Impaired Growth Hormone Secretion in Fibromyalgia Patients

Evidence for Augmented Hypothalamic Somatostatin Tone

Eduardo S. Paiva, Atul Deodhar, Kim D. Jones, and Robert Bennett

Objective. To determine whether female fibromyalgia (FM) patients exhibit a normal growth hormone (GH) response to an acute exercise stressor, and to assess the importance of somatostatin tone in the generation of this GH response.

Methods. Twenty female FM patients were compared with 10 healthy female controls. All subjects exercised to volitional exhaustion on a treadmill. A standard metabolic cart was used to monitor pulse, blood pressure, electrocardiography, oxygen uptake, carbon dioxide output, anaerobic threshold, and maximal workload. Blood was drawn for GH and cortisol measurements 1 hour before exercise, immediately before exercise, immediately after exercise, and 1 hour after exercise. One month later, testing that was exactly similar was performed, except all subjects were given pyridostigmine bromide (Mestinon; 30 mg orally) 1 hour before exercise.

Results. Compared with controls, FM patients failed to exhibit a GH or cortisol response to acute exercise ($P = 0.003$). After administration of pyridostigmine, 1 hour before exercise, the GH levels of FM patients increased 8-fold ($P = 0.001$), to a value comparable with that of controls. Pyridostigmine did not increase the cortisol response to exercise in FM patients. Pyridostigmine alone did not stimulate GH secretion in FM patients, nor did it improve exercise-induced GH secretion in controls. FM patients with normal insulin-like growth factor 1 (IGF-1) levels had an impaired GH response to exercise.

Conclusion. Three new findings are reported: 1) FM patients have a reduced GH response to exercise, 2) pyridostigmine reverses this impaired response, and 3) defective GH secretion in FM can occur in patients with normal IGF-1 levels. Because pyridostigmine is known to reduce somatostatin tone, it is surmised that the defective GH response to exercise in FM patients probably results from increased levels of somatostatin, a hypothalamic hormone that inhibits GH secretion.

Fibromyalgia (FM) is a common clinical syndrome characterized by widespread musculoskeletal pain, with a high prevalence both in the general population and among patients attending rheumatology clinics (1–4). Increasing evidence implicates a perturbation in the central mechanisms of sensory processing as being relevant to understanding the pain component of FM (5–7). Fibromyalgia is more than a state of chronic musculoskeletal pain, however, because most FM patients also experience fatigue, poor sleep, visceral pain (e.g., irritable bowel or bladder), exercise intolerance, and neurologic symptoms (e.g., dizziness, numbness, tingling) (8).

A theoretical model explaining the complexity of FM symptoms has been proposed, which links dysregulation of neuroendocrine/stress/pain mechanisms to disordered sleep–wake physiology (5). This evolving paradigm promotes the notion that FM is a stress-related syndrome, in which a disordered hypothalamic–pituitary–adrenal (HPA) axis acts as a final common pathway linking FM to other stress-related somatic and psychiatric syndromes (7,9,10). The HPA and the HP–growth hormone (GH) axis are closely linked in terms of the opposing influences of corticotropin-releasing hormone and somatostatin on GH secretion (11).

Defective GH secretion in FM was initially surmised based on the finding of low levels of insulin-like growth factor 1 (IGF-1; somatomedin C) in a subset of
FM patients (12–14). It was originally hypothesized that GH production in FM patients would be impaired because such production occurs predominantly during stages 3 and 4 of non-rapid eye movement sleep (12), which is disrupted in many FM patients (15). In the current study, the hypothesis was that an increased level of somatostatin is related to impaired GH secretion in FM patients. To test this hypothesis, the exercise-stimulated GH response in female FM patients and healthy controls was evaluated both before and after administration of pyridostigmine (a potent cholinergic agent). The rationale for this pharmacologic manipulation was the observation that increased cholinergic activity stimulates GH release by inhibiting hypothalamic somatostatin tone (16). Thus, an improvement in exercise-stimulated GH secretion after administration of pyridostigmine would suggest that FM patients have increased hypothalamic somatostatin tone.

**SUBJECTS AND METHODS**

Twenty women with a diagnosis of FM based on the 1990 American College of Rheumatology criteria (3) were recruited from a database of FM patients at Oregon Health Sciences University (OHSU). All patients were 18–60 years of age and were assessed for the following exclusion criteria: angina, uncontrolled hypertension, chronic obstructive pulmonary disease, hypothyroidism, severe depression, previous pituitary disease or surgery, and pregnancy. Using the same exclusion criteria, 10 healthy women were selected as controls. Other than sex, there were no specific selection criteria for either group. All subjects gave informed consent, and the OHSU review board approved the study.

Each subject underwent a treadmill test, using the modified Balke protocol (17). They exercised to the point of volitional exhaustion, which was defined when either of 2 goals was reached: 1) respiratory rate (RR) index (anaerobic threshold) of 1.0, indicative of anaerobic metabolism, or 2) exhaustion (Borg scale value of 10 (maximum perceived effort). Electrocardiography and blood pressure monitoring were performed every 5 minutes. All testing was performed between 10:00 AM and 2:00 PM. Blood was collected through an indwelling catheter 1 hour before exercise, immediately before exercise (time 0), immediately after exercise, and 1 hour after the end of exercise. GH and cortisol levels were measured at each time point. IGF-1 levels were measured 1 hour before the first treadmill test. Subjects were given a second treadmill test within at least 1 month of the first test. This second test was identical to the first, except all subjects were given 30 mg orally of pyridostigmine bromide (Mestinon) 1 hour before exercise.

IGF-1 was measured by immunoradiometric assay (Diagnostic Systems Laboratories, Webster, TX). The sensitivity of this assay is 0.80 ng/ml; the mean in-assay coefficient of variation (CV) is 2.6%, and the mean inter-assay CV is 4.5%. Human GH was measured by a noncompetitive chemiluminescence assay (Diagnostic Products, Los Angeles, CA). Sensitivity of this assay is 0.01 ng/ml; the mean intra-assay CV is 0.80 ng/ml; the mean intra-assay coefficient of variation (CV) is 2.6%, and the mean inter-assay CV is 7.9%.

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of the patients and controls*</th>
<th>Fibromyalgia (n = 21)</th>
<th>Controls (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>44.6 ± 8.2</td>
<td>47.0 ± 4.7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80.8 ± 16f</td>
<td>68.3 ± 13</td>
</tr>
<tr>
<td>Body mass index</td>
<td>29.05 ± 5.3</td>
<td>25.9 ± 4.6</td>
</tr>
<tr>
<td>VO2max, ml/kg/minute</td>
<td>18.6 ± 4.8</td>
<td>18.7 ± 4.4</td>
</tr>
<tr>
<td>RER at VO2max</td>
<td>1.20 ± 0.11</td>
<td>1.18 ± 0.06</td>
</tr>
<tr>
<td>Total exercise work, watts</td>
<td>144 ± 51</td>
<td>138 ± 56</td>
</tr>
<tr>
<td>IGF-1, ng/ml</td>
<td>189 ± 83</td>
<td>170.8 ± 50</td>
</tr>
<tr>
<td>Resting GH, ng/ml</td>
<td>0.66 ± 2.1</td>
<td>0.74 ± 1.49</td>
</tr>
<tr>
<td>Resting cortisol, ng/ml</td>
<td>7.7 ± 3.3</td>
<td>8.6 ± 3.0</td>
</tr>
<tr>
<td>% pre/postmenopausal</td>
<td>52/48</td>
<td>62/38</td>
</tr>
<tr>
<td>% taking HRT</td>
<td>30</td>
<td>25</td>
</tr>
</tbody>
</table>

* Unless indicated otherwise, values are the mean ± SD. VO2max = maximum volume of oxygen utilization; RER = respiratory exchange ratio; IGF-1 = insulin-like growth factor 1; GH = growth hormone; HRT = hormone replacement therapy.

† P = 0.043 versus controls.

**RESULTS**

Baseline characteristics of the FM patients and controls (Table 1) were comparable, except the mean weight of FM patients was 12.5 kg greater than that of controls (P = 0.043). However, there was no significant difference in body mass index (BMI) between the 2 groups. All participants were able to reach an anaerobic threshold at maximal exertion. There was no difference in the maximal mean values of respiratory exchange ratio, workload, or oxygen uptake (VO2max) between FM patients and controls. The mean IGF-1 and resting GH levels were not significantly different between the 2 groups.

After exercising to volitional exhaustion, the healthy controls exhibited an increase in GH, from a mean ± SD of 0.74 ± 1.49 ng/ml before exercise to a mean ± SD of 6.2 ± 6.1 ng/ml after exercise (P = 0.003). This increase was not influenced by pyridostigmine (P = 0.21) (Figure 1). Only 1 control subject did not demonstrate an exercise-induced increase in GH. This subject
had a low IGF-1 level (74 ng/ml), and although she did not have FM, she was presumed to have physiologic GH deficiency, because she exhibited a 40-fold increase in GH after administration of pyridostigmine followed by exercise.

Eleven of 20 FM patients exhibited no exercise-induced increase in GH level. Compared with controls, FM patients had a significantly reduced response to exercise \((P = 0.017\) by Fisher’s exact test) (Figure 1). On the whole, FM patients had a very modest exercise-induced change in GH levels, with a mean ± SD increase of 0.66 ± 2.1 ng/ml at time 0 to a mean ± SD of 1.66 ± 2.75 ng/ml \((P = 0.20)\) 1 hour after exercise (Figure 2). These results cannot be attributed to the greater mean weight of the FM patients, because there was no correlation between GH response and weight or BMI. However, following administration of pyridostigmine, 19 of 20 FM patients exhibited an exercise-induced increase in GH.

Overall, after administration of pyridostigmine, GH in FM patients increased from a mean ± SD of 0.57 ± 0.82 ng/ml to a mean ± SD of 4.7 ± 3.8 ng/ml \((P = 0.001)\) (Figure 2). This increase in GH was 8-fold higher than that associated with exercise stimulation without pyridostigmine and was similar to the increase seen in healthy controls. This result cannot be explained by the fact that the FM patients exercised to a greater intensity with the pyridostigmine protocol, because their maximal workload was only slightly increased (mean ± SD 44 ± 51 to 155 ± 33 watts; \(P = 0.42\)), and all achieved an RR index ≥1.0. Pyridostigmine without exercise did not stimulate GH secretion after 1 hour (Figure 2).

Backward stepwise regression analysis showed no relationship between exercise-induced changes in GH level and weight, BMI, VO2max, age, maximal workload at volitional exhaustion, or resting GH level, in either FM patients or controls. The presence of low levels of IGF-1 at baseline did not predict postexercise levels of GH in either group; this was true regardless of whether the cutoff level for IGF-1 deficiency was age-adjusted or predetermined.

Resting cortisol levels were not significantly different between FM patients and controls (Table 1). Cortisol secretion was slightly reduced by exercise in FM patients (mean ± SD 7.7 ± 3.3 ng/ml before and 7.4 ± 3.5 ng/ml after exercise; \(P = 0.77\)). Unlike the HP–GH axis, the HPA axis response to exercise was not influenced by prior administration of pyridostigmine in FM patients (1-hour postexercise value 6.2 ± 3.3 ng/ml with pyridostigmine treatment). Cortisol secretion was modestly increased by exercise in healthy controls (mean ± SD 8.6 ± 3.0 ng/ml before and 10.8 ± 3.8 ng/ml after exercise; \(P = 0.17\)). The postexercise cortisol level was significantly higher in controls compared with FM patients \((P = 0.02)\). There was no correlation between

**Figure 1.** Individual peak growth hormone (GH) responses for the 4 study groups. Each pair of symbols connected by a line represents the values for an individual subject from the immediate preexercise time and the immediate postexercise time.

**Figure 2.** Growth hormone (GH) levels in fibromyalgia (FM) patients after exercise. Exercise alone failed to stimulate GH secretion in FM patients, but administration of pyridostigmine bromide (30 mg orally) 1 hour before exercising normalized release of GH in these patients \((P = 0.005)\). Values are the mean ± SD.
hormone GH depends on the tonic balance of stimulatory growth thalamic hormones. The normal pulsatile secretion of the influence of both stimulatory and inhibitory hypo-
of FM patients. On balance, the literature to date supports the diseases) and found a very significant (healthy individuals and patients with other rheumatic IGF-1 levels in 500 FM patients and 152 controls (both contrast, investigators at our laboratory compared between the mean IGF-1 levels of the 2 groups, ~20% of the FM patients had low IGF-1 levels (19). In contrast, investigators at our laboratory compared IGF-1 levels in 500 FM patients and 152 controls (both healthy individuals and patients with other rheumatic diseases) and found a very significant \((P = 0.00000000001)\) reduction of IGF-1 levels in the FM population (14). Many FM patients studied by the latter group had normal IGF-1 levels, however, and it was concluded that about one-third of FM patients have probable GH deficiency.

The fact that the FM population in the current study had mean IGF-1 levels similar to those of controls is not, therefore, surprising, given the fact that we studied only 20 FM patients and 10 controls. Other studies have demonstrated low levels of GH in FM patients (23,24), and reduced GH secretion has been shown in various types of stimulation studies (13,14,24–26). On balance, the literature to date supports the notion that the HP–GH axis is dysfunctional in a subset of FM patients.

GH is the only pituitary hormone that is under the influence of both stimulatory and inhibitory hypothalamic hormones. The normal pulsatile secretion of GH depends on the tonic balance of stimulatory growth hormone–releasing hormone (GHRH) and inhibitory somatostatin (27,28). Under normal circumstances, production of GH occurs only when secretion of GHRH takes place in the setting of low levels of somatostatin tone. Many studies have shown that cholinergic stimulation with pyridostigmine reduces hypothalamic somatostatin tone, with a resultant up-regulation of GH release (16,29,30). Both physiologic and pharmacologic down-regulation of GH secretion is usually the result of increased somatostatin tone (11). For instance, the age-related decline in stimulated GH secretion is reversed by pyridostigmine (31,32). Exercise-induced stimulation of GH release is also blunted with aging and can be reversed by administration of pyridostigmine (31,33). The low levels of GH found in persons who are morbidly obese are increased by pyridostigmine (34). The depressed GH secretion that occurs as a result of excessive endogenous and exogenous corticosteroids is attributable to increased somatostatin tone and can be partially reversed by pyridostigmine (35).

Thus, the results of the current study suggest that hypothalamic somatostatin tone in FM patients is increased compared with that in age- and sex-matched controls. The reason for this is not immediately clear, but it is reasonable to hypothesize that there is a link with the perturbations of the HPA axis that have been reported in FM patients (36–38). According to this scenario, the pleiotropic actions of corticotropin-releasing factor (CRF) are thought to play a major controlling role. CRF is the major mediator of the HPA/sympathetic response to both physical and psychological stressors. Some FM patients have reduced HPA axis responsiveness to stressors in terms of cortisol secretion, even though they have enhanced adrenocorticotropic hormone (ACTH) response to CRF (37,39,40).

Increased GH secretion is the normal response to an acute stressor (such as exercise). Thus, it might seem paradoxical that a prolonged stress response could cause impaired GH secretion. However, in his description of the “general adaptation syndrome,” Hans Selye (41) envisaged 3 stages to the stress response: 1) an alarm reaction originates in the brain and spreads to the pituitary, where increased production of ACTH stimulates the adrenal cortex to secrete glucocorticoids and mineralocorticoids; 2) after prolonged exposure to the stressor, a second stage develops during which there is increasing secretion of corticosteroids (this is a regulatory physiologic response promoting survival processes while inhibiting nonessential processes); 3) in the third stage, an “exhaustion” ensues during which there is a progressive decline in the adaptive response and an increasing vulnerability to stress-related pathology. The first 2 stages of the general adaptation syndrome are
mediated by the stress-induced secretion of CRF (42). However, prolonged CRF secretion eventually down-regulates the density of CRF-1 receptors in the paraventricular nucleus of hypothalamus (43). Therefore, notwithstanding persistent CRF secretion, the physiologic effects on cortisol secretion ultimately become blunted (42); this is thought to be one mechanism by which the third stage of the general adaptation syndrome is mediated.

A second mechanism by which chronic stress is postulated to lead to a dysfunctional endocrine response is up-regulation of somatostatin tone by increased levels of CRF (13). A correlation between defective GH secretion in FM and Selye’s third stage of the general adaptation syndrome is intriguing but speculative. For instance, Neeck and Riedel hypothesized that a stress-induced increase in CRF is the common denominator linking the disturbed HPA axis and reduced GH secretion in FM (36), the critical link being the observation that CRF increases hypothalamic somatostatin tone (44,45). On the other hand, Torpy et al provided some evidence for a chronically reduced hypothalamic CRF tone and hypothesized that low IGF-1 levels in FM are a consequence of reduced GHRH secretion secondary to impaired non-adrenergic input (38). Van Denderen et al reported an impaired adrenergic response to exhaustive exercise in FM patients as well as a deficient cortisol response (as was also shown in this study) (46), thus providing some support for the reduced GHRH hypothesis.

The notion that an enhanced hypothalamic somatostatin tone results from increased CRF is not supported by the exaggerated response to CRF that has been reported (37,47). This result would not be expected in the setting of chronic oversecretion of CRF, because, in general, there is a reciprocal relationship between receptor density and the concentration of its cognate ligand. However, the complexity of endocrine regulation in terms of long, short, and ultrashort feedback loops, changes in ligand-binding proteins, induced and inherited changes in receptor density/function, and permissive/inhibitory effects of interacting hormones (e.g., the potentiation of CRF-induced release of ACTH by vasoressin) does not permit any definitive conclusions to be reached without performance of more sophisticated experiments.

There are several examples of human stress-related disorders other than FM in which patients exhibit evidence of impaired cortisol secretion: chronic pelvic pain syndrome (48), chronic fatigue syndrome (CFS) (49), posttraumatic stress disorder (50), and overtraining syndrome (51). All of these conditions are characterized by an increase in central HPA function with a paradoxical blunting of the adrenal cortisol response. Whether the blunted cortisol response in FM and these other conditions is a manifestation of central changes or a primary adrenal insufficiency is not currently clear, but a preliminary report of a 50% reduction in the size of the adrenal glands in patients with CFS supports the latter explanation (52).

Thus, the concept has arisen that FM and some other chronic disorders are characterized by a hypoactive stress response in terms of the HPA axis, GH axis, gonadal axis, and thyroidal axis, together with reduced sympathetic responses (13,36,53–55). This neuroendocrine dysfunction is often considered to be an epiphenomenon in the complex pathophysiology of FM (6,14,36), e.g., a secondary response to the stress of chronic pain and its association with human suffering. This introduces a psycho-physiologic dimension into the understanding of these hormonal perturbations, because environmental and developmental factors interact with genetic susceptibility in modulating an individual’s responses to chronic stressors (39,53,56–58).

In the current study, the defective GH secretion in all FM patients, even those with normal IGF-1 levels, was an unexpected finding. However, it is now apparent that although a low level of IGF-1 is usually indicative of adult GH deficiency (59), it is not a very sensitive measure and will miss up to 60% of GH-deficient patients older than age 40 years (60,61). The currently favored test to diagnose adult GH deficiency is the stimulated GH response to a combination of GHRH and an inhibitor of somatostatin tone such as pyridostigmine, arginine, clonidine, or insulin (60). The results of this study indicate that GH deficiency is probably more common in FM patients than was originally reported. Recognition of defective GH secretion in FM patients is of some practical relevance, because GH replacement therapy was shown to benefit FM patients in a 9-month placebo-controlled study (62). It would, therefore, be of interest to determine whether pyridostigmine could be used to provide long-term improvement of growth hormone production in FM patients.

REFERENCES
14. Bennett RM, Cook DM, Clark SR, Burckhardt CS, Campbell SM.