Letters to the Editor

INSULIN RESISTANCE AND COGNITIVE AGING IN LONG-LIVED AND SHORT-LIVED MICE

To the Editor:

In a recent Future History article in this Journal, Rasgon and Jarvik (1) suggested that insulin resistance may facilitate the onset of Alzheimer’s disease (AD) and may provide a mechanistic link between affective disorders and AD. In this context, it may be interesting to examine the association between alterations in insulin signaling and in cognitive aging in mice with major, genetically determined differences in these parameters.

Hypopituitary Ames dwarf (Prop1<sup>df</sup>) mice and growth hormone receptor knock-out (GHR-KO) mice have enhanced sensitivity to insulin. In these animals, both plasma insulin and plasma glucose levels are reduced (2–7), injections of insulin cause greater suppression of plasma glucose levels than is observed in normal mice from the same stocks (7,8), and acute stimulation of early steps of insulin signaling in the liver by exogenous insulin is markedly enhanced (6,7). The effects of aging on learning
ability and memory of these animals were examined using a passive avoidance task. In contrast to normal animals that exhibited the expected age-related decline of performance on this test, both Ames dwarf and GHR-KO mice maintained unaltered levels of cognitive function into advanced age (9,10). Young adult Ames dwarf and GHR-KO mice did not differ from normal animals of the same age in their ability to learn and remember, as assessed by this task. A recent study of GHR-KO mice confirmed these observations using a Morris water maze, a behavioral test designed to assess learning and spatial memory (11). Results of additional studies indicated that the superior cognitive ability of old Ames dwarf and GHR-KO mice as compared with old normal animals was not due to differences in locomotor activity, emotionality, pain thresholds, swimming speed, or other confounders (9–11). Thus, in two types of mutant mice, enhanced insulin sensitivity is associated with greatly attenuated and delayed cognitive aging. If these associations represent cause–effect relationships, the possible mechanistic links may include reduced insulin release and consequent reduction of insulin signaling in the brain (Al-Regaiey, Masternak, and Bartke, unpublished observations) and reduced oxidative damage to brain cells (12).

In contrast to growth hormone (GH)-deficient hypopituitary Ames dwarf mice and GH-resistant GHR-KO mice that are insulin sensitive, giant transgenic mice over-expressing GH are insulin resistant. In GH transgenic mice, plasma insulin levels are grossly elevated, while glucose levels are generally normal. Studies of early steps of insulin signaling demonstrated insulin resistance in the liver and in the skeletal muscle of these animals (13,14). Behavioral tests of GH transgenic mice revealed excellent learning ability at a young age followed by a rapid age-related cognitive decline (15). Inhibitory avoidance learning in 6-month-old GH-transgenic mice resembled values measured in 24-month-old normal animals (16). Thus, in GH transgenic mice, insulin resistance is associated with early and accelerated cognitive decline.

It is of possible interest in the context of this letter that glucocorticoid levels in GH transgenic mice are chronically elevated [reviewed in (17)], thus resembling findings in some affective disorders.

Although the observations summarized above are in excellent agreement with the proposal of Rasgon and Jarvik (1), the mechanisms responsible for these associations remain to be elucidated. It is presently unclear whether persistence of youthful levels of cognitive function in Ames dwarf and GHR-KO mice and early cognitive decline in GH transgenics are due to altered levels and actions of insulin or glucose within the brain. It is possible that differences between cognitive function of mutant, transgenic, and normal mice are due to one or more multiple secondary consequences of altered insulin resistance, or represent biomarkers of delayed aging in Ames dwarf and GHR-KO mice (4,18) and the apparently accelerated aging in GH transgenic mice (17). Regardless of the mechanisms involved, it is clear that, in mice, differences in insulin sensitivity are associated with major alterations in cognitive aging.

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