The Steroid Precursor Pregnenolone a "Forgotten" Diagnostic Marker and a Neurosteroidal Target in Chronic Fatigue Syndrome.

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OBJECTIVE

We tested the hypothesis that decreased pregnenolone levels are common in patients with fatigue as a symptom in various fatigue-associated syndromes/diseases.

BACKGROUND

Exercise intolerance and post-exertional malaise (PEM) with low energy levels, presumably caused by mitochondrial dysfunction, are thought to be common determinants of chronic fatigue syndrome (CFS). Pregnenolone (PR), the first steroid synthesized the 1930s, is the first and rate-limiting step in steroidogenesis, in which cholesterol is converted to pregnenolone only in the mitochondria (Figure 1), the precursor of all steroid hormones. PR was successfully used for fatigue in the 1940s (Pincus, 1945), later lost focus, presumed to be an inactive precursor, now shown to be an active neurosteroid (M.Vallee, 2016).

METHODS

Serum pregnenolone sulphate (PR-S) levels were analysed. Normal levels range from 27 to 80 ug/L depending on age. We studied patients with fatigue symptoms in different comorbidities:
40 patients with FMS /widespread pain (36 women/4 men),
21 patients with fatigue as a cardinal symptom (10 long covid, three postvac, three ME/CFS, five of unknown aetiology and 18 patients with MS (mean age 51.1 years, 30f/6m). PR-S serum levels were compared to a control group with migraine/back pain.

RESULTS

The mean PR-S level in the study group of 79 patients with fatigue symptoms was 31 ug/l (median 30) with the lowest values in FMS (24.5),normal values in MS (43,2) and low values (32,.5) in the rest of the group with fatigue symptoms.
The mean PR-S range in the control group of 35 patients with a mean age of 51.6 years was 44.6 ug/l (median 44).

CONCLUSIONS

These results suggest a high probability of low PR-S levels/PR deficiency in patients with fatigue symptoms, especially in FMS and ME/CFS patients.
As a limiting hormone for all biological steroid hormones, PR is a likely marker for mitochondrial dysfunction. This, together with the "forgotten" effects of PR as an active neurosteroid, may lead to possible future therapeutic approaches, as we now have the ability to measure PR levels and not just rely on clinical symptoms. Further big data studies are needed to prove the hypothesis that low PR-S levels cause a "supply chain" that explains the variety of symptoms in CFS and is of particular interest as a therapeutic target for CFS and post-exertional malaise (PEM).

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ILLUSTRATION