TRANSCRIPTIONAL EXPRESSION OF SEROTONERGIC REGULATORS IN LASER-CAPTURED MICRODISSECTED DORSAL RAPHE NEURONS OF SUBJECTS WITH MAJOR DEPRESSIVE DISORDER: SEX-SPECIFIC DIFFERENCES

Background. Women have twice the rate of depression as that of men. Clinical and human postmortem studies have provided evidence supporting the hypothesis that serotonin neurotransmission is reduced in major depressive disorder with gender-specific alterations noted in serotonin-related genes. While several serotonin-related genes have been investigated in the midbrain dorsal raphe of depressed subjects, there have been no studies examining gender-specific differences in serotonin genes in an select population of isolated serotonin-containing neurons of the dorsal raphe of major depressed subjects. Therefore, the present study was designed to quantify the cellular concentration of mRNA transcripts of several 5-HT-related genes in a pure population of serotonin-containing DR neurons in female and male subjects diagnosed with major depressive disorder (MDD) and in psychiatrically-normal control subjects matched for gender using laser-capture microdissection (LCM) of immunofluorescently-stained neurons and quantitative real time PCR.

Advance. The results of our study found that mRNA concentrations of the 5-HT1D receptor and the transcription factors, nuclear deformed epidermal autoregulatory factor-1 (NUDR) and RE-1 silencing transcription factor (REST), were significantly increased in dorsal raphe captured neurons of female MDD subjects compared to female control subjects. No significant differences were found for the transcripts in male MDD subjects compared to male controls. This study reveals sex-specific alterations in gene expression of the presynaptic 5-HT1D autoreceptors and 5-HT-related transcription factors, NUDR and REST, in dorsal raphe neurons of women with MDD.

Public Impact Statement/Significance. The present study represents the first report using LCM and Q-PCR to quantify mRNA transcripts in individual serotonin-stained dorsal raphe neurons of female and male MDD subjects and gender-matched control subjects. These findings reveal alterations in specific regulators of serotonin function that may provide clues for understanding the mechanisms associated with diminished serotonin neurotransmission and the higher incidence of depression in women.

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DECREASED EXPRESSION OF FREUD-1, A TRANSCRIPTIONAL REPRESSOR OF THE 5-HT$_{1A}$ RECEPTOR, IN THE PREFRONTAL CORTEX OF SUBJECTS WITH MAJOR DEPRESSION

**Background.** Clinical and human postmortem studies have provided evidence supporting the hypothesis that serotonin neurotransmission is reduced in major depressive disorder, with specific alterations noted in serotonin receptor subtypes. Recently, a nuclear protein complex, five’ repressor element under dual repression binding protein-1 (Freud-1), was identified that binds to promoter region of the serotonin 1A receptor and represses the transcriptional activity of the 5-HT$_{1A}$ receptor gene resulting in a decrease in endogenous 5-HT$_{1A}$ receptor mRNA, protein and binding sites. Since previous studies have reported alterations in 5-HT$_{1A}$ receptors in specific brain regions of depressed patients, we hypothesized that the 5-HT$_{1A}$ receptor transcription factor, Freud-1, may be altered in the brain of depressed patients and therefore contributes to the alterations in serotonin neurotransmission in subjects with major depressive disorder.

**Advance.** The results of our study found that Freud-1 protein concentrations were significantly reduced by 37% in the prefrontal cortex of male subjects with major depression relative to gender-matched male control subjects, but not significantly reduced in female subjects with major depression. We also found that Freud-1 protein levels were significantly decreased by 50% in the prefrontal cortex of younger depressed subjects that were less than 54 yrs of age, but were unchanged in the older depressed subjects relative to age-matched control subjects.

**Public Impact Statement / Significance.** These findings represent the first examination in human postmortem brain tissue of Freud-1, a transcriptional repressor of the 5-HT$_{1A}$ receptor gene, in prefrontal cortical specimens of subjects with major depressive disorder. It is intriguing to speculate that alterations in Freud-1 in depressed men may contribute to altered serotonin neurotransmission in depressed subjects and the age-related changes in the younger depressed subjects may suggest a role for Freud-1 in the developmental course of major depression.

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**Publication.**

GENDER-SPECIFIC DECREASE IN NUDR AND 5-HT1A RECEPTOR PROTEINS IN THE PREFRONTAL CORTEX OF SUBJECTS WITH MAJOR DEPRESSIVE DISORDER

**Background.** Clinical and human postmortem studies have provided evidence supporting the hypothesis that serotonin neurotransmission is reduced in major depressive disorder, with specific alterations noted in serotonin receptor subtypes. Recently, a nuclear protein complex, nuclear deformed epidermal autoregulatory factor-1 (NUDR), was identified that binds to promoter region of the serotonin 1A receptor and represses the transcriptional activity of the 5-HT$_{1A}$ receptor gene resulting in a decrease in endogenous 5-HT$_{1A}$ receptor mRNA, protein and binding sites. Since previous studies have reported alterations in 5-HT$_{1A}$ receptors in specific brain regions of depressed patients, we hypothesized that the 5-HT$_{1A}$ receptor transcription factor, NUDR, may be altered in the brain of depressed patients and therefore contributes to the reduction in 5-HT$_{1A}$ receptors in subjects with major depressive disorder.

**Advance.** The results of our study found that NUDR protein concentrations were significantly reduced by 42% in the prefrontal cortex of female subjects with major depression relative to gender-matched female control subjects, but not in male subjects with major depression. We also found that 5-HT$_{1A}$ receptor protein concentrations were significantly decreased by 46% in the prefrontal cortex of the same female depressed subjects, but no change in 5-HT$_{1A}$ receptor occurred in the male depressed subjects.

**Implications.** These findings represent the first examination in human postmortem brain tissue of NUDR, a transcriptional repressor of the 5-HT$_{1A}$ receptor gene, in prefrontal cortical specimens of subjects with major depressive disorder. But perhaps more importantly, our study documents a gender-specific alteration in both NUDR and 5HT$_{1A}$ receptor protein expression in the prefrontal cortex of female subjects diagnosed with major depression. It is intriguing to speculate that alterations in NUDR in depressed women may contribute to altered serotonin neurotransmission and thereby constitute one biological mechanism that may contribute to the greater incidence of depression in women.

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**Publications.**
