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PET IMAGING OF THE SEROTONIN 2A RECEPTOR (5-HT2A) AND SERTONIN TRANSPORTER (SERT) AND IN PERSONALITY DISORDERED SUBJECTS WITH INTERMITTENT EXPLOSIVE DISORDER-REVISED (IED-R)

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Abstract

Objectives: Reduced activity of the serotonin system has been implicated in impulsive violence and aggression using a variety of paradigms including measurement of CSF serotonin metabolites, hormonal response to serotonergic probes and imaging metabolic changes with serotonergic agents. Studies of brain lesions and metabolic imaging studies point to the oribitofrontal cortex (OFC) and the anterior cingulated gyrus (ACC) as key areas regulating the generation of aggressive behaviors.
This study assesses both pre- and postsynaptic serotonin function in subjects with impulsive aggressivity (subject meeting criteria for intermittent explosive disorder-revised, IED-R) using PET imaging of the SERT with [^{11}C]McN 5652 and the 5-HT$_{2A}$ with [^{11}C]MDL 100907, respectively.

Methods:
SERT: Ten patients (35 ± 9 years,18 to 51, 5M/5F) and ten healthy controls (34 ± 8, 23 to 49, 5M/5F) underwent a 120 min PET study after injection of [^{11}C]McN 5652. Regions of interest (ROIs) included the midbrain, thalamus, dorsal caudate, dorsal putamen, ventral striatum, amygdala (AMY), entorhinal cortex (ENT), hippocampus (HIP), parahippocampal gyrus (PHG) and the anterior cingulate cortex (ACC).
5-HT$_{2a}$ Receptors: Sixteen patients (35 ± 9 years, 20 to 52, 11M/5F) and sixteen healthy controls (33 ± 8, 23 to 50, 11M/5F) underwent a 90 min PET study after injection of [^{11}C]MDL 100907. ROIs included the dorsolateral, medial and orbital prefrontal cortices, the temporal (TEM), parietal and occipital cortices, the AMY, ENT, HIP, PHG and the ACC.
For both radiotracers regional distribution volumes (VT, mL/g) were derived with 1 tissue compartment (1TC) kinetic analysis. VT in the cerebellum was used to estimate the nondisplaceable distribution volume, V_2. Two parameters of sites availability were derived: BP (= VT_{ROI}-V_2, mL/g) and V_3" (= BP/V_2, unitless).

Results:
SERT: No significant differences in ROI volumes or V_2 were noted between the groups. SERT availability was significantly reduced in the anterior cingulate (ACC) in individuals with IED-R compared with controls. This reduction was noted using both BP (IED-R subjects, 3.1 ± 1.9 mL g^{-1}; control subjects, 5.0 ± 2.0 mL g^{-1}, p = 0.04) and V_3" (IED-R subjects, 0.15 ± 0.09; control subjects, 0.26 ± 0.09, p = 0.02). No significant differences in BP or V_3" were observed in other ROIs
5-HT$_{2A}$ receptors: No significant differences in ROI volumes or V2 were noted between the groups. 5-HT$_{2a}$ receptor availability was significantly elevated in subjects with IED-R compared to controls in the ACC, TEM and ENT. This elevation was noted using both BP and V_3" (for example, in ACC, BP: IED-R subjects, 53.6 ± 13.0 mL g^{-1}, control subjects, 42.9 ± 13.2 mL g^{-1}, p = 0.03; V_3" IED-R subjects, 2.5 ± 0.6, control subjects, 2.1 ± 0.4, p = 0.03).

Conclusions: These results are consistent with the hypothesis of reduced SERT and increased 5-HT$_{2a}$ receptor availability in cortico-limbic regions in IED-R. These results might stem from a lower density of 5-HT terminals in patients, resulting in lower 5-HT function and compensatory upregulation of 5-HT$_{2a}$ receptors. If confirmed, these results provide a rationale for the treatment of pathological aggressivity with selective serotonin reuptake inhibitors (SSRI).