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Is There A Thyroid-Cortisol-Depression Axis?

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The association between thyroid insufficiency and depression was recognized over a century ago,[1] and evidence of a significant relationship is compelling. The rate of hypothyroidism among the intractably depressed exceeds 50%,[2] and some studies have found rates of depression as high as 100% among the severely hypothyroid.[3] Subclinical thyroid insufficiency has been found in depressives at frequencies four times that of normal populations.[4] The use of thyroid hormone to treat depression dates back at least 50 years,[5] and reports describing resolution of depression following thyroid hormone treatment have been supported by studies.[6]

A mechanism of action, however, has yet to be identified. Currently, the use of the T_3 fraction of thyroid hormone to potentiate the activity of anti-depressant drugs is a common strategy. Indeed, the effect of some of these drugs is thought to be at least partially due to their impact on TH in the brain. Recent studies document a thyroid hormone effect on the neurotransmitters serotonin and norepinephrine, with changes in neurotransmitter synthesis and receptor sensitivity being noted.[7] Interestingly, T_3 can increase the activity of serotonin in the brain,[8] while serotonin has been shown to inhibit thyroid function.[9] Although a complex system of interaction between thyroid hormone and neurotransmitters has been recognized and examined, no clear-cut explanation for the effect of thyroid hormone on depression has emerged. This author suggests a mechanism by which thyroid hormone may resolve depression, via modulation of the stress hormone cortisol.

Chronic dysregulation of the hypothalamic-pituitary-adrenal axis and resultant high cortisol levels are common findings in depression.[10] Excess cortisol has been shown to inhibit the activity of neurotransmitters in the brain,[11] and resolution of depression following normalization of cortisol levels has been demonstrated.[12] It has long been recognized that an increase in thyroid hormone levels enhances the metabolic clearance of cortisol. So effective is this action, that it poses a risk of adrenal crisis to thyroid hormone users who lack adequate cortisol reserves. Perhaps, then, a thyroid hormone-induced drop in cortisol, and subsequent potentiation of neurotransmitters, is the mechanism by which thyroid hormone relieves certain cases of depression. It may be that the subset of responders to thyroid treatment are the same ones with high cortisol as a contributory factor. Yet another question arises. If selective serotonin and norepinephrine reuptake inhibiting drugs affect thyroid hormone as well as neurotransmitters in the brain, could part of their activity be due to a thyroid hormone effect on brain cortisol levels? Further studies are needed to examine these possibilities.

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