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Possible Role for Hepcidin in Acute Neuroleptic Malignant Syndrome

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Letter to Editor

Acute reductions in serum iron levels are frequently associated with neuroleptic malignant syndrome (NMS) [1,2] and have been implicated in the progression of catatonia to NMS [3-5]. Iron catalyzes dopamine synthesis through its role as a cofactor for tyrosine hydroxylase [6], and modulates expression of the dopamine (D2) receptor and dopamine transporter proteins [7]. However, it is unlikely that abrupt changes in serum iron affect the course of NMS via effects on central dopamine neurons because iron does not readily cross the blood-brain barrier, brain iron turnover is slow, and brain iron content is independent of peripheral iron levels [8], so it is unlikely that abrupt changes in serum iron affect the course of NMS via effects on central dopamine neurons. Others have suggested that acute hypoferremia in NMS is one element of a larger acute phase reaction. The acute phase reaction is a nonspecific response to tissue injury that is mediated chiefly by interleukin [6,9] which is associated with increased SNS sympathetic nervous system activity [10], a major component of NMS pathophysiology [11]. There is no consensus regarding the pathoetiology of tissue injury in NMS, but dramatic elevations of creatine kinase (CK) and myoglobinuria are common features [1], indicating that skeletal muscle tissue injury is often present.

Serum iron and CK levels are strongly negatively correlated in acute NMS [2], and in an acutely psychotic patient time-lagged linear regression analysis demonstrated that changes in serum iron was shown to account statistically predicted for almost 70% of the serum CK variance several days later [12]. CK in NMS is covaries nonlinearly related exponentially (i.e., nonlinearly) with to increases in other muscle enzymes (aspartate aminotransferase, alanine transaminase, and lactic acid dehydrogenase) and can exhibit massive elevations too massive to be attributed solely to myolysis, observations best explained by reference to well established models of tissue injury in which increased enzyme synthesis figures prominently [13]. The principal site of protein synthesis is the endoplasmic reticulum, and endoplasmic reticulum stress recently has been shown to induce the genetic expression of hepcidin, an acute phase protein that reduces serum iron levels by triggering degradation of the cellular iron exporter ferroportin [14]. Thus, endoplasmic reticulum stress associated with dramatically increased enzyme production in NMS may also induce hepcidin production, leading to abrupt reductions in circulating iron. Notably, hepcidin is also strongly induced by interleukin [6,14] which may act synergistically with endoplasmic reticulum stress to increase hepcidin levels further.

This hypothesis that muscle injury in NMS induces both CK and hepcidin production, with the latter leading to abrupt reductions in serum iron, is speculative, but it does provide a plausible physiological basis for the frequently observed link between acute hypoferremia and CK elevation in NMS. If this mechanism is confirmed, hepcidin levels might provide a relatively sensitive and specific diagnostic marker for the most acute forms of NMS. Clinical investigation appears warranted.

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