# Evidence for Metabolic Abnormalities in the Muscles of Patients with Fibromyalgia

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Widespread muscle pain, fatigue, and weakness are defining characteristics of patients with fibromyalgia (FM). The aim of this review is to summarize recent investigations of muscle abnormalities in FM, which can be classified as structural, metabolic, or functional in nature. Histologic muscle abnormalities of membranes, mitochondria, and fiber type have been well described at both the light microscopic and ultrastructural levels. These structural abnormalities often correlate with biochemical abnormalities, defective energy production, and the resultant dysfunction of FM muscles. The observed abnormalities in FM muscles are consistent with neurologic findings and disturbances in the hypothalamic-pituitary-adrenal axis. Functional changes in FM muscles are assessed most directly by strength and endurance measurements, but pain and psychologic factors may interfere with accurate assessments. To compensate for diminished effort, the decreased efficiency of the work performance by patients with FM can be verified from P-31 magnetic resonance spectroscopy (MRS) data by calculation of the work/energy-cost ratio for various tasks. In the disease course, muscle abnormalities may be elicited by intrinsic changes within the muscle tissue itself and/or extrinsic neurologic and endocrine factors. The accurate assignment of intrinsic or extrinsic factors has been substantially clarified by a recent surge of experimental findings. Irrespective of the multifaceted causes of muscle dysfunction and pain, an in-depth understanding of the muscle defects may provide ideas for characterization of the underlying pathogenesis and development of new therapeutic approaches for fibromyalgia syndrome.

## Introduction

Fibromyalgia (FM) is characterized by widespread muscle pain, as well as tender points, fatigue, and weakness. A better understanding of the defects and abnormalities in muscle tissues of patients with FM may suggest approaches to symptomatic relief and potentially useful therapeutic interventions. Over the past decade, considerable progress has been made in identifying morphologic and biochemical abnormalities in these painful, dysfunctional muscles. Most, if not all, of the observed anatomic and metabolic abnormalities correlate to the clinical findings of pain, weakness, and fatigue [1•,2•]. Pain and fatigue, as well as sleep disturbances and depression, may have a negative impact, resulting in decreased daily activities and a deconditioned state. However, the structural and metabolic defects in muscles are not solely related to decreased daily activity because many patients have normal employment and domestic routines. Moreover, deconditioning itself is not generally associated with persistent pain or tender points.

The major factors responsible for the debilitating pain in patients with FM have been actively discussed for more than a decade. On the basis of current data, some investigators propose that both intrinsic abnormalities of muscle and extrinsic factors derived from the nervous and endocrine systems may account for persistent pain. In the early stages of the disease, localized pain is detected in a large number of patients [3•]. This pain can result from intrinsic factors (*eg*, disturbances in the microcirculation, ischemia, and decreased ATP concentrations) which excite the intramuscular nociceptors. Intensified local pain may then develop into chronic, generalized allodynia/hyperalgesia by sensitization of the nociceptive cells in the dorsal horn or brain stem along with modulation of pathways in the brain [3•]. Thus the observed alterations in levels of pain modulators, namely, serotonin, substance P (SP), and nerve growth factor (NGF), in the CSF of patients with FM may be of major importance [4,5••]. Disturbances in the hypothalamic-pituitary-adrenal axis may amplify and promote the extent and intensity of neurotransmitter imbalance [6••,7]. The related deficits in growth hormone (GH), somatomedin-C (insulin-like growth factor [IGF]-1), and thyroid stimulating hormone (TSH) curtail ATP production and muscle tissue repair following exercise and exertion [8••,9•,10].

This review focuses on recent investigations of abnormalities of muscle structure, impaired energy metabolism, decreased strength, and aerobic endurance. Muscle abnormalities will be correlated with disturbances in the neuro-

**Table 1. Histologic studies of muscle tissue in patients with fibromyalgia**

| Muscle studied | Biopsy Procedure | Microscopic findings | Reference |
|---|---|---|---|
| Trapezius, Deltoids, and Quadriceps | Open biopsy of tender points | Moth-eaten and ragged red fibers, abnormal mitochondria | Henriksson [11], 1982 |
| Trapezius | Open biopsy of tender points | Mild changes in both controls and patients | Yunus [12], 1989 |
| Quadricep muscles | Needle biopsy | Rubber-band morphology | Bartels [13], 1986; Jacobsen [14], 1991 |
| Quadricep muscles | Needle biopsy | Abnormalities and duplication of membranes, mitochondrial abnormalities | Drewes [15], 1993 |
| Quadricep muscles (V. Lateralis) | Semi-open biopsy | Reduced capillary numbers and decreased enzyme activities | Lindh [17], 1995 |
| Trapezius | Open biopsy of tender points | Reduced numbers of capillaries | Bengtsson [18], 1989 |
| | | Reduced numbers of capillaries, thickened endothelium, moth-eaten and ragged red fibers, abnormal mitochondria | Lindman [16], 1991 |
| Various muscles | Open biopsy | Type-II fiber atrophy, increased lipid droplets, ragged red fibers, cytochrome oxidase defect | Pomgrantz [19], 1998 |

*Adapted from* Olsen *et al.* [1•]

logic and endocrine systems, which impact significantly on patient status. Trials of therapeutic approaches based on potential pathogenetic pathways in muscle also will be considered.

## Histologic Muscle Abnormalities

### Microscopic examination of fibromyalgia muscle structure

Many histologic abnormalities have been described in fibromyalgia muscles using both light and electron microscopy (Table 1). These histologic findings are important because cellular abnormalities can be often related to metabolic defects and clinical symptoms. One of the early investigations of tender areas of various muscles of patients with FM described fibers with a moth-eaten appearance, abnormal mitochondria, and ragged red fibers, which are usually associated with mitochondrial myopathies [11]. A subsequent double-blind study of the trapezius muscles of patients with FM and normal controls found only mild changes in both groups of subjects [12]. In follow-up investigations, several laboratories did detect abnormalities with electron microscopy, namely, abnormal muscle cell membranes, mitochondria with irregular cristae, and ragged red fibers in patients with FM but not in normal subjects [15,16]. Three carefully controlled investigations of the quadriceps and trapezius muscles demonstrated that capillary microcirculation was compromised in the patients with FM but not in the controls [16–18]. In addition, thickening and structural derangements of the capillary endothelium were observed [16].

More recently, Pongrantz and Späth [19] noted that the most common abnormality in FM muscle biopsies is type-II fiber atrophy, which is present in many other conditions (*eg*, disuse atrophy and steroid myopathy). An increase in lipid droplets and a slight proliferation of mitochondria in type-I fibers appeared to correlate with the duration of disease. The authors were able to confirm the appearance of ragged red fibers, which showed accumulation of lipids, abnormal mitochondria with disrupted cristae, single fiber defects of cytochrome-c-oxidase, and deletions of the mitochondrial genome. The authors make the interesting proposal that these abnormalities of the ragged red fibers are suggestive of "an atypical encephalomyopathic mitochondrial disorder as a fibromyalgia subgroup or a sign of earlier muscle aging."

The degenerative muscle changes in membranes, mitochondria, and capillary vessels may be related to defects in membrane ion channeling, oxygen and metabolite transport, and ATP production via oxidative phosphorylation. The decrease in activity of the oxidative enzymes, 3-hydroxy-CoA dehydrogenase, citrate synthase, and cytochrome oxidase, support the proposal of defects in oxidative metabolism and ATP synthesis, resulting in weakness and fatigue [17,19].

### Attempted detection of pain modulators in fibromyalgia muscle tissues

A novel approach to histologic examination of FM muscle tissue is to determine whether putative mediators or modulators of the pain response may be produced locally within the muscle tissue. One recent study has examined this question using surgical biopsies of deltoid muscle tissues from 10 patients with FM and 10 healthy normal controls [20]. The reverse transcriptase-polymerase chain reaction (RT-PCR) technique was applied to the RNA prepared from the muscle specimens using primers that were designed to detect the following five substances implicated in pain modulation in patients with FM: substance P (SP), serotonin (5-hydroxytryptamine), galanin, pituitary adenyl cyclase activating polypeptide, and secretoneurin.

Assays for the five modulators were performed as in situ RT-PCR or APAAP immunochemical reactions on muscle tissue sections of 6 μm thickness. None of these pain modulators were detected in normal controls, and only one patient with FM had an abnormal finding, which was the presence of mRNA for the galanin receptor. This very limited study showed that the five substances were not produced in peripheral muscle tissue. Nonetheless, these histologic techniques for in situ RT-PCR may be useful in the design and execution of future experiments to look at other potential mediators.

## Muscle Strength and Function in Patients with Fibromyalgia

### Strength testing

Decreased muscle strength in FM has been documented in numerous publications. Grip strength was reduced by 40% ($P<0.01$) in patients with FM as compared with normal controls [21,22] and maximum voluntary contractile force (MVC) of the hand by 26% ($P<0.05$) [23]. For static endurance work tests of the shoulder, as well as isometric and isokinetic strength measurements of knee extension, the patients with FM showed significant decreases ranging from 41% to 66% [17,21,24]. In our own studies using P-31 magnetic resonance spectroscopy (MRS) for determination of metabolite levels, the initial evaluation of MVC and the subsequent work performance during exercise were both decreased by about 40% ($P<0.001$) in patients with FM [25••]. Several investigations have shown that electrical stimulation of FM wrist or quadricep muscles can elicit as much as an 80% increase in strength performance [26,27]. These studies suggest that pain during exercise may reflexly inhibit maximal contractions by patients with FM. Although some investigators have not found significant differences in muscle strength or performance between patients with FM and controls [28,29], the majority of studies have demonstrated statistically significant reductions in strength and function of patients with FM. The percent reductions, ranging from 26% to 63%, depended on the specific muscle group and type of exercise. The discrepancy with those who did not observe significant differences may be explained on the basis of different exercise protocols and testing techniques.

### Aerobic fitness and endurance in patients with fibromyalgia

Reduced aerobic fitness in fibromyalgia syndrome (FMS) was documented by Bennett *et al.* [30], who studied a group of patients with FM and carefully matched control subjects. These data are compatible with the investigation by Norregaard *et al.* [31,32] using a graded scale to measure the amount of time spent each day in various activities. On the basis of the activity record, they were able to estimate daily energy consumption, which was significantly lower in patients with FM as compared with sedentary controls. The lack of endurance in patients with FM may be a reflection of significantly lower blood flow in exercising muscles of patients with FM and abnormal distribution of oxygen in FM muscles [28,29]. Aerobic endurance in patients with FM can be improved by supervised physical fitness training, as demonstrated by McCain *et al.* [33,34] and Mengshoel *et al.* [35,36] [30]. In addition to substantial improvements in cardiovascular fitness and endurance, partial relief from pain was observed in most of these supervised programs.

## Metabolic Abnormalities

### Fibromyalgia muscle metabolism

P-31 magnetic resonance spectroscopy (MRS) offers a useful noninvasive and quantitative approach to measuring muscle metabolism. Concentrations of the high energy phosphate compounds required for contraction, namely, ATP and phosphocreatine (PCr), can be determined in resting and exercising muscles using MRS. This technique has been shown to be of value in the characterization and longitudinal management of a number of metabolic, mitochondrial, and inflammatory disorders of muscle [37,38].

Our recent report demonstrated the presence of significant metabolic abnormalities in the muscles of patients with FM as detected by P-31 MRS [25••]. In this study, 12 patients with FM and 11 normal controls were examined at rest and during a standardized exercise protocol, as previously employed in studies of subjects with dermatomyositis [38]. The spectroscopy coil for measuring ATP, PCr, and inorganic phosphate (Pi) was placed directly over the quadriceps muscles [39]. Following a baseline rest period of 6 minutes, the muscles of each subject were evaluated during 6 minutes of intermittent lifting by contraction of the quadriceps at 25% MVC and then at 50% MVC.

Absolute levels of both ATP and PCr were significantly lower (15%) in muscles of the patients with FM than in the normal control subjects at rest and during exercise at 25% MVC (Table 2). These findings are in rather close agreement with biopsy determinations, which showed reductions in ATP and PCr of 17% and 21%, respectively, in tender sites of the trapezius muscle in patients with FM as compared with nontender sites in the anterior tibialis or with muscles of normal controls [40]. The reduced levels of ATP and PCr in the patients' muscles correlated inversely with clinical observations of weakness or pain as measured on a visual analog scale (VAS) [40]. Reduction of ATP in erythrocytes of patients with FM has been observed, suggesting that this may be a more general systemic phenomenon than previously thought [41,42]. All metabolic abnormalities in the muscles of patients with FM were less severe than those previously reported for very weak subjects with dermatomyositis [38].

Decreased efficiency in FM muscle performance was confirmed by additional calculations of the energy reserve or phosphorylation potential (PP), according to

**Table 2. Comparison of P-31 metabolite levels in muscles of normal controls and patients with fibromyalgia**

| Subjects | Rest | | | Exercise (25% MVC) | | |
|---|---|---|---|---|---|---|
| | ATP* | PCr | Pi | ATP | PCr | Pi |
| Controls (*n*=11) | 5.5 ± 0.2 | 24.7 ± 0.5 | 3.3 ± 0.1 | 5.5 ± 0.2 | 21.1 ± 0.8 | 6.5 ± 0.2 |
| Patients with FM (*n*=12) | 4.7 ± 0.2 | 21.3 ± 0.5 | 3.2 ± 0.2 | 4.8 ± 0.1 | 18.6 ± 0.8 | 5.9 ± 0.3 |
| *P* Value | < 0.0039 | < 0.0001 | NS | < 0.015 | < 0.03 | NS |

FM—fibromyalgia; NS–not significant; PCr–phosphocreatine; Pi–inorganic phosphate.
* Values are expressed as the mean ± SEM mmoles/Kg wet weight of muscle.
*Adapted from* Park *et al.* [25••].

**Table 3. Phosphorylation potential, work, and total oxidative capacity**

| Subjects | PP, *mmoles-1* | V, *joules/min* | $V_{max}$ | $V / V_{max}$ |
|---|---|---|---|---|
| Controls (*n*=11) | 378 ± 86 | 80 ± 5 | 220 ± 17 | 0.37 ± 0.01 |
| Patients with FM (*n* = 12) | 145 ± 34 | 48 ± 8 | 124 ± 17 | 0.38 ± 0.02 |
| *P* Value | < 0.01 | < 0.003 | < 0.001 | NS |

FM— fibromyalgia; NS—not significant; PP—phosphorylation potential; V—work; $V_{max}$—total oxidative capacity.
Values are expressed as mean ± SEM
*Adapted from* Park *et al.* [25••].

Chance *et al*. [43]. Because PP was a value obtained in resting FM muscles, no correction was required for the possibility of decreased effort. This value for the muscles of the patients with FM was 60% lower than normal values ($P$<0.01) (Table 3). The explanation for the reduced work performance (V) during exercise may be explained in part by this low PP, as well as by the decreased work/energy-cost ratio (pounds lifted/[Pi/PCr]) and low total oxidative capacity ($V_{max}$), which were approximately 55% below normal values ($P$<0.001) [25]. These low values indicate that oxidative phosphorylation was significantly impaired in the patients with FM. The fraction of oxidative capacity used during the exercise ($V/V_{max}$) was the same for patients and controls, which means that the patients used the same amount of energy to perform less work (Table 3). This would be expected to translate into the clinical symptom of decreased endurance, which is commonly observed in FM.

The P-31 MRS data have been subjected to an artificial neural network analysis in order to detect differences between patients with FM and normal controls [44]. The neural network is a computerized pattern recognition process which has been applied to various clinical problems [45,46]. Indeed, the neural network successfully distinguished patients with FM from normal controls, thereby confirming the presence of abnormalities in FM.

A very important consideration in interpretation of P-31 MRS data is the selection of the normal control group. For our controls, the work- and home-related activities were similar to those of the patients, so that the observed metabolic differences are not readily attributable to differences in levels of activity [25••]. The control subjects used in this study are in many ways most desirable, as representing the capacity for normal daily activity which patients with FM desire to attain through therapeutic regimens.

A possible explanation for metabolic defects in muscles of patients with FM is deconditioning. In order to study this possibility, regression analyses were performed on activity indicators (M-HAQ scores, stairs climbed, leisure activities, weakness, and fatigue) versus important metabolic parameters (ATP, PCr, and PCr/Pi). There were no significant correlations between any of the activity indicators and metabolic parameters. Pain was the only parameter that was inversely correlated with ATP and PCr levels [25••]. Indeed, uncontrolled factors (*eg*, pain and neuroendocrine disturbances) could affect biochemical parameters or muscle performance.

In contrast to our findings of low ATP and PCr levels in FM muscles, several other laboratories did not show abnormalities in FM data obtained with P-31 MRS [29,47–50]. These disparities may be explained by differences in technological and experimental design. First, we measured the absolute concentrations of ATP and PCr, which offers the possibility of detecting abnormalities that might otherwise be missed. Other investigators reported only ratios of metabolites, namely, PCr/Pi or PCr/ATP. Ratios may well be similar in patients with FM and controls, but the concentrations of important metabolites in patients that make up the ratios may be substantially below normal values. Secondly, we examined the quadriceps muscles, whereas other groups studied the trapezius, calf muscles, anterior tibialis, or wrist flexors. His-

**Table 4. Abnormalities in $Mg^{2+}$ and ATP levels in fibromyalgia quadricep muscles**

| Subjects | [Mg free]* | [MgATP] | [ATP free] | [ATP Total] |
|---|---|---|---|---|
| Controls (*n*=11) | 0.96 ± 0.11† | 4.99 ± 0.18 | 0.31 ± 0.03 | 5.31 ± 0.20 |
| Patients with FM (*n* = 12) | 0.67 ± 0.05† | 4.40 ± 0.12 | 0.37 ± 0.03 | 4.77 ± 0.12 |
| *P* Value | < 0.03 | < 0.01 | NS | < 0.03 |

FM—fibromyalgia
*expressed as mmoles/Kg weight of muscle
† values represent mean ± SEM
*Adapted from* Niermann *et al.* [54], and Park *et al.* [55].

tologic data suggest that abnormalities are more easily detected in the quadriceps muscles, where normal control subjects have few abnormalities. Lastly, the exercise regime for our MRS examinations differed from that of all the other protocols. The results of other investigations may be valid for their particular calculations and experimental conditions.

The P-31 MRS study by Jubrias *et al.* [50] did demonstrate a quantitative difference between patients with FM and sedentary controls following strenuous exercise. The FM muscles showed increased levels of phosphodiesters (PDE), which are thought to reflect damaged membranes, possibly due to lipid peroxidation and altered calcium levels. These MRS results are concordant with histologic findings of abnormal membranes. The presence of elevated PDE levels in exercising FM muscles was subsequently confirmed by Park *et al.* [25••], but not by Simms and Hrovat [51]. Elevated PDE levels are known to occur in Duchenne muscular dystrophy and in the process of normal aging.

### Magnesium levels in fibromyalgia muscles

Magnesium is an important metabolic element because it is required for most, if not all, enzymatic reactions involving ATP. This includes the many oxidative phosphorylation enzymes, which produce the ATP required for muscle contraction. Magnesium levels in FM erythrocytes have been reported to be both normal and decreased [52,53]. Because blood levels of magnesium do not necessarily reflect tissue measurements, we determined the FM muscle concentrations of this cation using P-31 MRS [54,55]. During exercise, the differences between patients with FM and controls were quite pronounced (Table 4). Unbound [MgFree] was 31% lower in patients with FM ($P$<0.03), and the enzymatically active ATP complex, [MgATP], was decreased by 12% ($P$<0.001). Clauw *et al.* [56] have shown an inverse correlation between muscle magnesium levels and pain tolerance. The findings from these two laboratories suggest the following defects: [1] decreased metabolic energy production of ATP and [2] potentiation of pain by decreasing the inhibitory effect of Mg on the N-methyl-D-aspartate (NMDA) receptor sites.

Abraham and Flechas [53] proposed a rationale for the combined use of magnesium and malic acid in the treatment of patients with FM. For their initial open label trial with Super Malic®, a combination of magnesium hydroxide and malic acid, the authors reported substantial relief from pain. Russell *et al.* [57••] designed a more rigorous double-blind, placebo-controlled pilot study, which showed no improvements in patients with FM receiving low-dose Super Malic®. However, in a subsequent 6-month open-label dose escalation trial, significant reduction in pain was observed, as measured by HAQ scores, pain on VAS, and TPI. Further trials of Super Malic® may prove beneficial for pain reduction in FMS.

### Oxygen tension and blood flow

An abnormal distribution of oxygen has been demonstrated by placing an oxygen-sensitive probe directly on a surgically exposed tender point of FM trapezius muscle [58]. This distribution phenomenon may have been the result of focal ischemia due to decreased blood flow. Significantly lower blood flow in exercising FM muscles as compared with well-matched control subjects was demonstrated by Bennett *et al.* [59] employing a $^{133}$Xenon blood clearance technique. Additional support for disturbances in blood flow was provided by experiments showing that a sympathetic block increased blood flow and diminished pain [60]. The previously mentioned morphologic changes in the decreased capillary bed along with thickened endothelium may impair the exchange of gases and metabolites [61,62].

More recently, an unexpected finding of increased oxygen tension in the erector muscles of the spine in patients with FM was reported by Strobel *et al.* [63], who used polarographic oxygen fine-needle probes to make 200 measurements in each subject. The mean tissue $pO_2$ in mmHg was 40.6 for the patients as compared with 34.6 for the healthy controls. Unfortunately, no statistical analyses were performed on these data. The results of this study contradicted the findings of Lund *et al.* [58]. If these data by Strobel *et al.* [63] are confirmed by other investigators, alternative explanations will need to be developed. One intriguing possibility is that decreased oxygen utilization by FM muscle would result in increased oxygen tension. Such "paradoxical oxygenation" has been described using near infrared spectroscopy in metabolic myopathies, including those with deficiencies of cytochrome oxidase, myophosphorylase, or phosphofructo-kinase [64]. Certain weak patients with dermatomyositis also show "paradoxi-

cal oxygenation" [65]. Decreased rates of extraction of oxygen from circulating blood could be due to deficiencies in oxidative metabolism in mitochondria or to capillary abnormalities that prevent normal tissue exchange.

### Metabolic abnormalities: case studies

The characteristic features of fibromyalgia, namely, widespread pain with tender points, can be observed as part of other well-defined syndromes. Two recent case reports describe patients with FMS in whom well-defined metabolic derangements were later uncovered.

*Myoadenylate deaminase deficiency*

The subject of this report was a 53-year old woman with a 10-year history of fatigue and myalgias [66]. She had palpable muscle irregularities and worsening of pain following exertion. Many routine laboratory tests, including thyroid studies, were normal. A diagnosis of fibromyalgia was made. She pursued a program of weight lifting and aerobic exercise, but this provided no relief. Due to the persistent and unremitting nature of her symptoms, a muscle biopsy was performed. Type-II muscle fiber atrophy was seen on histologic analysis. Subsequently, an ischemic forearm test was conducted and showed abnormal lactic acid production. Further genetic testing at the DNA level revealed that she was heterozygous for a mutation of the AMPD-1 gene responsible for the syndrome of myoadenylate deaminase (MAD) deficiency. The pattern of aberrant gene expression was consistent with the secondary or acquired form of MAD deficiency. The authors point out that although the ischemic forearm test is a very useful way to diagnose this relatively common disorder, some reports do not measure ammonia as well as lactate during the testing, and therefore some cases of MAD deficiency will be missed. They cite a study in which 10 patients with FM were said to have normal ischemic forearm tests. However, ammonia levels were not reported, and it is possible that some patients with underlying MAD deficiency might have gone undetected. The observation that this metabolic defect can result in many of the same clinical symptoms as FM suggests that alterations of muscle metabolism could contribute to the pathogenesis of this disorder, in at least some patients [67,68•].

*Hyperkalemic periodic paralysis*

A Swedish group has reported the case of a 38-year-old woman with a 20-year history of fatigue [69]. She subsequently developed tender points, and a diagnosis of FM was made. Many routine laboratory tests were normal. She was treated with amitriptyline and an exercise routine. However, symptoms continued without any improvement, and she noted general worsening in cold weather. Two years later, she was thoroughly re-evaluated with no abnormalities found. In addition, there was now a history of muscle pains and weakness in her 10-year-old son. After one episode of exertion, he had a witnessed attack of muscle paralysis. A more extensive family history then revealed that other relatives, including the proband's father and grandfather, had persistent muscle pain and weakness which in some cases was incapacitating. Both the proband and her son had normal muscle bulk, and there was no evidence of myotonia induced by room temperature or manipulations such as percussion or handshake. However, with forearm cold water testing, both subjects showed stiffness and myotonia of the hand muscles. The woman was given a test dose of potassium hydrochloride (2 grams), which produced rapid but reversible paralysis. Serum potassium levels remained within the normal range. EMG studies performed at room temperature in both the woman and her son were normal. Biopsies obtained from the quadriceps muscles were normal at both the light microscopic and ultrastructural levels. The woman was treated with a thiazide diuretic to maintain the serum potassium level at 3.5 mmol/L and a beta agonist agent to use for acute paralytic attacks. Her diet was modified to include frequent, high-carbohydrate meals. Some of the symptoms were improved on this regimen.

The authors of this report note that some patients with FM might in fact have such a channelopathy and that it is conceivable that therapies for this or related disorders could become available. They also note that when a diagnosis of FM is made, the treating physicians should be aware that underlying myopathic disorders are in the differential diagnosis, and further clinical investigations may be warranted in some patients.

## Discussion

Muscle pain, tender points, and fatigue represent primary complaints for most patients. Pain is accentuated during sustained muscle exertion and recedes upon cessation of activity. The focal nature of this pain was demonstrated by injection of local anesthetic agents. First, the tender points were far more sensitive to the insertion of the needle than the adjacent muscle [70]. Secondly, epidural injection of lidocaine in patients with FM totally abolished pain, even in the tender points, whereas saline had no effect [71]. Thus, FM muscle pain was at least partially of peripheral origin. The focal pain may originate from peripheral defects, both morphologic and biochemical, which may also promote the symptoms of weakness and fatigue [72••]. In addition, the multiple peripheral defects can interact with central factors to account for cellular abnormalities as well as pain, weakness, and fatigue (Fig. 1).

### Peripheral factors

Major peripheral defects in FM muscles were observed in the capillary bed with abnormally thickened endothelium, impaired diffusion, and decreased blood flow [3•,15–18] (Fig. 1, central cycle). This could lead to decreased oxygenation and reduced ATP synthesis via oxidative phosphorylation in mitochondria [25••,30,40]. These findings, along with the decreased phosphorylation potential (PP) and total

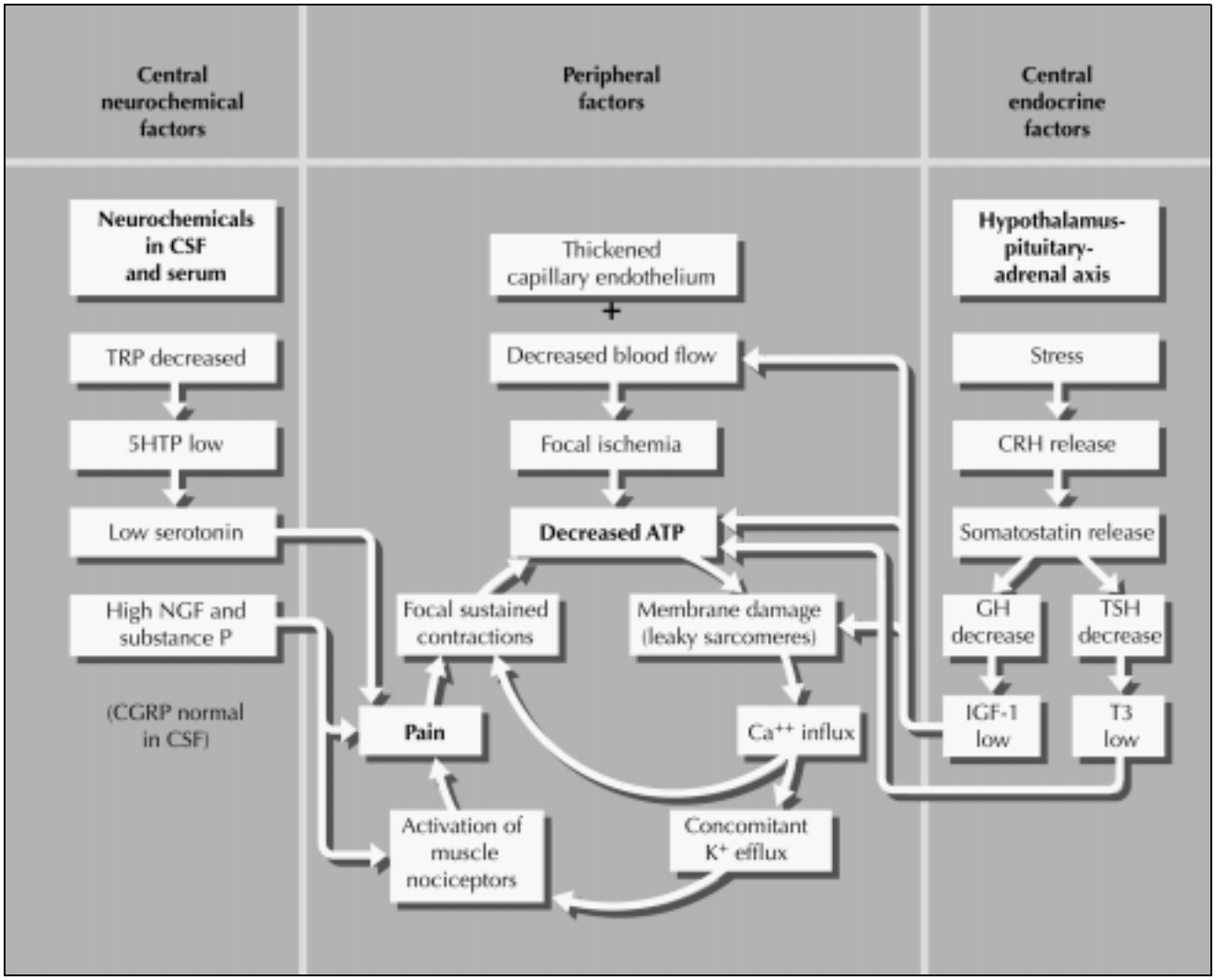


**Figure 1.** Diagram of proposed interactions of peripheral and central factors leading to pain and muscle dysfunction in FMS. In the FM muscle, the decreased capillary bed volume and thickened endothelium could lead to focal areas of ischemia and impaired ATP production via mitochondrial oxidation. Ischemia and ATP deficit cause membrane damage leading to increased Ca 2+ influx and accompanying K+ efflux, which activates the pain nociceptors in muscle. Increased pain produces diminished muscle activity and sustained contractions, thereby completing the peripheral cycle which accentuates the intrinsic abnormalities in muscle. The pain of central origin is augmented by decreases in central factors such as the antinociceptive serotonin, which inhibits transmission of the pain signals. Levels of neurotransmitters which amplify pain signals are increased, namely, NGF and substance P. The stress of heightened pain perception produces peripheral endocrinological changes resulting in greater somatostatin release from the hypothalamus, with subsequent inhibition of GH and TSH. The resultant depression of IGF-1 and T3 affects the muscle per se by preventing muscle membrane repair following exercise, reduced O2 consumption and impaired ATP synthesis. The overall picture is one of complex peripheral and central interactions, which act to promote muscle pain, weakness and fatigue in FM patients.
CGRP—calcitonin gene-related peptide; CRH—corticotropin-releasing hormone; GH—growth hormone; 5HTP—5-hydroxytryptophan; IGF-1—insulin-like growth factor-1; NGF—nerve growth factor; TRP—tryptophan; TSH—thyroid stimulating hormone.

oxidative capacity ($V_{max}$), offer a partial explanation for the reduced work performance of the patients [17,21,24,25••].

Bennett [72] proposed that muscle pain in patients with FM may also be caused by the focal areas of ischemia with decreased ATP levels. Indeed, low levels of ATP in FM muscles inversely correlate with increased levels of pain [25••]. Diminished strength and endurance could also result in part from pain, which reflexly inhibits voluntary contraction. Damaged muscle membranes due to ischemia and lack of ATP may permit $Ca^{2+}$ influx into sarcomeres, producing even greater ATP deficits with further membrane damage, as evidenced by increased phosphodiesters (PDE) [50]. $Ca^{2+}$ influx is accompanied by $K^+$ efflux, which causes activation of the nociceptor pain pathway, thereby amplifying the peripheral cycle of metabolic abnormalities, induction of pain, weakness, and fatigue.

## Central factors

Abundant evidence exists indicating that patients with FM have a heightened general pain sensitivity, which may be sus-

tained and amplified by continuous upgrading of peripheral nociceptive input [73] (Fig. 1, left panel). The proposed basis for this enhancement of secondary hyperalgesia is the activation of the N-methyl-D-aspartate (NMDA) receptors, which synergistically interact with substance P (SP) [74,75]. In fact, the NMDA receptor antagonist, ketamine, attenuates pain and pain thresholds when administered intravenously to patients with FM [76••]. Substantial support for the neurochemical pathogenesis of FM resides in the observation that concentrations of neurotransmitters that facilitate nociception, namely, SP and nerve growth factor (NGF), are significantly elevated the in CSF of patients with FM [5,77]. By contrast, serotonin, which inhibits the release of SP by afferent neurons, is decreased in CSF [78]. These three modifications of neurotransmitter levels in CSF all act in the direction of amplification of pain perception.

The stress elicited by enhanced generalized pain and other circumstances can produce significant endocrinologic changes in the hypothalamic-pituitary-adrenal axis, as demonstrated by Crofford *et al.* (6••,79) (Fig. 1, right panel). The perturbed circadian rhythm, due to the disturbed CRH and cortisol levels, leads to augmented somatostatin release from the hypothalamus. Somatostatin then mediates a down-regulation of secretion of growth hormone (GH) and thyroid stimulating hormone (TSH) from the pituitary gland [9•,10]. Deficiencies of GH and its major mediator, insulin-like growth factor-1 (IGF-1), could contribute to multiple symptoms in FMS: reduced strength and endurance, fatigue, inadequate repair of muscle following exercise, leaky membrane abnormalities with impaired $Ca^{+}$ transport, and muscle pain [80•]. Daily GH administration to women with FM and low IGF-1 levels affords significant improvement in the number of tender points and general clinical status [8••]. The reduction in TSH secretion by the pituitary gland and the accompanying decrease in the thyroid hormone T3 would result in lower oxygen consumption. Changes in oxygen availability may relate to the focal ischemic areas in muscle and the well-known impairment of mitochondrial oxidative phosphorylation and ATP synthesis [10] (Fig. 1, middle cycle).

## Conclusions

The peripheral defects in FM muscles per se can be correlated with the central disease manifestations of the abnormal levels of neurochemical transmitters and perturbed endocrine status. Most of the experimental data from studies of peripheral and central abnormalities are consistent with the picture of a multidimensional disease with close interrelation between organ systems. The increased knowledge base derived from clinical and scientific studies has provided many incentives for drug therapies, such as GH, serotonin reuptake inhibitors (tramadol), NMDA receptor antagonists (ketamine), magnesium (Super Malic®), as well as supervised exercise programs [81••]. As technology and genetic approaches are advanced, one can anticipate clearer elucidation of the pathogenesis and etiology of FM.

## Ackowledgments

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- •• Of major importance

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