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LETTER TO THE EDITOR

In Vivo Assessment of Aging Changes in Serotonin Function

In their commentary on our review article "Serotonin in Aging, Late-Life Depression, and Alzheimer's Disease: The Emerging Role of Functional Imaging," Lerer and colleagues summarize the literature evidence for aging alterations in neuroendocrine-mediated serotonergic function. The findings of Lerer et al. (1996), McBride et al. (1990), and Mann et al. (1995), among others, provide *in vivo* support for aging changes in the function of the serotonin (5-HT) system, which is generally consistent with postmortem work (Marcusson et al. 1984a; Marcusson et al. 1984b) and functional imaging data (Meltzer et al. 1998; Rosier et al. 1996; Wong et al. 1984). Our review focused primarily on the larger body of literature from postmortem assays as the major guiding force in directing investigations with PET imaging and new selective 5-HT ligands. However, we recognize the significant contribution that neuroendocrine challenge studies have made to enhance understanding of the functional integrity of the 5-HT system in aging and disease. Thus, we are grateful to Lerer and colleagues for their excellent synopsis of an important collection of physiologic studies.

Similar to imaging, neuroendocrine challenge techniques offer significant advantages over postmortem studies in their capacity to examine dynamic physiologic processes and for serial investigations in individual subjects. However, such studies do not provide spatially localizing information that is available through imaging approaches. For example, as indicated by Gelfin et al. (1995), there is uncertainty as to whether the 5-HT1A-mediated hypothermic response is effected through a postsynaptic mechanism or via presynaptic autoreceptor function. With PET imaging, the regional distribution of changes in the specific binding of 5-HT ligands can distinguish cortical postsynaptic 5-HT1A receptors from autoreceptors in the raphe nucleus region of the midbrain (Figure 1). Further, neuroendocrine challenge studies remain a somewhat indirect approach to assessing the integrity of neurotransmitter system function, since a blunted response may be explained by differences in pharmacokinetics among subject groups; a defect in neurotransmitter-receptor interaction, second messenger systems, or downstream hormonal response; and/or alterations in the modulatory effects of other neurotransmitter systems. For example, findings of a positive correlation in women and a negative correlation in men between age and ACTH response to ipsapirone are not entirely consistent with postmortem evidence of aging changes in 5-HT1A binding (Gelfin et al. 1995) and suggest that the relative contribution of such factors may be difficult to determine with neuroendocrine challenge methods.

As discussed by Lerer and colleagues (1996), we also have considered the theory that aging reductions in 5-HT function may serve as a susceptibility factor in the development of late-life depression. However, preliminary data acquired in our laboratory has failed to demonstrate a greater loss of specific 5-HT2A binding with [^{18}F]altanserin and PET imaging in late-life depressed patients relative to age-matched healthy individuals (Meltzer et al. 1997; Meltzer et al. in press). This finding suggests a more complex picture, perhaps one involving requisite alterations in the functional status of other 5-HT receptor subtypes or non-5-HT neurotransmitter systems necessary for the development of depression in the elderly. Also, the nature of the interaction among markers of central 5-HT function, additional biological variables (e.g. medical comorbidity, cerebrovascular disease), and social factors (e.g. bereavement, social isolation) as potential contributors to late-life mood disorders is largely unknown.

The challenge for the future will be to apply what we have learned about the complex effects of age on 5-HT-mediated brain function to design future studies aimed at addressing remaining questions. This knowledge, acquired through a variety of experimental methods, can

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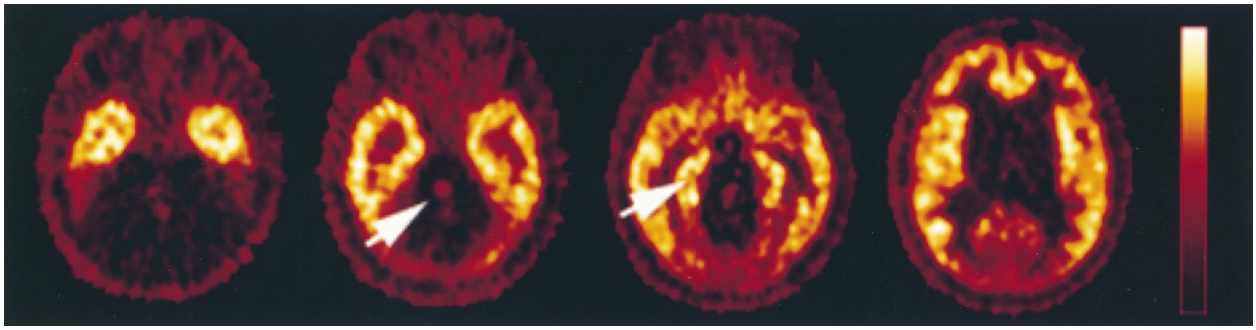

Figure 1. Select PET images acquired in a healthy 74-year-old man with [^{11}C]WAY100635 (summed over 15 - 60 min. post-injection) demonstrate the distribution of 5-HT1A receptors, including autoreceptors in the midbrain region of the raphe nucleus (mid-left image, arrow) and postsynaptic 5-HT1A receptors in the hippocampus (mid-right image, arrow) and other cortical areas. Lack of binding in the cerebellum, where there are negligible concentrations of 5-HT1A receptors, is demonstrated in the left-most image.

only help to provide a grater understanding of the role of 5-HT systems in neuropsychiatric disorders of late life, such as depression and Alzheimer's disease.

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