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LETTER TO THE EDITOR

Neuroendocrine Evidence for Age-Related Decline in Central Serotonergic Function

In their interesting review, Cidis Meltzer et al. (1998) consider the possible role of serotonin (5-HT) neuron and neurotransmitter loss in late life depression and Alzheimer's disease. Unfortunately, their summary of age-related changes in the 5-HT system does not take into account evidence from neuroendocrine challenge studies that is highly relevant.

McBride et al. (1990) found that the plasma prolactin response to oral challenge with the 5-HT releasing agent, fenfluramine, was blunted in normal subjects older than 30 years, as compared to younger subjects. Based on studies using concurrent administration of 5-HT receptor antagonists, the prolactin response to fenfluramine is mediated by serotonergic receptors of the 5-$HT_{2A/2C}$ subtype (see Newman et al. 1998). Lerer et al. (1996) examined normal subjects over a wider age range and found an inverse relationship between prolactin response to fenfluramine and age. In both studies, the age-related decline was more marked in females. In depressed patients, as compared to normal subjects, blunted prolactin responses to fenfluramine were demonstrated in younger, but not in older, subjects, and the age related decline in fenfluramine-induced prolactin release seen in normal subjects was absent (Lerer et al.). Similar results were reported by Mann et al. (1995), although a much lower age cut-off (30 years) was applied. We (Lerer et al.) postulated that age-related decline in serotonergic function may render older people more susceptible to depression and contribute to added severity of the clinical picture.

Age-related effects on 5-HT_{1A} receptor-mediated responses have also been observed. Gelfin et al. (1995) found significant effects of normal aging on temperature and hormone responses to the 5-HT_{1A} receptor agonist, ipsapirone. Ipsapirone-induced hypothermia, which is putatively (but not definitively) mediated by 5-HT neurons in the raphe nuclei, was negatively related to age, and blunting in older subjects was demonstrable in males and females. Hormone (ACTH and cortisol) responses to ipsapirone were reduced in older, as compared to younger males, but were enhanced in older, as compared to younger females (Gelfin et al.). Enhanced cortisol and ACTH responses to ipsapirone in older females are consistent with loss of responsiveness of the HPA axis to negative feedback, which manifests as an age-related increase in the ACTH response to CRF in females but not males (Seeman and Robbins 1994). We (Gelfin et al.) postulated that, in older women, this phenomenon may obscure an age-related decline in 5-HT_{1A} receptor function, which is demonstrable in both genders in the hypothermic response to ipsapirone and in males in the ACTH and cortisol responses.

Thus, contrary to the observation of Cidis Meltzer et al. (1998), support for an age-related decline in central serotonergic function is not limited to postmortem studies and animal models but is provided by *in vivo* studies in humans using neuroendocrine challenge paradigms. Such approaches are likely to be even more informative when used in conjunction with the functional imaging techniques that Cidis Meltzer et al. identify as holding particular promise for further elucidation of central serotonergic function in normal aging, depression, and Alzheimer's disease.

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