Serotonin and Depression

Disturbances in central serotonin (5-hydroxytryptamine, 5-HT) have been reported to occur in a variety of psychiatric disorders, e.g., depression, certain anxiety states, schizophrenia, and alcoholism. The situation has been called chaotic, with 5-HT disorders classified as being nonspecific and 5-HT having been qualified, ironically, as a "neurotransmitter of all seasons." I disagree with these viewpoints and clarify my point of view by summarizing some old data and then focusing on some recent findings of my own group.

Serotonin disturbances in the brain were first reported in depression. They were inferred to exist based on the finding of lowered basal and postprobenecid concentrations of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) in a subgroup of patients suffering from major depression, melancholic type. Initially, depressed patients with and without demonstrable disturbances in central 5-HT seemed psychopathologically indistinguishable. Interpreting the available data at that time, we introduced in 1971 the concept of biochemical heterogeneity of (endogenous) depression. Some forms, we postulated, are linked to disturbances in 5-HT functions, whereas others are not or are but to a much lesser extent. The same syndrome, we postulated, could be the ultimate outcome of various pathophysiological processes.

Subsequent studies of our group, however, made the postulate of a separate 5-HT depression untenable. They indicated that increasing 5-HT availability alone is not a sufficient antidepressant measure. This finding argues against a predominantly 5-HT-related type of depression.

First, we demonstrated in a double-blind, placebo-controlled comparative study that 5-hydroxytryptophan (5-HP) is an active antidepressant, whereas tryptophan is not. Next, we showed that both 5-HT precursors increase central 5-HT metabolism to an equal extent but differ in their effect on catecholamine (CA) metabolism: 5-HTP augments it, tryptophan does not.

In some patients, moreover, the therapeutic effect of 5-HP wears off during the second month of treatment. This phenomenon is paralleled by normalization of CA metabolism, whereas 5-HT metabolism remains increased. Addition of tyrosine restores the therapeutic effect and the enhancement of CA metabolism.
Combining tryptophan with tyrosine, finally, raises the therapeutic effect of tryptophan above the significance level. These data argues against the existence of a separate 5-HT depression and suggest that combined augmentation of 5-HT and CA availability provide the best conditions for antidepressant activity.

Another hypothesis regarding the presence of 5-HT disturbances in only a subgroup of depression is their relatedness to a particular psychopathological dimension that might occur in depression but might be absent as well. This hypothesis seems plausible in the light of recent observations, the relevant dimensions being disregulation of aggression, anxiety, and (possibly) mood.

5-HT and Aggression

In 1976 Asberg et al. reported that depression with and without 5-HT disturbances are distinguishable in that suicide attempters accumulate in the 5-HT-disturbed group. This finding was confirmed by many, though not all, investigators. Low CSF 5-HIAA appeared not to be restricted to depressed suicide attempters but was also found in those who were not depressed and not psychotic as well as in the suicide attempters who were not depressed but were psychotic.

Low CSF 5-HIAA not only relates to inwardly directed aggression but was also found in individuals in whom disturbed aggression regulation manifested in outwardly directed aggression (murders, violent offences, severe personality disorders).

Therefore it appears that 5-HT disturbances are related to dis-regulation of aggression, irrespective of the direction the aggression takes. In one study we found additional evidence in favor of the hypothesis. We compared 25 patients with major depression and low 5-HIAA with 25 patients who had the same syndrome and normal 5-HIAA in terms of suicide frequency and interpersonal hostility. The low 5-HIAA group exceeded the normal 5-HIAA group in both suicide frequency and frequency of signs of outwardly directed aggression.

In summary, 5-HT disorders (suggestive of decreased central 5-HT metabolism), originally linked to (a subgroup of) depression, seem to be related to a particular psychopathological dimension—disturbed aggression regulation—irrespective of the direction the aggression takes and irrespective of diagnosis.

5-HT and Anxiety

A second psychopathological dimension seems to be 5-HTergically regulated: anxiety. The subject only recently became an issue of systematic study, but the preliminary data seem intriguing. The biological psychiatry group in Utrecht reported the apparent therapeutic effect of clomipramine and 5-HTP in panic disorder using a double-blind, placebo-controlled design. Both drugs are strong 5-HT agonists but not selective ones. The involvement of the 5-HT component, however, became plausible when it was demonstrated that the selective 5-HT uptake inhibitors zimelidine and fluvoxamine had the same antipanic and antianxiety effects in panic disorder patients. The effectiveness of selective 5-HT reuptake inhibitors in panic disorder patients was confirmed by several authors using fluoxetine and trazodone.

Clomipramine has been reported to be effective in obsessive compulsive disorder, which in the present classification is also considered to be an anxiety disorder.