The hyperserotonemia of autism spectrum disorders

Mulder, Erik Joan

Chapter 6

Reactivity of Serotonin in Whole Blood

Erik J. Mulder
George M. Anderson
Ido P. Kema
Ruud B. Minderaa

This chapter is a comment on
Humble M, Bejerot S, Bergqvist PB, Bengtsson F (2001)
Reactivity of serotonin in whole blood: Relationship with drug response in obsessive-compulsive disorder. Biological Psychiatry 49:360–368, it has been published as a letter to the editor in
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To the Editor:

We read with interest the recent paper of Humble and colleagues (Humble et al 2001) on the relationship between changes in whole blood serotonin (5-HT) and drug response in obsessive-compulsive disorder (OCD). The authors concluded that a rapid decrease of whole blood (i.e., platelet) 5-HT during treatment with the serotonin reuptake inhibitors paroxetine and clomipramine was associated with poor clinical response. We would like to make several comments regarding the study's data and interpretation.

1. It appears that circulating platelets use their membrane 5-HT transporter to take up 5-HT from the plasma throughout their 8- to 12-day life span; once taken up, little platelet 5-HT is released until the platelet is cleared from the circulation (Aranda et al., 1994; Heyssel, 1961). Changes in platelet 5-HT usually occur slowly because of the slow turnover of this pool. Conversely, the rate of 5-HT decrease occurring after transporter blockade will be more rapid in subjects with shorter platelet life spans. The authors' suggestion that changes in metabolic processes might account for the observed differences in rates of 5-HT decrease seems unlikely given the sequestered nature of platelet 5-HT.

2. Future studies on the relationship between changes in platelet 5-HT levels and drug response should attempt to assess the role of platelet lifespan in possible subgroup differences in 5-HT decreases or 'reactivity.' The possible influence of platelet life span could be approached through measurement of platelet count and estimation of platelet half-life.

3. Inspection of Figure 2 of the report reveals that all patients with less than a 60% decline in platelet 5-HT in the first week of treatment were receiving paroxetine. These patients contributed greatly to the negative correlation ($r = 0.61$) observed between percent decrease in 5-HT at 1 week and the OCD response at 12 weeks. Thus, it appears that differences in the immediate biochemical effects of paroxetine versus clomipramine, along with differences in long-term clinical response, might have contributed to the apparent association between 5-HT decline and medication response.

4. One patient with the poorest clinical response (~30% increase in OCD symptom score) and the greatest decrease in 5-HT (-98% at 1 week) also contributed substantially to the negative association between response and 5-HT decrease. This subject appears to be an outlier in the context of the other study subjects and when compared with the previously reported decreases seen after several weeks of 5-HT reuptake inhibitors, however. Rarely do platelet 5-HT levels decline by more than 95%, even after months of treatment. Such an extensive decline is even less likely after only 1 week of treatment given the slow turnover of platelet 5-HT.

5. The reported mean baseline level of whole blood 5-HT (654 nmol/L, 115 ng/mL) is lower than most previously published values (e.g., Flachaire et al., 1990; Kema et al., 1992). It is not clear that the methods used for sample preparation would have led to complete or corrected recoveries of 5-HT. Serotonin is particularly vulnerable to oxidative degradation during thawing of whole blood; losses at that stage would not have been accounted for if the internal standard was added afterward.

6. The authors cited two previous reports of increased platelet 5-HT efflux in autism; however, it should be noted that the cited findings were not replicated in subsequent studies and that the present consensus is that 5-HT efflux is not altered in autism (Boullin et al., 1982).

Although of potential importance, several factors lead us to suggest that the reported association be viewed as quite tentative and in need of replication. If the negative correlation between 5-HT decrease and response is substantiated, the relevant platelet physiology prompts consideration of the role of platelet life span in the association.

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