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Reply to Joseph et al.

To the Editors:

Joseph et al. (1984) describe five subjects who showed a "substantial" increase in plasma cortisol in response to 5HTP administered without a decarboxylase inhibitor. Based on this uncontrolled finding and results quoted previously by Meltzer et al. (1983), they feel that our conclusion that 5HTP "is not useful as a provocative test for serotonergic function" is premature. Two points should be considered:

1. Our conclusion that serotonin (5HT) precursors "do not seem to provide a reliable index of human postsynaptic serotonergic activity" was based not merely on the effect of 5HTP on cortisol secretion, but on the effect of two precursors (tryptophan and 5HTP) on four pituitary hormones (cortisol, thyroid-stimulating hormone, growth hormone, and prolactin).

2. As to the plasma cortisol concentration after loading with 5HTP, we found a decline in plasma cortisol in all subjects, which can be explained by the diurnal variation in cortisol secretion and the occasional superimposition of one or more peaks. These peaks were seen both before and after administration of 5HTP and probably represented "spontaneous" bursts in cortisol secretion. Statistical analysis, however, did not reveal any effect (Westenberg et al., 1982*a*). This irregular profile strongly impedes the interpretation of drug effects on cortisol secretion.

A comparison with the results of Joseph et al. is not possible because they did not describe the methods of their study. However, there is at least one difference between our method and that of Joseph et al. In our study subjects were pretreated with a decarboxylase inhibitor (carbidopa) to prevent peripheral decarboxylation. Without pretreatment with a decarboxylase inhibitor, 5HTP is readily converted to 5HT in the liver (Westenberg et al., 1982*b*). Differences in 5HTP metabolism and distribution and/or an effect of carbidopa might be responsible for this discrepancy in response.

The second question raised by Joseph et al. concerns a presumed discrepancy between the pharmacokinetics of 5HTP in our study on hormone response to 5HT precursors (Westenberg et al., 1982*a*) and our article on the kinetics of 5HTP (Westenberg et al., 1982*b*). In the latter study, we found a rather complex absorption pattern of 5HTP in healthy subjects: Plasma 5HTP concentrations displayed double peaks in most subjects, and peak concentrations were attained between 1.2 and 3.7 hours for the first peak and between 3.5 and 6.8 hours for the second peak. Similarly, peak concentrations of 5HTP were attained at about 3 hours in most subjects in our study on hormone response to 5HT precursors.

The delay in absorption and the fact that 5HTP was undetectable in 3 out of 14 subjects might be explained by a retarded gastric emptying of the enteric coated tablets in recumbent patients. A similar explanation has been advanced for the biphasic absorption pattern of 5HTP.

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