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LETTER TO THE EDITOR

Serotonin Transporter and Seasonal Variation in Serotonin Function

Recently, Hanna and colleagues reported an association of serotonin transporter (5-HTT, SLC6A4) gene promotor variants (5-HTTLPR) with blood serotonin content, including seasonal variation (Hanna et al. 1998). The 5-HTT gene promoter has two common alleles, designated long (*l*) and short (*s*), that affect 5-HTT transcriptional efficiency and transporter function (Lesch et al. 1996). Hanna et al. reported that subjects with the *l/l* and *l/s* genotypes had significantly higher blood serotonin content than subjects with the *s/s* genotype. Furthermore, subjects with the *l/l* genotype displayed significant seasonal variation in blood 5-HT content.

To confirm and extend these findings, we studied individuals in whom cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) had been measured. CSF 5-HIAA levels closely correlate with serotonin metabolism in frontal cortex and more closely reflect brain serotonin function than whole blood serotonin. A total of 191 unrelated Finns (141 primarily alcoholic offenders [abstinent, drug-free, and on a closed ward for >2 months] and 50 controls) were evaluated for the 5-HTTLPR genotype and CSF 5-HIAA levels (Nielsen et al. 1994, Mazzanti et al. 1998). Informed consent was obtained after full explanation of the purpose and nature of the study.

No significant difference in CSF 5-HIAA levels was observed across the three genotypes (*l/l*, 74.5 ± 23.8 (SD) nM; *l/s*, 66.8 ± 30.9 nM; *s/s*, 71.6 ± 32.1 nM; two-factor analysis of variance (ANOVA), F = 1.41, df = 2,189, p = .25). No significant difference was observed between the grouped *l/l* and *l/s* genotypes versus the *s/s* genotype (two-factor ANOVA, F = 0.088, df = 1,190, p = .77) as was found by Hanna et al. However, a trend in the expected direction was observed when the *l/l* genotype was compared to the *l/s* and *s/s* genotype (*l/l*, 74.5 ± 23.8 nM; *l/s* + *s/s*, 68.0 ± 31.1 nM; two-factor ANOVA, F = 2.16, df = 1,190, p = .14), consistent with the proposed dominant action of the *s* allele (Lesch et al. 1996).

In this particular sample, significant biannual seasonal variation in CSF 5-HIAA was not evident. Because seasonal variation in CSF 5-HIAA has been previously observed in controls but not in alcoholics, we also evaluated whether there was a significant interaction of alcohol diagnosis with 5-HTTLPR on seasonality. There was not. In their sample, Hanna et al. apparently were also unable to detect biannual variation in whole blood serotonin [in controls and obsessive–compulsive disorder (OCD) patients] (Hanna et al. 1998), but did find a significant relationship of seasonality of whole blood serotonin to 5-HTTLPR genotype. To conform to Hanna et al., the year was divided from April to September versus October to March. As shown in Figure 1, no interaction was observed between the 5-HTTLPR and seasonal variation in CSF 5-HIAA levels (two-factor ANOVA, F = 1.48, df = 2,185, p = .23). Furthermore, no significant difference in CSF 5-HIAA seasonal variation was observed in subjects with the *l/l* genotype (two-factor ANOVA, F = 2.51, df = 1,64, p = .12) as observed by Hanna et al., although a trend in the expected direction was detected.

There are several possible explanations for this lack of replication. Our population was comprised of 191 unrelated Finnish alcoholics and controls. Hanna et al. (1998) used a population of related individuals from 20 Michigan families. Obsessive–compulsive disorder was present in 20 of 70 subjects. ANOVA calculations assume unrelated subjects and, therefore, Hanna et al. may have overestimated their finding's significance. The relationship of 5-HTTLPR to serotonin function, including seasonal variation, may be stronger in families with OCD. The most important difference between our study and Hanna et al. was that we measured CSF 5-HIAA, which

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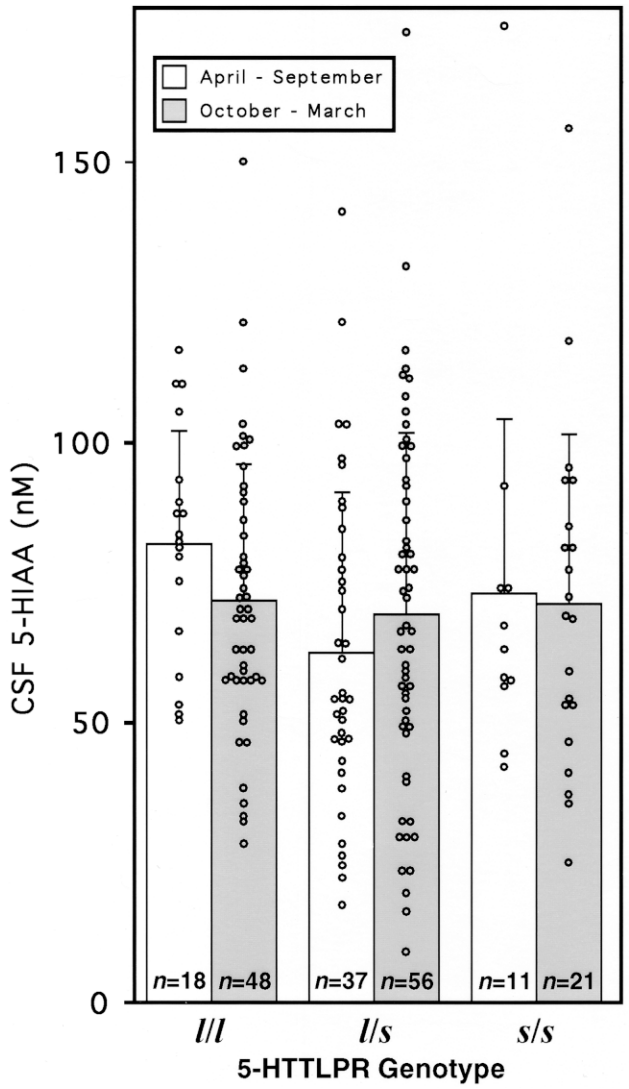

Figure 1. Seasonal variation of CSF 5-HIAA according to 5-HTTLPR genotype; error bars indicate SD.

correlates with serotonin activity in the brain; whereas, Hanna et al. measured whole blood serotonin. The brain and platelet serotonin transporter are identical, but 5-HTTLPR may more strongly influence whole blood serotonin levels than brain serotonin function indexed by CSF 5-HIAA.

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REFERENCES

Hanna GL, Himle JA, Curtis GC, Koram DQ, Weele JV-V, Leventhal BL, Cook EH (1998): Serotonin transporter and seasonal variation in blood serotonin in families with obsessive–compulsive disorder. Neuropsychopharmacology 18:102–111

Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Muller CR, Hamer DH, Murphy DL (1996): Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274:1527–1531

Mazzanti CM, Lappalainen J, Long JC, Naukkarinin H, Eggert M, Linnoila M, Goldman D (1998): Role of the serotonin transporter polymorphism in anxiety related traits. Unpublished observations

Nielsen DA, Goldman D, Virkkunen M, Tokola R, Rawlings R, Linnoila M (1994): Suicidality and 5-hydroxyindoleacetic acid concentration associated with a tryptophan hydroxylase polymorphism. Arch Gen Psychiatr 51:34–38