Skeletal Muscle in Alloxan Diabetes

A Comparison of Isometric Contractions in Fast and Slow Muscle

STEPHEN F. PAULUS AND J. GROSSIE

SUMMARY

Diabetes was produced by withholding insulin treatment from previously alloxanized female rats. Isometric contraction was assessed in soleus and extensor digitorum longus (EDL) muscles removed 2 h to 32 days after insulin withdrawal. Directly induced contractions were measured in vitro at 20°C. In soleus muscles from severely diabetic rats, average twitch and tetanic forces were normal or slightly greater than that of controls of similar age, whereas in EDL, marked decreases appeared in both twitch and tetanic forces. Soleus muscle from severely diabetic rats was not depolarized as already reported in EDL. After 16 and 32 days in the diabetic state, soleus muscles from moderately diabetic rats generated average tetanic forces that were equal to that found in age-matched controls, whereas EDL tetanic forces were significantly ($P = <0.01$) weaker. Average specific twitch force in diabetic soleus muscles was greater than age-matched controls after 16 and 32 days in the diabetic state. In diabetic soleus muscle, significant increases in the average half relaxation time and twitch duration were seen after prolonged (16 and 32 days) periods of diabetes. No changes were seen in the same temporal parameters of the twitch in diabetic EDL muscle. A greater atrophy appeared in EDL than in soleus after 16 and 32 days of uncontrolled diabetes. **DIABETES 32:1035–1039, November 1983.**

Types of skeletal muscle fibers show many differences in biochemical, morphologic, and contractile properties. The response of fast and slow muscle to endocrine diseases is also varied. Chao et al.[1] examined various fiber types in streptozotocin-diabetic rats and found that mitochondria of fast-oxidative-glycolytic (FOG) and slow oxidative (SO) fibers show less distinct cristae and an increase in electron dense granules. Mitochondria in fast-glycolytic (FG) fibers were fewer but the remaining showed few morphologic changes. Armstrong et al.[2] suggest that SO fibers in diabetic rats do not atrophy as much as FOG and FG types. Soleus muscle in diabetic rats shows little impairment in peptide chain initiation whereas muscles with a high proportion of fast twitch fibers do show such an impairment although after extended periods, diabetes resulted in impaired protein synthesis in both muscle types.[3] Insulin appears to enhance glucose uptake and lactate release to a greater extent in soleus than fast twitch extensor muscle.[4] Acetoacetate decreased glucose uptake, lactate release and glucose oxidation in soleus muscle but in extensor muscle acetoacetate had little effect on either glucose uptake or lactate release.[4]

Differences in insulin binding with skeletal muscle are also apparent. Soleus muscle binds a greater amount of insulin than extensor muscle and the insulin-induced uptake of 2-deoxy-d-glucose is greater in soleus than extensor muscle.[5] The specific relation between insulin binding, glucose uptake, and contractile parameters is unknown but one report shows that an addition of insulin to muscles in vitro results in a depression of subtetanic contractions of soleus leaving extensor muscle contraction unaffected.[6]

Many other structural and biochemical alterations cannot presently be directly related to contractile changes. However, these differences in response of muscle types to insulin or the diabetic state prompted us to examine for possible differences in isometric contraction parameters and resting membrane potentials in diabetic soleus muscle. Since insulin applied in vitro[7–9] or in vivo[10] increases the resting membrane potential, it appears logical to expect the loss of insulin to lead to a depolarization of the muscle, presumably through a loss of internal K and Na gain. The latter has been shown by Moore et al.[11] This postulated depolarization should be followed by a reduced contractile force. However, if a depolarization is due directly to a loss of insulin, it should appear in any type of diabetic skeletal muscle. On the other

From the Department of Physiology, Ohio State University, College of Medicine, 1645 Neil Avenue, Columbus, Ohio 43210.
Address reprint requests to Dr. J. Grossie at the above address.
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hand, if a depolarization is seen in one but not another muscle type, it would suggest that factors secondary to an insulin loss were responsible for the resting potential decrease when the latter is observed. This report primarily displays a comparison of isometric contractile parameters and secondarily verifies the suspected lack of a depolarization in soleus muscle from severely diabetic rats. The data show specific but dissimilar changes in isometric contraction in extensor digitorum longus and soleus muscles in the diabetic state.

METHODS

Diabetic rats were created by withholding insulin treatment from animals previously treated with alloxan monohydrate (50 mg/kg). The details of this procedure were identical to those already reported.[12] Blood samples for glucose and βOH butyrate analysis were taken from the abdominal aorta after removal of the muscle. The enzymatic method of Williamson and Mellanby[13] was used to determine the butyrate content whereas glucose was determined by glucose oxidase. Alloxanized animals were considered diabetic only if the urine glucose level was at least 0.25 g/dl (Chemstrips, Bio-Dynamics, Indianapolis, Indiana) and plasma glucose level at least twice that of comparably treated controls. Diabetic rats were subsequently classified as severe or moderately diabetic based on dependence on exogenous insulin. Severely diabetic rats lost more than 10 g · day^{-1} and could not survive beyond 4–5 days without insulin. Weight loss in moderately diabetic rats was less than 10 g · day^{-1} and these animals could survive indefinitely without exogenous insulin.

At periods of 2 h to 32 days after the final insulin injection, the soleus (SOL) or extensor digitorum longus (EDL) muscle was removed during ether anesthesia. To preserve the muscles in a viable condition, no attempt was made to remove and assess contractions in both EDL and SOL from the same animal. After removal, stainless steel hooks were tied directly to the tendons and the muscle was mounted vertically in Ringer solution. One hook was connected to a force transducer (Statham G1-8-350) and the other to a glass rod. The stray compliance in the recording system was 2×10^{-4} mm/g. Muscles were stimulated by placing platinum plate electrodes parallel to the longitudinal axis of the muscle. Resting length of the muscle was established by stimulation at a frequency of 0.1 s^{-1} and adjusting the muscle to length which produced the maximal twitch force.[14] The stimulus pulse duration was 0.1 ms. Twitches in both muscles were produced at a frequency of 0.1 s^{-1}. Tetanic stimulation was 100 s^{-1} for 1 s. The isometric contractions were recorded oscillographically (Electronics for Medicine) at a chart speed of 10 cm · s^{-1}. Both twitch and tetanus were normalized to a unit cross-sectional area of the muscle. Muscle length required for this expression was obtained before removal of the muscle from the animal. EDL length was measured at full extension of the ankle and toes whereas soleus muscle length was measured at full flexion of the ankle. After contractile measurements, muscles were gently blotted and weighed. For each of six recorded twitches in each muscle the contraction time (Tc), half relaxation time (½RT) and twitch duration were obtained and averaged. Differences in averages between groups of normal or diabetic rats were not considered statistically significant unless $P = <0.01$.

Resting membrane potentials were measured by standard intracellular microelectrode technique. After removal, soleus muscles were placed in the recording chamber and cleaned of extraneous matter. Voltage recording micropipettes filled with 3 M KCl had tip resistances of 5–20 MΩ. They were connected to a high impedance electrometer, the output of which was connected to an oscilloscope and a high impedance digital voltmeter. Resting potentials were read to the nearest 1.0 mV and recorded manually.

The physiological solution used for both voltage and contractile recordings was as follows (in mM): NaCl, 135; KCl, 5; $MgCl_2$, 1; Na_2HPO_4, 1; $NaHCO_3$, 15; $CaCl_2$, 2; glucose, 11. After equilibration with O_2 (95%) and CO_2 (5%) the pH was 7.16. Oxygenation and pH regulation were assured by delivering the O_2-CO_2 mixture to the solutions continuously.

RESULTS

Average plasma glucose and blood β-OH butyrate levels from control and alloxanized rats are shown in Table 1. Rats classified as severely diabetic were significantly more ketotic than moderately diabetic animals but glucose levels were not significantly different from the latter until 4 days after insulin removal. At the 16- and 32-day intervals, butyrate levels were lower but still remained significantly higher than controls. No effort was made to determine any degree of recovery from the diabetic condition. Data on isometric contractile parameters of both EDL and soleus muscles show that measurements taken on day 0 (2 and 6 h after the AM insulin treatment) are not significantly different from age-matched control muscles although small (9%) decreases in EDL specific twitch and tetanic forces were observed (Table 2). Changes in other contractile parameters did not appear at this time. In muscle from rats classified as severely diabetic specific twitch and tetanic forces in soleus muscle were slightly but generally not significantly ($P = >0.01$) elevated, whereas the same parameters in EDL muscle showed precipitous significant decreases over the 2–4-day study period (Table 2). In soleus muscles Tc, ½RT, and twitch duration were slightly increased but these parameters were unchanged in EDL muscle.

In the present recording conditions, resting membrane potentials in four normal soleus muscles averaged -73 ± 0.4 mV ($N = 107$ cells). In four soleus muscles removed from alloxanized rats 2 or 6 h after the AM insulin treatment, resting potentials in 114 cells averaged -74 ± 0.4 mV. In two soleus muscles from severely diabetic rats 2 days after insulin withdrawal, the average potential in 64 cells was -75 ± 0.5 mV. EDL muscles from similar severely diabetic rats were always significantly depolarized from -78 mV to about -63 mV as already shown.[12]

In rats which were classified as moderately diabetic, specific twitch and tetanic forces in soleus were unchanged for up to 4 days after insulin withdrawal (Table 2). By 16 and 32 days, however, specific twitch force gradually increased to a significantly higher level after 32 days in a diabetic state. Absolute twitch force decreased to significantly lower levels by day 32 (Table 2). Furthermore, Tc, ½RT, and duration of the soleus twitch gradually increased and by 32 days without insulin, Tc had increased 54%, ½RT increased 169%, and

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TABLE 1
Average plasma glucose, blood β-OH butyrate levels and weights of EDL and SOL from diabetic and age-matched control rats

Condition	Days off insulin	Plasma glucose (mg/dl ± SE)	Blood β-OH butyrate (μmol/ml ± SE)	Muscle wet weights	
				EDL (mg ± SE)	SOL (mg ± SE)
Control	0–4	283 ± 18 (20)	0.10 ± 0.03	93 ± 6	81 ± 4
Alloxan + insulin	0	362 ± 102 (10)	0.21 ± 0.13	85 ± 3	83 ± 5
Moderately diabetic	2	744 ± 87* (7)	2.07 ± 0.71	90 ± 4	79 ± 2
Severely diabetic	2	731 ± 46* (14)	7.66 ± 1.45*	82 ± 2	70 ± 4
Moderately diabetic	4	641 ± 43 (9)	1.45 ± 0.60*	86 ± 4	71 ± 2
Severely diabetic	4	1133 ± 92* (9)	7.98 ± 1.13*	86 ± 6	64 ± 3*
Control	16	236 ± 19 (15)	0.05 ± 0.013	107 ± 4	95 ± 5
Moderately diabetic	16	760 ± 38* (24)	0.92 ± 0.20*	64 ± 6*	65 ± 3*
Control	32	236 ± 28 (14)	0.08 ± 0.04	110 ± 3	102 ± 4
Moderately diabetic	32	672 ± 31* (28)	0.95 ± 0.25	61 ± 7*	57 ± 3*

*P = <0.01.

the total duration of the twitch had increased to over 2.5 times that of muscle from age-matched control rats. An example of these changes can be seen in Figure 1. In diabetic soleus muscle, relaxation times following both twitch and tetanic contractions were both extended considerably. In EDL muscle, the diabetic state did not induce changes in temporal parameters of the twitch nor were there effects on relaxation following the tetanus. Figure 1 also shows that the diabetic condition did not alter the ability of either muscle to maintain tetanic force. Specific tetanic force in soleus muscle was unaffected regardless of the length of time insulin was withheld whereas specific tetanic force in EDL muscle began to decline 2 days without insulin and remained significantly weaker than age-matched controls for the 32-day duration of the study. Absolute tetanic force decreased significantly as mass declined in both muscles.

TABLE 2
Isometric contraction of EDL and soleus (SOL) muscles after various periods of alloxan diabetes compared with age-matched controls

Condition	Days off insulin	Muscle (n)	Twitch					Tetanus	
			Force (g)	Force (g/cm²)	Tc (ms)	½RT (ms)	Duration (ms)	Force (g)	Force (g/cm²)
Control	0–4	SOL(9)	29 ± 1	862 ± 39	87 ± 4	136 ± 9	613 ± 27	115 ± 5	3408 ± 86
		EDL(11)	71 ± 2	2247 ± 68	25 ± 1	27 ± 1	160 ± 8	179 ± 4	5645 ± 115
Diabetes + insulin	0	SOL(5)	29 ± 1	797 ± 32	91 ± 2	124 ± 4	603 ± 19	122 ± 4	3329 ± 106
		EDL(5)	60 ± 3*	2043 ± 127	22 ± 1	27 ± 2	141 ± 2	152 ± 4	5156 ± 140
Severely diabetic	2	SOL(5)	31 ± 1	1000 ± 41	99 ± 4	169 ± 11	834 ± 61*	126 ± 9	4056 ± 164*
		EDL(9)	46 ± 3*	1654 ± 121*	22 ± 1	25 ± 1	141 ± 11	132 ± 6*	4793 ± 257*
Moderately diabetic	2	SOL(3)	30 ± 3	885 ± 82	108 ± 6	166 ± 7	730 ± 18*	113 ± 3	3308 ± 29
		EDL(4)	72 ± 2	2309 ± 116	28 ± 1	33 ± 1	166 ± 8	167 ± 8	5335 ± 175
Severely diabetic	4	SOL(5)	28 ± 2	1005 ± 52	111 ± 9	212 ± 35	862 ± 105	101 ± 8	3574 ± 186
		EDL(4)	32 ± 5*	1177 ± 147*	24 ± 4	22 ± 3	143 ± 17	94 ± 20*	3360 ± 632*
Moderately diabetic	4	SOL(4)	27 ± 1	862 ± 19	106 ± 6	165 ± 13	711 ± 45	109 ± 5	3492 ± 70
		EDL(6)	61 ± 1*	2108 ± 61	22 ± 2	24 ± 1	129 ± 7	147 ± 6*	5097 ± 141
Control	16	SOL(8)	33 ± 1	915 ± 86	104 ± 4	165 ± 13	778 ± 51	139 ± 7	3801 ± 309
		EDL(7)	79 ± 3	2340 ± 71	23 ± 1	28 ± 1	130 ± 8	202 ± 7	5886 ± 184
Moderately diabetic	16	SOL(14)	30 ± 1	1048 ± 36	124 ± 8	265 ± 34*	1248 ± 121	104 ± 5*	3635 ± 140
		EDL(10)	53 ± 6*	2355 ± 167	25 ± 3	30 ± 2	145 ± 12	107 ± 15*	4655 ± 395
Control	32	SOL(8)	35 ± 2	853 ± 43	93 ± 2	128 ± 5	616 ± 22	162 ± 7	3988 ± 104
		EDL(6)	86 ± 3	2457 ± 63	24 ± 1	27 ± 1	123 ± 6	203 ± 7	5777 ± 56
Moderately diabetic	32	SOL(15)	28 ± 1	1135 ± 41*	143 ± 7*	345 ± 17*	1559 ± 84	98 ± 5*	3985 ± 116
		EDL(13)	53 ± 5*	2499 ± 132	27 ± 2	32 ± 2	136 ± 8	112 ± 15*	4990 ± 300*

*P = <0.01.

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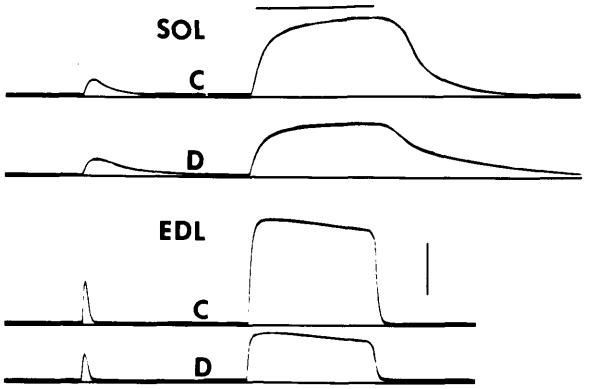

FIGURE 1. Twitch and tetanic contraction recordings of SOL and EDL muscles from two 32-day diabetic (D) and two age-matched control (C) rats showing the extended relaxation times of diabetic SOL muscle following both twitch and tetanus and the resistance of both EDL and SOL muscles to fatigue during tetanic contraction. Horizontal bar at the top of this figure represents the period of tetanic stimulation for all four muscles. Vertical bar at the lower right represents 100 g.

Muscle atrophy was prominent in both soleus and EDL muscles by 16 and 32 days without insulin. Table 1 shows average EDL and soleus weight of only muscles involved in the contractile studies. In animals in which soleus muscle contraction was studied, one EDL was also removed and weighed. These data showed that the normal average ratio of EDL to soleus muscle weight was 1.17 ± 0.05 at the 16-day interval, whereas the same ratio for diabetic rats was significantly lowered to 0.96 ± 0.03. By 32 days the normal ratio was 1.2 ± 0.06 and significantly higher than the average for diabetic rats of 0.90 ± 0.04. Therefore, atrophy was more prominent in EDL than soleus muscle, but the ratios of wet to dry weight for each muscle remained normal regardless of degree of atrophy.

DISCUSSION

The data show that diabetes exerts specific but different effects on the isometric contractile properties of EDL and soleus muscles. In severe insulin-dependent diabetes where hyperglycemia and ketoacidosis are profound, soleus muscle twitch and tetanic forces are either maintained or enhanced, whereas that of EDL muscle decreased considerably. This difference is probably linked to the depolarization of EDL muscle in this severe form of diabetes. Soleus muscle maintains a virtually normal isometric force and resting potential despite the severe diabetic condition. Measurements of resting potential in diabetic soleus muscle were not actually warranted. In view of the contractile forces generated in diabetic soleus muscle and the fact that depolarization inhibits the mechanical system,[15] only a few studies were needed to confirm a normal resting potential in the diabetic state. This was accomplished and an exhaustive study of the electrical properties of diabetic soleus muscles was not indicated and was not pursued. Soleus muscle has a high capacity for oxidation of fatty acids and ketones,[16–18] a property which may be an important distinction in the present context in that demands on the internal buffering system of soleus would not be as great as in EDL. Previous data show that EDL muscle from severely diabetic rats repolarize when external Cl is removed[12] and chloride is involved in the regulation of internal pH in soleus[19] and perhaps other skeletal muscle via a Cl-HCO_3 exchange. Resting potentials in both soleus and EDL are Cl dependent,[20] and it appears possible that the depolarization in EDL may be linked to Cl and pH regulation and not a direct result of an insulin loss per se on Na and K transport. These interactions, however, have not been explored at present.

The profound increase in Tc, ½RT, and twitch duration in soleus muscle, not seen in EDL, bears a strong resemblance to papillary muscle from diabetic rats where shortening velocity is also depressed.[21] A probable contributing factor in papillary muscle is a significant decrease in myosin and actomyosin ATPase activity found in diabetic heart muscle.[22] In skeletal muscle, a hyperbolic relation exists between Tc and specific activity of myosin ATPase.[23] However, the extended ½RT and twitch duration found in diabetic soleus muscle suggests that the rate of Ca sequestration by the sarcoplasmic reticulum (SR) may be decreased. In isolated SR fragments from diabetic rat hearts, Ca uptake in the absence of oxalate was much lower than that from normal rats and Ca-Mg ATPase activity was also reduced.[24] A suppression of Ca uptake by the SR could be a key factor in both the increased Tc and the elevated twitch force seen in diabetic soleus muscle.

After extended periods of diabetes (16 and 32 days) soleus tetanic force remained normal but that of EDL muscle decreased significantly. This fact coupled with an apparent higher rate of atrophy in EDL muscle suggest that contractile proteins in EDL not only are broken down more readily than soleus, but in the process may lose some of their force generating ability. This possible molecular pathology has not been defined.

It has not been determined that the loss of insulin per se directly produces any of these changes. In their studies on heart muscle Malhotra et al.[25] confirmed a hypothyroid status of diabetic rats but also reported that thyroid replacement failed to reverse the depressed Ca activity of actomyosin and myosin ATPase in diabetes. Ca uptake by the SR is depressed in hypothyroid conditions,[26] an event which is expected to suppress the rate of relaxation following contraction. An increased twitch duration has been observed in EDL muscle from hypothyroid rats[27] but no such effect is seen in diabetic EDL muscle.

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