LETTER TO THE EDITOR

On Age and Serotonin Receptor Binding in the Human Brain

Demographic data provided by Joyce et al. (1993) reveal a statistical oversight that may call into question their conclusions on serotonin-1A and serotonin-2 receptor binding in subjects with schizophrenia, and in suicide victims with affective disorder. The authors state on p 317 that "there were no significant differences in the mean age or PMI between the controls, schizophrenic cases, or nonschizophrenic suicide cases"; examining the ages of the subjects in Table 1 reveals that the controls were significantly older than the schizophrenic cases and the nonschizophrenic suicide cases by two decades and three decades, respectively (one way ANOVA with unequal groups, $F = 7.351$ and $p < .004$).

These significant differences in age between subject groups make it difficult to interpret the reported increases in serotonin-2 and serotonin-1A receptor binding in schizophrenic subjects and in suicide victims with affective illness. The authors report a significant increase in serotonin-2 receptor binding in the cingulate and in the temporal cortex in schizophrenic subjects as compared to controls. Serotonin-1A receptor binding is increased in the anterior cingulate, midcingulate, and motor cortex (precentral gyrus) in schizophrenic subjects, and increased in the entorhinal cortex of suicide victims as compared to controls. Because the controls were two decades to three decades older than the subject groups, a putative increase in binding in younger subject groups may only reflect the normal age-induced decline in binding in older controls, rather than disease-related changes in serotonin receptor binding. Age must be eliminated as a contributing variable in the binding changes because two other groups have observed a decrease in serotonin-2 receptor binding in schizophrenia (Mita et al. 1986; Arora and Meltzer 1991). The decrease in serotonin uptake sites in schizophrenia observed by Joyce et al. is an important finding despite the differences in age between the subject groups as age does not appear to affect this marker (Andersson et al. 1992).

Several studies have established a strong age-related decrease in serotonin-2 and serotonin-1A receptor binding in numerous brain regions. For example, serotonin-2 receptor binding is negatively correlated with age in several regions including the temporal cortex, frontal cortex, occipital cortex, cingulate cortex, and hippocampus (Wong et al. 1984; Cheetham et al. 1988; Arango et al. 1990; Gross-Isseroff et al. 1990; Stockmeier et al. 1992). Whereas not all of these studies have observed an age-induced decrement in serotonin-2 receptor binding in the temporal cortex (Cheetham et al. 1988; Gross-Isseroff et al. 1990), a recent study in 37 subjects confirmed earlier observations of a considerable age-related decrement in these sites in temporal, frontal, parietal, and occipital cortex (Blin et al. 1993). In addition, serotonin-1A receptor binding is negatively correlated with age in temporal, cingulate, and frontal cortex, hippocampus, and the precentral gyri and postcentral gyri (Middlemiss et al. 1986; Dillon et al. 1991; Stockmeier et al. 1992). The cumulative weight of these studies, using several radioligands in either membrane preparations or tissue sections from many brain areas, documents that control and subject cases should be matched for age when measuring serotonin-2 or serotonin-1A receptor binding.

The authors mention a potential concern that the observed changes in serotonin-2 and serotonin-1A receptor binding may be related to age, but dismiss this concern by citing different patterns of increased binding between subjects with schizophrenia and subjects with affective illness that committed suicide. This conclusion by the authors may be correct, but many other variables need to be controlled across subject groups before such a conclusion can be supported, and an effect of age dismissed. In addition to differences in age, variables in the subject groups such as psychoactive sub-

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010
0893-133X/94/$7.00

stance abuse history, comorbidity of Axis I disorders, duration and type of Axis I disorders in suicide/affective group, different collection sites for tissues, and antipsychotic versus antidepressant drug histories make "different patterns of increased binding" difficult to interpret.

The observation by Joyce et al. that serotonin receptor and uptake sites may be altered in subjects with schizophrenia is an important contribution to the hypothesis that serotonin, as well as dopamine, is involved in the pathophysiology of schizophrenia. Confirmation of these observations in age-matched groups of subjects should lead to major advances in understanding schizophrenia.

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