The kinetics of creatine kinase (CK) and adenylate kinase (AK) activities were monitored in intact diaphragm muscle by \(^{18}\text{O}\) phosphoryl oxygen exchange to assess whether these two phosphotransferases provide an interrelated function integral to high energy phosphoryl metabolism. This possibility was examined by quantitating the net rates of CK- and AK-catalyzed phosphoryl transfer in comparison to the total cellular ATP metabolic rate when CK activity in the intact diaphragm muscle was progressively inhibited by 2,4-dinitrofluorobenzene. In noncontracting muscle from untreated rats, net rates of CK- and AK-catalyzed phosphotransfer were equivalent to 88 and 7\%, respectively, of the total ATP metabolic rate. These results were compared with reported \(^{31}\text{P}\) NMR analyses of total creatine phosphate metabolism. This possibility was examined by quantitative relationship between the sum of the net rates of CK-and AK-catalyzed phosphotransfer compared with the total cellular high energy (ATP) metabolic turnover rate in intact diaphragm muscle, increases in net AK-catalyzed phosphotransfer were found to be directly proportional to the frequency of stimulated muscle contraction (12), and the stoichiometry between net AK-catalyzed phosphoryl transfer and anaerobic glycolytic ATP generation was nearly equivalent over a greater than 20-fold range of stimulated fluxes (13). The interpretation of these results was that AK-catalyzed phosphotransfer functionally couples ATP-consuming processes with anaerobic glycolytic ATP generation (13).

These studies of the dynamic behavior of phosphotransferase activities in intact diaphragm muscle also indicated that CK- and AK-catalyzed phosphoryl transfer may be functionally interrelated; marked increases in the rate of AK-catalyzed phosphotransfer occurred when CK catalytic velocity was suppressed in muscle deprived of oxygen (13). The interpretation that this represented a compensatory increase in the activity of one phosphotransferase to offset the impaired activity of another translated into CK and AK representing closely interrelated phosphotransfer systems integral to cellular energy metabolism. If so, it would help to explain at least in part how muscle performance and metabolic integrity remain relatively intact when CK activity is markedly suppressed (6, 7) or depleted (8) as described above.

The investigations reported here were intended to determine if and to what extent AK-catalyzed phosphotransfer can replace phosphoryl transfer catalyzed by CK when the latter activity becomes impaired. This was assessed by determining the quantitative relationship between the sum of the net rates of CK- and AK-catalyzed phosphotransfer compared with the total cellular high energy (i.e., ATP) metabolic turnover rate in intact diaphragm muscle. These quantitative assessments were made by \(^{18}\text{O}\) phosphoryl oxygen exchange analysis, which measures only net enzyme-catalyzed phosphoryl fluxes (12–15) in contrast to \(^{31}\text{P}\) NMR analysis using saturation transfer which, measures total unidirectional phosphoryl exchange rates (16). These phosphoryl transfer rates were measured when CK catalysis was progressively suppressed by treatment of intact diaphragm muscle with the CK inhibitor, 2,4-dinitrofluorobenzene (DNFB).

The results show that in noncontracting rat diaphragm muscle net CK-catalyzed phosphoryl transfer is equivalent to nearly 90\%, whereas AK-catalyzed phosphotransfer accounts for about 7\% of the total ATP metabolic flux. Impairment of intracellular CK activity by DNFB results in a quantitative
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Preparation and Incubation of Rat Diaphragms—Diaphragms were obtained from anesthetized (50 mg kg⁻¹ pentobarbital, intraperitoneally) male Sprague-Dawley rats (150–200 g) fed standard rat chow ad libitum. The procedures for incubating, stimulating, and preparing the tissue for analysis of ¹³⁵O content of metabolite phosphoryls has been described in detail (12, 14). Briefly, after excising the diaphragms, the muscle was dissected free of the rib cage, washed, and preincubated in physiological buffer (12) continuously bubbled with O₂/CO₂ (95%/5%). The whole diaphragms were preincubated for 40 min in the oxygenated medium without stimulation in the absence or the presence of DNFB (50–200 μM) before they were transferred to medium enriched in 25–40 atom % ¹³⁵Owater (Monsanto Co. and Isotec) not containing DNFB and incubated for an additional 1, 2, or 4 min before they were freeze-clamped with aluminum blocks cooled with liquid nitrogen. The frozen tissues were ground to a fine powder in liquid nitrogen and extracted with 3 m perchloric acid at –10 °C. Small samples of powdered tissue were assayed for glutathione (17, 18) and RNA (7). The details of procedures for purification of nucleotides, CrP, and Pi, and isolation of specific metabolite phosphoryls for analysis of ¹³⁵O content was carried out as described previously (12–15).

Analysis of the ¹³⁵O Content of Phosphoryls—Following enzymatic transfer of the β- and γ-phosphoryls of ADP and ATP and phosphoryls of CrP (via γ-ATP) to glyceraldehyde 3-phosphate, the latter was converted to the trimethylsilyl derivative as described previously (12, 14). The ¹³⁵O enrichment of the phosphoryls of γ-ATP, β-ATP, β-ADP, CrP, and Pi, was accomplished using gas chromatography-mass spectrometry (Hewlett-Packard 5970B mass spectrometer) by analysis of the ion masses (m/z) 357, 359, 361, and 363 corresponding to phosphoryl species of ¹³⁵O₂ to ¹³⁵O₄, respectively. The trimethylsilyl derivative of orthophosphate yielded mass ions (m/z) 299, 301, 303, 305, and 307 corresponding to species of orthophosphate containing from 0 to 4 atoms of ¹³⁵O.

Analysis of ¹³⁵O Phosphoryl Labeling Data—The net rate of AK-catalyzed phosphoryl transfer in the intact muscle was calculated from the rate of appearance of ¹³⁵O-containing β-phosphoryls in ADP and ATP (12). These β-phosphoryls derive from the γ-phosphoryls of ATP, which undergo more rapid replacement with ¹³⁵O-labeled phosphoryl species. The in situ net velocity of AK catalysis is, therefore, a function of both the rates of AK-catalyzed phosphoryltransfer and the kinetics of AK-γ-¹³⁵OATP. The net AK-catalyzed phosphoryl transfer rate was determined by the rate of appearance of CrP species with ¹³⁵O-labeled phosphoryls. The phosphoryl of CrP also derives from γ-ATP. To assure that the precursor γ-ATP was more rapidly replaced with ¹³⁵O-labeled species of phosphoryl than CrP, DNFB-treated diaphragms in which CK-catalyzed phosphoryl transfer was diminished (while the rate of γ-ATP labeling with ¹³⁵O was relatively unaffected) were used to create this circumstance (see “Results”). A computer model (Stella, High Performance Systems, Lyme, NH) of AK catalysis was used to estimate the net velocities of AK-catalyzed phosphorylation of AMP as described previously (12) from the rates of formation of β-¹³⁵OADP and β-¹³⁵OATP, which could also be used to determine the rate of the reverse chemical reaction of AK. The generation of AM and ATP from 2 ADP. A similar computer model (14) was used to estimate the net rates of CK-catalyzed phosphorylation of creatine (Cr) from the rates of formation of ¹³⁵OCrP in DNFB-treated diaphragms. These progressively inhibited rates of CK catalysis were used to determine the uninhibited rate by extrapolation (see Fig. 5).

Statistics—All values shown represent means ± S.E. unless otherwise indicated. Differences between means were assessed using Student’s t test.

RESULTS

Estimation of Net CK Velocity in Intact Rat Diaphragm Muscle—A problem in determining accurate net CK-catalyzed phosphoryl transfer rates in the intact rat diaphragm muscle cells is posed by the very similar rates of ¹³⁵O-enriched phosphorous appearance in CrP and in the γ-position of ATP (14). Because the ¹³⁵O-enriched γ-phosphoryl of ATP is the precursor of CK-catalyzed formation of ¹³⁵OCrP, the most accurate rates are obtainable by modeling kinetic data when the rate of γ-¹³⁵OATP generation is faster than that of ¹³⁵OCrP appearance (12, 14).

To deal with this potential problem, a strategy was devised to reduce the rate of CrP metabolism to less than that of γ-ATP by decrementally suppressing the activity of CK in the intact muscle with a relatively selective inhibitor of this enzyme and then determining the uninhibited velocity by extrapolation. An agent frequently used to inhibit CK activity in numerous types of cells is DNFB (17).

The effectiveness of DNFB to impair CK activity after treatment of intact rat diaphragm muscle with the inhibitor followed by cell disruption and in vitro assay of CK activity is shown in Fig. 1. Because the inhibitory action of DNFB is time-dependent, an optimal duration of tissue exposure was pretested and determined to be 40 min for the range of concentrations used (50–200 μM). When assessed in extracts of diaphragm muscle treated with 50, 100, or 200 μM DNFB, CK activity was found to be inhibited by 49, 65, and 84%, respectively. This corresponds to previous reports (17) of the effectiveness of DNFB to inhibit CK activity in different types of cells by ex vivo assessment. In the inset of Fig. 1 it is shown that the tissue concentrations of CrP and ATP were relatively
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unaffected by 50 or 100 mM DNFB but that at 200 mM the concentration of CrP was decreased by 10% and that of ATP was decreased by 37%.

In intact rat diaphragm muscle, the activity of CK determined by the rate of appearance of $^{18}$O-labeled phosphorlys in endogenous CrP exhibited a similar sensitivity to the inhibitory action of DNFB (Fig. 2) as that shown by the $\text{ex vivo}$ assessment (see Fig. 1). This inhibition of CK-catalyzed $^{18}$O phosphoryl labeling of CrP was equivalent to 35, 75, and 98% suppression of the intracellular CK activity with 50, 100, and 200 mM DNFB, respectively. The relative rate of $^\gamma$-ATP appearance was not diminished but rather increased, at least during the first 2 min of monitoring the DNFB treated muscles (Fig. 2, inset). This probably resulted from a disproportionate amount of the newly generated $^\gamma$-ATP not transferring its $^{18}$O-labeled $^\gamma$-phosphoryl to Cr because the CK catalyzing this reaction was inhibited.

Reduction by DNFB of CrP turnover rate to a level substantially lower than that of $^\gamma$-ATP permitted estimation of net velocities of CK in intact muscle using computer modeling of the $^{18}$O phosphoryl labeling kinetics (12, 14). These calculated net catalytic rates were used to construct the plot in Fig. 3 showing the relationship between the inhibition of $^{18}$O labeling of CrP versus computer-derived estimates of net CK velocities in intact rat diaphragm muscle. This relationship is very nearly linear, and the intercept on the abscissa, representing the uninhibited CK velocity in the intact muscle cells, was equal to $146 \pm 8$ nmol-min$^{-1}$ mg protein$^{-1}$.

Relationship between CK- and AK-catalyzed Net Phosphotransfer Rates in DNFB-treated Rat Diaphragm Muscle—It had been reported previously (13) that in rat diaphragm muscle in which CK activity was found to be diminished when the tissue was oxygen-deprived, there was a reciprocal increase in net AK-catalyzed phosphoryl transfer rate. To study whether this occurs in muscles when CK activity is directly inhibited by DNFB treatment, the rate of AK-catalyzed $^{18}$O appearance in the $\beta$-phosphoryls of ADP and ATP was examined in rat diaphragm muscle treated with the CK inhibitor DNFB. That the in situ activity of AK-catalyzed phosphotransfer increases when CK activity is inhibited by DNFB is clearly demonstrated in Fig. 4. The rates of AK-catalyzed appearance of $^{18}$O-labeled species of $\beta$-ADP (as well as $\beta$-ATP, not shown) are enhanced incrementally with concentrations of DNFB that progressively inhibit CK activity in the intact muscle (Fig. 2).

In Fig. 5 the net rates of CK- and AK-catalyzed phosphoryl transfer as a function of DNFB concentration are compared, and the relationship of these phosphotransfer rates to the total cellular ATP flux are also shown. The total ATP turnover rate determined by total $^{18}$O appearance in cellular metabolites (12, 14) was equal to $166 \pm 12$ nmol-min$^{-1}$ mg protein$^{-1}$ in the muscle not treated with DNFB. This basal ATP metabolic flux, which also corresponds to ATP turnover rates estimated from oxygen consumption data (14), was reduced by 11, 20, and 39% with 50, 100, and 200 mM DNFB, respectively (Fig. 5). The net CK velocity in the control muscle was shown in the earlier experiment (see Fig. 3) to be equal to $146 \pm 8$ nmol-min$^{-1}$ mg protein$^{-1}$. This is equivalent to about 88% of the total ATP metabolic flux. In this basal state (i.e., noncontracting and without DNFB) the net phosphoryl transfer rate catalyzed by AK (i.e., conversion of ADP) was determined to be $12 \pm 0.6$ nmol-min$^{-1}$ mg protein$^{-1}$, which was equivalent to approximately 7% of the total ATP flux; net phosphoryl transfer catalyzed by AK plus CK could therefore account for 95% of the total ATP metabolic flux in the control muscle. Treatment with increasing concentrations of DNFB resulted in decremental lowering of the net CK-catalyzed phosphotransfer velocity so that at 200 mM DNFB, this catalytic activity declined approximately 98%. The response of the AK-phosphotransfer system was virtually the reciprocal of that exhibited by the CK system (Fig. 5). Treatment with increasing concentrations of DNFB led to incrementally greater rates of net AK-catalyzed phosphotransfer so that at 200 mM DNFB the net AK velocity increased from $12 \pm 0.6$ to $96 \pm 3.1$ nmol-min$^{-1}$ mg protein$^{-1}$.

The percentage of the total ATP flux attributable to phosphoryl transfer catalyzed by AK increased from 7% without DNFB to the equivalent of 19, 45, and 94% with 50, 100, and 200 mM DNFB, respectively. CK-catalyzed phosphotransfer, on the
for the muscles treated with 100 and 200 μM DNFB. The percentage of the β-phosphoryl oxygens of cellular ADP replaced with 18O is shown as a function of time at the indicated concentrations of DNFB. The appearance of 18O-labeled β-phosphoryl was determined in the same diaphragms that 18O-labeling of the phosphoryl of CrP shown in Fig. 2 was determined, and the experimental details are the same as described in Fig. 2. Each value shown is the mean of duplicate diaphragms analyzed in triplicate. No value varied by more than 5% from the mean. This is a representative experiment of two very similar experiments from which almost identical results were obtained. Very similar effects of DNFB were observed on 18O labeling of β-ATP (not shown).

### Stoichiometry between Net CK-catalyzed Phosphotransfer and Total Cellular ATP Metabolic Flux—The analysis of CK- and AK-catalyzed phosphotransfer in noncontracting, intact muscle cells by 31P phosphoryl oxygen exchange analysis shows that the sum of the net fluxes catalyzed by CK (88%) and AK (7%) can account for most of the ATP metabolized in the noncontracting rat diaphragm muscle. This could be interpreted to indicate that in this basal state most all of the newly generated molecules of ATP are processed by either the CK or AK phosphotransfer system.

The CK catalytic rates determined here by 18O phosphoryl oxygen exchange analysis differ by more than an order of magnitude with those determined by 31P NMR saturation transfer technology (16, 20). This difference undoubtedly stems from the different kinetic parameters quantified by these procedures. 31P NMR analysis assesses total unidirectional phosphoryl exchange rates catalyzed by CK (16), whereas the 18O phosphoryl oxygen exchange measurements (12-14) assess net phosphoryl flux (i.e., appearance of newly generated molecules of [18O]CrP). A difference of the magnitude found between these total and net flux measurements is predictable if phosphoryl transfer by CK catalysis was accomplished, as previously suggested (13), by the mechanism of vectorial ligand conduction (21).

According to this mechanism this difference would represent the average number of CK-catalyzed equilibration reactions involved in the transport of a newly synthesized molecule of CrP from its site of generation to an ATP utilization site, where ADP is re-esterified to ATP by Crp. Total unidirectional CK-catalyzed phosphoryl flux measured by 31P NMR saturation transfer technology has been reported (20) to be equivalent to 7,000 nmol-mg protein−1 min−1 in noncontracting rat quadriceps muscle. By 18O phosphoryl oxygen exchange analysis the net CK-catalyzed phosphoryl flux in noncontracting rat diaphragm was 146 nmol-mg protein−1 min−1. Therefore, a first approximation of the average number of CK-catalyzed equilibration reactions involved in the transfer of a newly synthesized molecule of CrP from its generation to utilization sites would be 7,000 × 146 or 48. This is a provisional value because no 31P NMR saturation transfer measurements have been made with rat diaphragm for a direct comparison with the measurements made here. Measurements by 18O phosphoryl exchange that we have made in rat gastrocnemius muscle indicate that net CK-catalyzed phosphoryl flux is lower than in diaphragm, so the number of total transfers in the gastrocnemius would be greater than the 48 estimated here.

The basic construct of the previous (13) and current working models of the operation of the AK- and CK-catalyzed phosphoryl transfer systems defines their importance in coupling ATP-consuming and ATP-generating processes through rapid equilibration of reactants along a series of CK- or AK-catalyzed reactions. The latter is viewed as a prerequisite for the operation of a vectorial ligand conduction system (21) and is consist-

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2 P. Dzeja and N. Goldberg, unpublished observations.
ent with the theoretical principles governing the behavior of near equilibrium reactions comprising intracellular flux transfer chains (26–29). By this mechanism each phosphorylbearing molecule entering at one end of the chain of reactions promotes propagation of sequential equilibrations resulting in simultaneous release of an equivalent molecule at the distal end. Thus, at steady state, the time for accomplishing this should be negligible. The delay in increased muscle O2 consumption noted during the “rest to work” transition (30) could represent the interval required for this series of equilibrating reactions to achieve the new steady state.

Additionally, this mechanism would also help to resolve the problem created by the abundant and very catalytically active myofibrillar and cytosolic CK and AK enzyme protein molecules with the potential to bind and catalytically transform ATPase-generated ADP before it could freely diffuse from its site of generation to an ATP regenerating site (22–25). Another feature of this proposed conduction system underscoring its potential thermodynamic efficiency is its capability to operate with minimal or no concentration gradient of reactants (31–33). This could explain why sought after changes in cellular adenine nucleotide concentrations are most often not observed even with marked increases in metabolic flux (34).

Relationship and Plasticity of AK and CK Catalysis in Situ—The results showing that chemical inhibition of CK activity by DNFB in intact diaphragm muscle leads to reciprocal increases in the rate of AK-catalyzed phosphotransfer are consistent with the view that these two enzyme activities share a comparable functional importance. On the other hand, the expression of CK in these muscle cells may have been intended to provide for a specific function that AK may not take over in toto. How phosphotransfer function is shifted from the CK to the AK system is not presently understood, but it appears to involve the recruitment of the activity of pre-existing AK enzyme protein. There is no detectable increase in the total activity of AK assayed in extracts of muscle obtained after DNFB treatment (not shown). This ostensibly rapid and efficient switch from CK- to AK-catalyzed phosphotransfer is consistent with the coexistence of AK and CK in discrete subcellular locales (4, 22, 23). This may indicate that when ADP from ATP hydrolysis cannot be processed by CK and accumulates to a small but critical localized concentration favoring the Km requirement of AK for ADP, AK takes over the metabolic processing of this ADP.

The effect of acute suppression of CK catalytic capability by an agent such as DNFB may not be identical to the outcome resulting from chronic impairment of CK activity achieved, for example, by gene deletion (8) or protracted feeding of creatine analogs (6, 7). Chronic CK impairment may involve other adaptive, phosphotransfer-related changes not yet defined. This was concluded from observations that protracted feeding of creatine analogs, cyclocreatine, markedly suppressed CK-catalyzed phosphorylation of Cr (77%) and also increased rat diaphragm muscle AK-catalyzed phosphotransfer (9-fold), but the sum of the net transfer of phosphoryls catalyzed by only these two enzyme systems accounted for no more than 75–80% of the total ATP metabolic flux.

Another characteristic of this shift from CK to AK catalysis is the plasticity with regard to the ATP-generating process to which the phosphotransfer system is functionally coupled. From earlier experimentation showing nearly equivalent stoichiometry between net phosphoryl transfer by AK and lactate production (14), it appeared that phosphotransfer catalyzed by AK was linked to the production of ATP by anaerobic glycolysis. The present experiments indicate otherwise: AK-catalyzed phosphotransfer can also be linked to oxidatively produced ATP. This is apparent when CK-catalyzed phosphotransfer is impaired by DNFB; net AK-catalyzed phosphotransfer exceeds by severalfold net anaerobic glycolytic ATP generation, as indicated by the rate of lactate production (not shown). In other words, under circumstances where CK catalysis is impaired but oxidative phosphorylation remains operational (i.e., unlike the circumstance previously tested (14)), a large proportion of net phosphoryl transfer catalyzed by AK can be accounted for by ATP generated by oxidative phosphorylation.

These results expand the potential importance and versatility of the AK component in the previously proposed models of the operation of the AK and CK phosphoryl transfer systems. What the specific role(s) or advantages may be of one or the other system and the extent to which the networking of these two phosphotransferase systems may vary among tissues or species or even from one metabolic circumstance to another will require further exploration.

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