# Pathophysiology of the Glucocorticoid Myopathy - a Short Review

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**Abstract**

Chronic exposure to high doses of glucocorticoids leads to muscle wasting and to loss of its strength. The condition is known in clinical practice as glucocorticoid myopathy. Explanation of the pathophysiology of this myopathy necessitates answers to the following questions: 1. Is glucocorticoid myopathy caused primarily by the impaired excitation of the muscle fibre and/or impairment of excitation-contraction coupling or is it the result of metabolic changes in the skeletal muscle fibre affecting one or both of the other two functional compartments: contraction executing and energy providing compartment? 2. Is protein catabolism, which underlies muscle wasting the result of the decreased protein synthesis or increased protein degradation or both? 3. Which mechanisms and reactions leading to the myopathic changes of the muscle fibre are we dealing with at the molecular level? In this paper an attempt has been made to provide a short information on how are the above questions answered today. In our study a good correlation was found between the fall in total acetylcholinesterase activities in various muscles and the fall in their weights after chronic dexamethasone treatment. Acetylcholinesterase was therefore proposed as a model protein at investigations of the pathophysiological mechanism leading to the myopathic glucocorticoid effects.

**Keywords**: glucocorticoids, glucocorticoid myopathy, pathophysiology, skeletal muscle, acetylcholinesterase.

*BAM 2 (4): 261-268, 1992*

Chronic overproduction of the adrenal steroids as for example in Cushing's syndrome or chronic treatment by synthetic, especially fluorinated glucocorticoids leads to a marked wasting of muscle and loss of strength. The condition is known in clinical practice as glucocorticoid myopathy. It is selective in a sense that type 2 fast-twitch glycolytic muscle fibres are affected the most while type 1 slow-twitch oxidative fibres are spared. The pathophysiology of glucocorticoid myopathy could not be understood without answering the following questions: 1. Is glucocorticoid myopathy caused primarily by the impaired excitation of the muscle fibre and/or excitation-contraction coupling or is it the result of metabolic changes in the skeletal muscle fibre affecting one or both of the other two functional compartments: contraction executing and energy providing compartment? 2. Is protein catabolism, which underlies the observed muscle wasting the result of the decreased protein synthesis or increased protein degradation or both? 3. Which processes and reactions leading to the myopathic changes of the muscle fibre are involved in the glucocorticoid action at the molecular level? In this paper we want to provide a short information on how and to which extent are the above questions answered today. In our review attention is also paid to the glucocorticoid effects on the cholinergic components synthesized in the skeletal muscle. These effects are usually neglected at reviewing glucocorticoid myopathy, most probably because the glucocorticoid action on the cholinergic components has not been causally related to the myopathy itself. However, muscular cholinergic components i.e. acetylcholine receptor (AChR) and acetylcholinesterase (AChE) have been extensively studied from various other aspects and their biosynthetic pathway is relatively well defined. These molecules could therefore serve as the suitable model at investigations of the glucocorticoid effects on the protein metabolism in the skeletal muscle. It is known that the activity of AChE in the muscle is reduced after glucocorticoid treatment [6] and it is very probable that at least some features of the glucocorticoid action on the synthesis of AChE could be extrapolated on the metabolism of other muscle proteins. The results of the study oriented to one, well-defined protein as AChE might there-

fore be helpful at explaining general glucocorticoid effects on the protein metabolism in the skeletal muscle and therefore at explaining some features of glucocorticoid myopathy.

*Pathophysiology of the glucocorticoid myopathy*

1. Is glucocorticoid myopathy the result of impaired excitation of the muscle fibre and/or altered function of the excitation-contraction coupling?

It is known that glucocorticoid hormones have diverse actions in the nervous system (reviewed by McEwen et al [25]). Since corticosteroid hormones change cellular excitability and neuronal activity (reviewed by Joëls and de Kloet [20]), the possibility that at least part of the observed glucocorticoid effects on the skeletal muscle are secondary to the effects on the nervous system could not be simply excluded. However, experimental studies did not support the neuropathic hypothesis: motor nerve conduction, neuromuscular transmission [18] and histological appearance of nerve [31] were normal in steroid-treated animals. It was also found that steroid treatment did not alter the spindle afferent activity onto the motor neurons [31]. The spontaneous and evoked EMG patterns in patients are usually normal except for somewhat decreased voltage and frequency of firing and with practically absent fibrillation potentials [18, 31]. All these data strongly suggest that the primary disfunction leading to the glucocorticoid myopathy is located in the skeletal muscle fibre and not in the nerve or neuromuscular junction. Trying to answer the question, which is the primary disorder of the muscle fibre leading to the myopathy Gruener and Stern [18] suggested that glucocorticoids might act by decreasing the excitability of the sarcolemma. According to their proposal the decrease in excitability results from prolonged depolarisation combined with a change in the voltage dependence of sodium channel activation and inactivation. Prolonged depolarisation was suggested to be the result of increased resting membrane permeability to sodium ions caused by glucocorticoid action. Authors [19] - on the basis of their experimental results - even proposed therapy of glucocorticoid myopathy by diphenylhydantoin, which reduces sodium permeability, but the results were not promising. Later on, Ruff and co-workers [30] again explored the possibility that glucocorticoid-induced muscle weakness and atrophy resulted from impaired muscle membrane excitability. Opposite to Gruener and co-workers [18] they observed that reduction in twitch and tetanic tension never preceded atrophy. When expressed per gram of muscle these two parameters were even increased after glucocorticoid treatment. These results are in good agreement with the conclusion of Vignos et al [40] who found normal strength in triamcinolone treated rabbit EDL muscle when measurements were normalised by comparing contractile data based on the cross-sectional area of the control and treated muscles. Failure to find any effects of glucocorticoids on the contractile speed or strength of rat soleus (slow) and gastrocnemius muscle (fast) was also reported by Gardiner and Edgerton [14]. As demonstrated by Ruff et al [30] the depolarisation of EDL muscle could be observed only *in vitro* at sub physiologic temperatures, while EDL fibres studied *in vivo* were not depolarised and had normal action potential amplitudes and thresholds [30]. Observations of Wilcox et al [42] who studied corticoid induced myopathy in hamsters were also in accord with the view that steroid myopathy could be explained by a loss of muscle mass rather than by the intrinsic impairment in contractile function. At present, generally accepted opinion is that glucocorticoids do not produce muscle weakness by impairing sarcolemmal excitability or excitation-contraction coupling, but that the weakness results from muscle atrophy.

2. Is protein catabolism underlying muscle atrophy caused by decreased protein synthesis or/and increased protein degradation?

The question, which of these theoretical causes of protein catabolism is responsible for the reduced amount of muscle proteins observed at the glucocorticoid myopathy has also been a matter of dispute. Namely, net protein catabolism can theoretically be the result of (1) a reduction in rates of protein synthesis with no change in degradation (2) an acceleration in rates of degradation with normal rates of synthesis, or (3) changes in both processes. The question, which of these theoretical causes of protein catabolism are we dealing with at the glucocorticoid myopathy has also been a matter of dispute. The high rapidity with which rat skeletal muscles were losing weight in response to cortisone treatment was the argument of Goldberg and Goodman [16] at their suggestion that changes in both protein synthesis and protein degradation are involved, however it must be noted that hypophysectomised rats were used at their experiments. Lower ratio: time in active state vs. time in inactive state of fast-twitch fibres in comparison to slow-twitch fibres was suggested as the explanation for higher sensitivity of fast-twitch muscles to the glucocorticoid treatment.

Clark and Vignos [8] studied corticosteroid myopathy in rabbits and - using tritium labelled leucine - found that in both slow-twitch and fast-twitch muscles fibre proteins are degraded several times faster in the corticosteroid-treated group in comparison to control. The increase in protein degradation in soleus was in contradiction with the fact that no atrophy was observed in this muscle in their experiments. Authors themselves admitted that their method based on labelled leucine follow up was not appropriate for the study since leucine after being released could be reincorporated into the proteins. Kayali et al [23] found continuously decreased protein synthesis for 30-50% in corticosterone treated rat muscle, while protein degradation in muscles in which protein synthesis was blocked by cycloheximide became first increased (1 to 4 days) and fell later (4 to 8 days) to the control level. A promoted breakdown of contractile protein, myosin and actin in the muscle during glucocorticoid administration was also reported by Tomas, Munro and co-workers [38] who observed enhanced excretion of 3-methylhistidine in glucocorticoid

treated rats. Seene and Alev [32] and Seene et al [33] studied the effect of ten days dexamethasone treatment on the myofibrillar proteins of rat muscle and found that muscles with high oxidative potential are less sensitive to the catabolic action of dexamethasone. In fast-twitch white muscles, where the oxidative capacity is low, the alkaline proteinase activity as well as the rise in the number of lysosomes was more pronounced. Authors suggested that glucocorticoid myopathy is a result of elevated degradation of contractile proteins that begins in the myosin filaments and then spreads to the thin filaments and the Z-line. Glucocorticoid-mediated increase in peptidase or proteinase activity was also reported by Clark and Vignos [9]. The explanation of glucocorticoid myopathy as the result of increased protein breakdown was strongly opposed by Shoji and Pennington [35] who studied the rates of muscle protein breakdown and synthesis in the rat EDL muscles isolated from rats treated by cortisone for 1-3 days. Cortisone administration inhibited significantly the rate of protein synthesis after 1-3 days treatment and also reduced significantly the rate of protein breakdown per muscle after 3 days treatment. To reconfirm these results in an *in vivo* system, Shoji, by dividing daily urinary excretion of 3-methylhistidine by the 3-methylhistidine pool of the skeletal muscle, measured fractional rates of breakdown of myofibrilar protein. According to his results the loss of myofibrilar protein induced by cortisone administration is not caused by increased protein breakdown but by decreased protein synthesis. The same was the conclusion of Rannels and Jefferson [29], who found protein degradation and cathepsin D activity remained unaffected in muscles of rats treated by cortisone for 5 days. That the corticosteroid atrophic effects on skeletal muscle primarily arose from the corticosteroid ability to inhibit protein synthesis was also reported by Kelly et al [22]. It could be concluded that presently there is no doubt that the decreased rate of protein synthesis is the primary cause of glucocorticoid myopathy. The extent to which increased protein breakdown contributes to the myopathic changes seems not to be the solved question, however according to the present knowledge it seems to play a minor role in comparison to decreased protein synthesis.

3. Is the energy-providing compartment of the muscle fibre affected by the glucocorticoid treatment?

In some studies steroid myopathy was shown to be associated with an alteration of muscle carbohydrate metabolism as well as with mitochondrial alterations (see Ruff [31]) seen by electron microscopy. Based on these observations a suggestion has been made that processes responsible for providing energy i. e glycolysis and oxidative respiration are impaired and that such impairment may be an important factor in the pathogenesis of this disorder. It was reported that steroid treatment of rabbits lowered both liver and muscle glycogen phosphorylase activity [37] and that steroids increased muscle glycogen synthetase activity [34]. In a lesser extent steroid treatment also interfere with muscle oxidative capacity (see Ruff [31]). Since the glycolytic metabolism appeared to be more impaired than the oxidative capacity, Vignos and Green [39] suggested that the resistance of individual fibres to glucocorticoids depend in part on the ability to compensate for blockade of glycolytic activity by converting to oxidative metabolism, which should explain higher resistance of slow-twitch oxidative fibres to glucocorticoid myopathy in comparison to fast-twitch glycolytic fibres. Explanation that the lack of energy underlies the glucocorticoid myopathy is however questionable, since it was shown that ATP is not depleted in such conditions.

4. Which is the molecular mechanism underlying glucocorticoid-mediated reduced rate of protein synthesis in the skeletal muscle?

The mechanism of glucocorticoid action underlying the impairment of protein synthesis in the skeletal muscle fibre has not yet been elucidated though the mechanism by which steroids control transcription has been intensively studied in the past ten years. First step in the steroid action is binding to the steroid receptor, which is located in the cytosol. Cloning and sequencing of this receptor revealed its primary structure; it can be divided into three domains that determine hormone binding, nuclear translocation, DNA binding and transcriptional activation properties. The corticoid-receptor complex travels to the cell nucleus and binds to high-affinity binding sites (glucocorticoid responsive element-GRE) in chromatin (reviewed by Beato [3] and Evans and Arriza [12]). This in turn, led to the induction or repression of a limited number of genes (approximately 50 to 100 per cell [11]). Further events leading to reduced protein content in skeletal muscle and release of aminoacids are still a rather open question. Rannels et al [28] who found reduced rate of synthesis of skeletal muscle protein for 55% also found a loss of tissue RNA for 15% in skeletal muscles of rats treated for 5 days with cortisone. The remaining reduction was suggested to be the result of impaired initiation process of translation. An inhibitory regulator protein acting through reduction of eIF-2 initiation factor activity (this effect was suggested to be secondary to the reduced RNA content) was proposed as an explanation for the disproportionally strong inhibition of protein synthesis in regard to moderate decrease in RNA content. These results were later confirmed by Rannels and Jefferson [29]. Dissociation of polysomes into ribosomal subunits [27], reduced incorporation of amino acids into nascent protein [4, 27] and defective peptide chain initiation [9, 28] also suggest impaired translation process as the cause of reduced rate of protein synthesis in glucocorticoid treated muscle. However, recently Goodlad and Clark [17] studied the behaviour of RNA polymerase I- and RNA polymerase II-directed transcription in nuclei isolated from skeletal muscles of dexamethasone treated rats. In the case of RNA polymerase I-mediated transcription they found a loss of template-engaged enzymes indicating the existence of an inhibition of initiation of transcription while the rate of elongation of bound enzyme remained unaltered. The number of RNA polymerase II-

chromatin bound enzymes was increased, but the mean polynucleotide elongation rate was reduced. Results suggested the possibility that glucocorticoids impair the elongation stage of transcription in skeletal muscle by increasing the frequency of premature termination of transcripts. Reduced RNA content could not be explained by increased RNA degradation since no evidence was obtained for any increase in ribonuclease activity in muscle nuclei of treated rats. It seems therefore that both impaired transcription and impaired translation contribute to the reduced rate of protein synthesis in the skeletal muscle. Another question is whether the observed effects result from the direct glucocorticoid action or are they mediated by some "second messenger". The requirement of protein synthesis for many of the steroid hormone-mediated gene inductions led to the idea that mediator protein(s) are necessary for such inductions. "Glucocortin", a 17 kdalton protein, the mRNA of which doubles within only 15 minutes of dexamethasone addition in all target tissues investigated, was suggested as a serious candidate for such " second messenger" [10].

5. The influence of glucocorticoid treatment on the metabolism of the cholinergic components in the skeletal muscle fibre.

As already mentioned, neuromuscular transmission appears normal at glucocorticoid myopathy. That was the most probable reason that so little attention was paid on what is going on with the cholinergic components in the skeletal muscle, when this myopathy was studied. However, the influence of glucocorticoids on the muscular components of the cholinergic system was studied as a part of investigations of another muscular disease myasthenia gravis. Several studies were carried out starting with the hypothesis that the beneficial effects of glucocorticoid treatment of patients with myasthenia gravis are - besides their immunostatic effect - the result of glucocorticoid action on the components of the neuromuscular junction.

Some authors reported direct effects of corticosteroids on the transmission in the neuromuscular junction [24, 43], however in comparison to the effects on the protein synthesis these effects do not seem to play any substantial role in the mechanism of the glucocorticoid actions on the skeletal muscle. Chokroverty et al [6] found 45% reduction of AChE activity in quadriceps femoris muscle of hamsters due to chronic glucocorticoid treatment. Also, some AChE bands disappear on PAGE electrophoresis. These results suggested that the condition improvement of the myasthenia gravis patients, observed after glucocorticoid treatment might be the result of increased acetylcholine concentration due to reduced AChE activity. However observed fall in AChE activity was obviously not the result of general impairment of the synaptic proteins since no significant differences could be found between control and prednisolone treated hamsters when morphometric study of the endplate structure was carried out [7]. It is interesting that Gibson and Pollock [15] found practically the same (47%) reduction in the cholinesterase (ChE) activity in homogenates of the rat anococcygeus muscle, which is smooth muscle and which even not receives cholinergic innervation.

In our *in vivo* experiments Albino female rats weighing about 180 g were treated with dexamethasone (4.5 mg/kg body weight) until they lost 15% of their initial body weight. At such decrease in body weight, the redistribution of weights among particular tissues, shown in Fig. 1 were observed. Increase (insignificant) in liver weight for 3%, loss (insignificant) in brain weight for 5% and loss (significant) of skeletal muscle weight from 13% (diaphragm) to 26% (EDL) was observed in comparison to control rats. In accord with previous reports predominantly fast twitch muscle EDL lost more of its weight than predominantly red muscle soleus. An exception is the resistance to the glucocorticoid effects observed in the diaphragm, which also contains a considerable proportion of the fast twitch muscle fibres. Food consumption and water balance did not differ significantly between treated and control group, proving that the effects observed were not the result of reduced appetite or disturbed water balance. Nitrogen balance was slightly negative in the treated group indicating glucocorticoid-mediated reduction of protein synthesis. Total AChE activity was lost in all muscles studied and the loss was in good proportion with the loss of muscle weight (Fig. 2) suggesting that AChE behaves as the 'typical' muscle protein under the glucocorticoid treatment. However, within the muscle fibre, the glucocorticoid effects were not uniform. AChE from the endplate-rich region was relatively spared in comparison to the AChE from the endplate-free region in all muscles tested (Fig. 3) suggesting either different metabolism of AChE or different glucocorticoid effects or both in the two compartments.

In contrast to the observations *in vivo* are the results of studies carried out recently on muscle cultures. To the opposite of the catabolic effects described before, these studies suggest a stimulatory effect of glucocorticoids on the muscle development and on the synthesis of the cholinergic components. Askanas et al [1] found increased number of AChRs and AChR aggregates in human muscle cultures treated with hydrocortisone. Significant increase of total surface AChRs but not of AChE on cultured human muscles treated with dexamethasone was also reported by Kaplan et al [21]. Authors suggest that the clinical improvement observed in myasthenic patients treated with steroids is due not only to an effect on the immune system but also to a direct effect on muscle. In accord with this report are the results of Braun et al [5] who found increased level of myotube AChR expression in cultures of rat myogenic cells treated with prednisolone. This effect was associated with increases in the number and size of the formed myotubes and was - as suggested by the authors - very probably mediated by one or more extracellular proteins the synthesis of which were induced by prednisolone. Recently the same group reported [41] that among steroids only corticoids and among them especially glucocorticoids stimulate myogenesis in primary cultures of newborn-rat

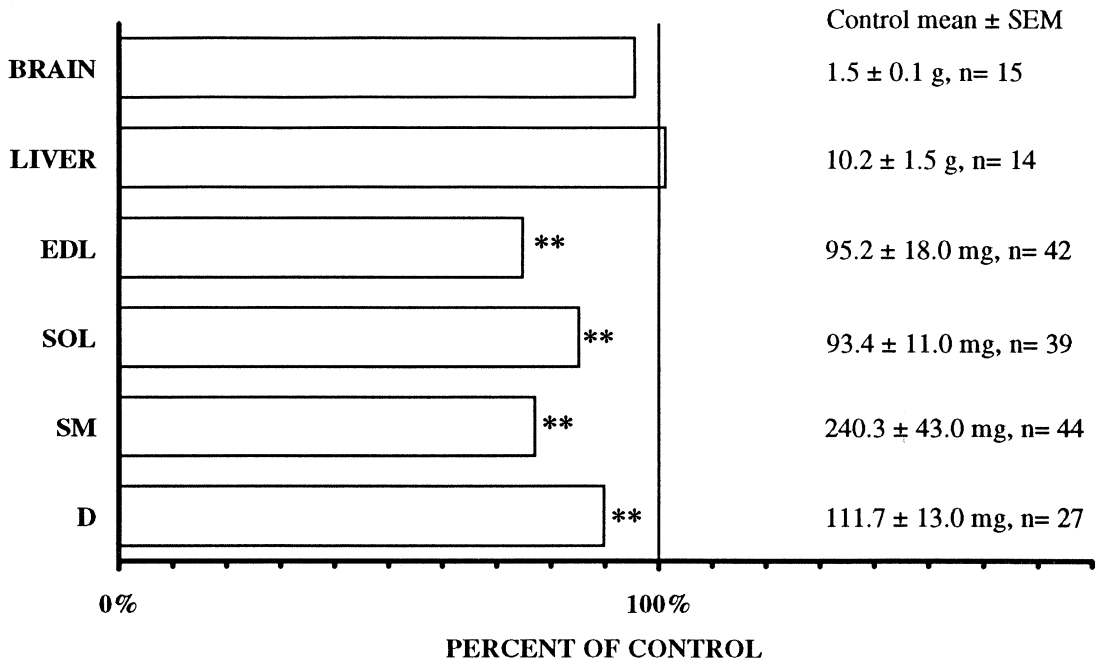


*Figure 1. Effect of chronic dexamethasone treatment (4.5 mg/kg body weight) on the fresh weights of brain, liver and four muscles: extensor digitorum longus (EDL), soleus (SOL), sternomastoideus (SM) and diaphragm (D). Tissues were isolated when 15% of the initial body weight was lost, which took from one to three weeks. Weight changes are expressed as per cent of controls. Absolute control values ± SEM are given on the right. Asterisks denote a significant difference between control and treated group: ** $p < 0.01$.*

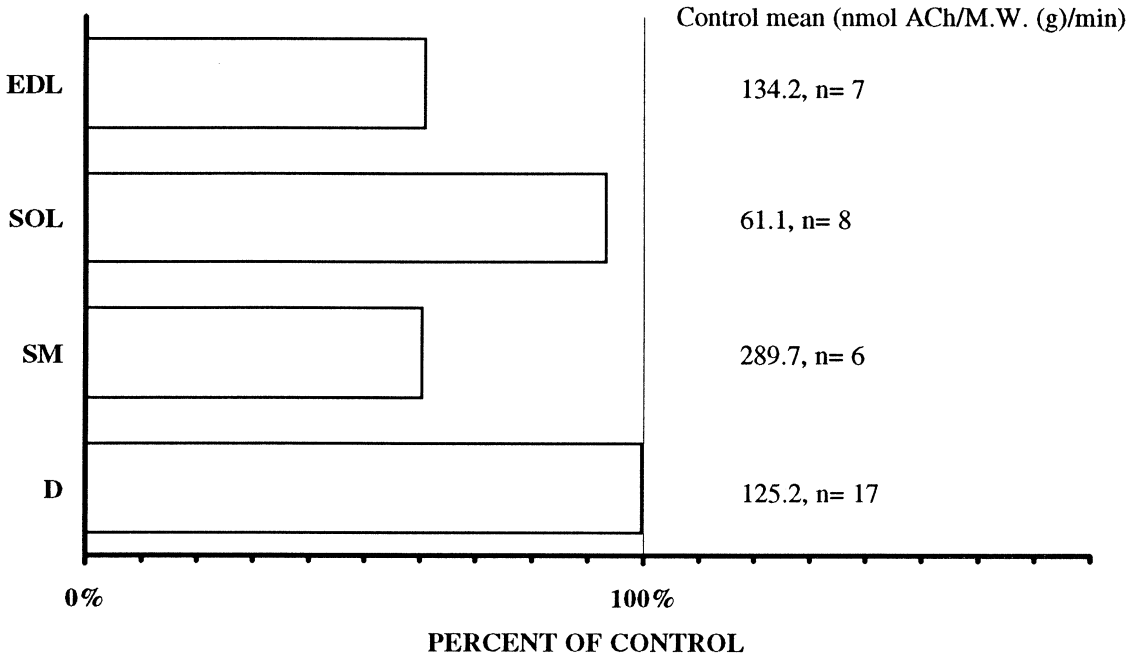


*Figure 2. Effect of dexamethasone (4.5 mg/kg body weight) on the total AChE activity in the same muscles as in Fig. 1. Total activity was calculated from the determined specific activities and from the muscle weights. Effects are expressed as per cent of controls. Controls values (means) are given on the right.*

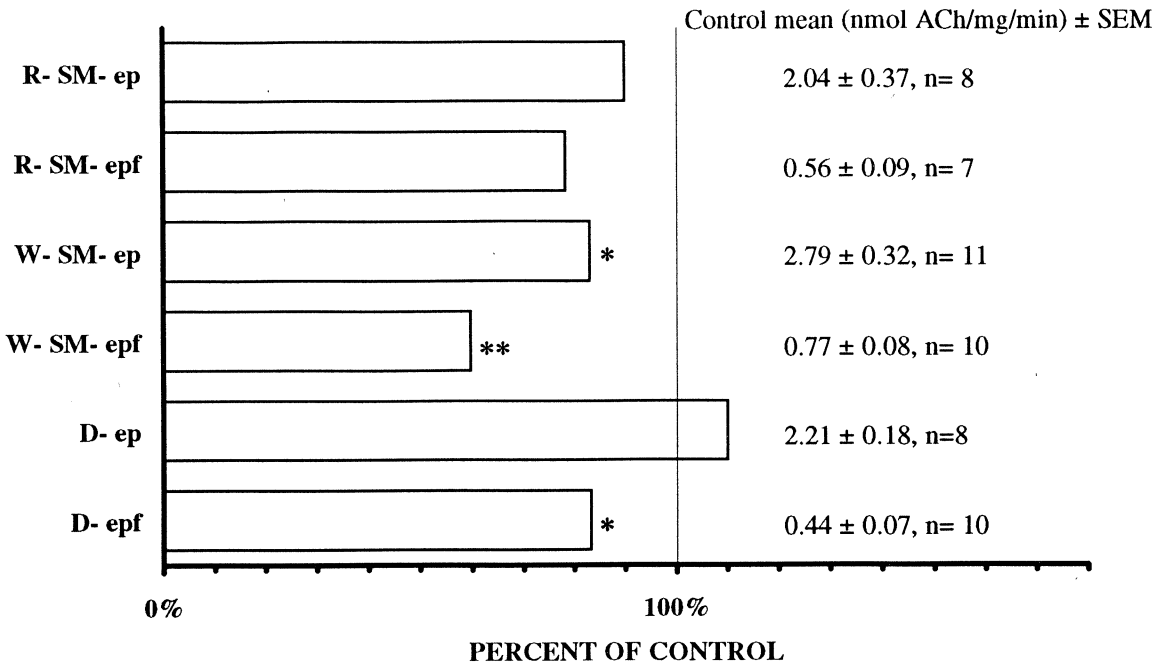


*Figure 3. Effect of dexamethasone (4.5 mg/kg body weight) on the specific AChE activity in the endplate-rich (ep) and in the endplate-free (epf) regions of the red part of SM (R-SM), white part of SM (W-SM) and diaphragm (D). Controls SEM ± are given on the right. Asterisks denote a significant difference between the control and treated group *: $p < 0.05$, **: $p < 0.01$.*

skeletal muscle cells as a twofold increase in AChR expression indicated. Stimulatory effects of glucocorticoids on the organisation of the postsynaptic membrane and even the increase of AChE was observed by Askanas et al [2], who also suggested that long-term beneficial effects of glucocorticoids might be due to their stimulatory action on myogenesis. However, an attempt to improve regeneration *in vivo* by low dose dexamethasone proved unsuccessful [26].

Apparent contradiction between the myopathic effects observed *in vivo* and the myogenesis-stimulating effects observed *in vitro* can be explained by the dual role of the corticoid hormones in the mammalian organism. While their function is - together with the function of the thyroid hormones, whose receptors belong to the same receptor superfamily - necessary for the normal ontogenetic development of the organism [12], glucocorticoids assume another i.e. stress-defence role when the organism matures (rewieved in Flower [13]). In muscle cultures, which are formed from the mononuclear satellite cells we are practically dealing with the repeated ontogenetic muscle development. In such conditions myogenesis-stimulating effect of glucocorticoids is therefore the expected one. On the other hand treatment of mature organism *in vivo* simulates the physiologic response to stress. The purpose of decreased protein synthesis in skeletal muscle observed during stress is to enrich amino acid pool in plasma, enabling in this way substrates for the processes in central organs like heart and liver, which are essential for defence [13]. Mechanism of this defence reaction, developed through evolutionary processes, is therefore based on the ability of glucocorticoid hormones to distinguish between more and less essential proteins from the point of survival in stress situations. It might be speculated that this ability extends also on the subcellular level of muscle fibre, meaning that proteins, which are more essential for normal cell function and survival are spared as long as possible, while more "disposable" proteins are sacrificed first. Our observations that functionally important synaptic AChE is relatively spared in comparison to the extrasynaptic AChE, whose function is unknown, support such speculations. Further investigations aiming to verify this hypothesis and to elucidate from this point certain features of glucocorticoid myopathy are now going on in our laboratory.

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