed by the warmer air to the south. At the time of maximum development, such an ice sheet should have, in a north-south line, an asymmetrical profile, with the steepest slope at the south end of the line, and with most of the profile appearing as a gentle northward slope, tapering off in northern Canada. The southern slope would be of the order of 1 degree.

Further, except for early growth, such an ice sheet should be actively moving only in the zone of the steep southern slope; it should be essentially stagnant in the zone of the gentle northern slope. Such an ice sheet should have, at the time of maximum development, its greatest thickness (and hence the area of greatest scour, deepest depression, and highest rebound) near the southern limits.

A south-facing topographic barrier should have a strong effect on the behavior of the jet stream. Studies in the Himalaya Mountain area (*3*) show that the jet stream passes north of the mountains during summer and south of the mountains during winter. Perhaps an ice barrier such as I have described would not be passed on the northern side; if it were, the jet stream would have no suitable source of moisture with which to nourish the northern slope.

The jet stream is associated with two zones of air, one to the north and the other to the south. At 5000 to 10,000 feet, the northern zone is much the colder, with a temperature differential of the order of tens of degrees Celsius (*4*). Localization of the jet stream south of an ice barrier might serve to stabilize, geographically, this northward temperature gradient and, thereby, help to preserve the ice sheet.

If this is correct, the jet stream would aid in the development of the asymmetrical north-south profile of the ice sheet, and it would be indirectly responsible for the concentration of glacial scour near the periphery of the ice.

An asymmetrical ice sheet with the maximum bulk of the ice centered in the Great Lakes area leads to certain conclusions regarding isostatic loading and rebound, tilting, and the distribution of various ice-formed geomorphic features.

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3 June 1955

Stilbestrol-Contaminated Feed and Reproductive Disturbances in Mice

Serious reproductive disturbances, including scrotal hernia and persistent estrus, have been encountered in the breeding colony of white Swiss mice at the Rocky Mountain Laboratory as a result of inadvertent contamination of pelleted feed with diethylstilbestrol (stilbestrol) during processing in a mill previously used to prepare cattle supplement that contained the drug. Persons in charge of breeding colonies of mice and other small laboratory animals, as well as individuals using these animals for certain endocrinological studies (bioassay for estrogenic activity, pregnancy tests, hormone research), should be alerted to this potential hazard. Although a detailed account of our experience is in preparation, we should like to recount the highlights for the immediate benefit of others who may be confronted with the problem.

The mouse feed used at this institution is prepared according to our formula by a local feed mill. It is delivered in 3000-lb lots at 7 to 10 day intervals. Four separate lots of the pellets were shown to have appreciable estrogenic activity by bioassay (*1*) in 7 to 9-g female mice. None of the basic ingredients (soybean meal, corn, alfalfa meal, and meat and bone scrap) that had been used in preparing these lots of pellets showed such activity when they were similarly tested.