

Appendix A14.23

Reelin

Recent postmortem studies have revealed that an unexpected molecule may be involved in the pathophysiology of severe neuropsychiatric disorders, including manic-depressive illness and schizophrenia (Impagnatiello et al., 1998; Fatemi et al., 2000; Guidotti et al., 2000; Fatemi et al., 2001). Reelin is a member of a growing group of diverse proteins whose absence is associated with an almost identical phenotype—inversion of cerebral cortical layers and reduction/absence of cerebellar foliation. Costa and coworkers first showed that reelin protein and mRNA were reduced in several brain areas in both schizophrenic and psychotic bipolar patients, leading to their suggestion that reelin deficiency may be a vulnerability factor for psychosis independent of diagnosis (Costa et al., 2001, 2002; Guidotti et al., 2000). Subsequently, Fatemi et al. (2000), confirmed Costa's findings but extended similar reductions in reelin protein in hippocampi of non-psychotic bipolar and depressed patients, suggesting that reelin deficiency was not a marker of psychosis alone (Fatemi et al., 2000; Fatemi 2001a,b, 2002). In a similar vein, Hong et al. showed that blood levels of reelin were extremely low to undetectable in children afflicted with a variant of lissencephaly. These children had various mutations involving the RELN gene and exhibited severe delays in neurologic and cognitive development (Hong et al., 2000).

Later, Fatemi et al. (2001b, 2002) showed deficits in reelin protein in brain and blood of subjects with autism, another neurodevelopmental disorder which exhibits significant cognitive dysfunction in association with a vulnerability towards defective reelin inheritance (Persico et al., 2001; Fatemi, 2001b, Fatemi et al., 2002). Recent results from this laboratory (Fatemi, Sary, Earle, Araghi-Niknam & Egan, unpublished observations) showed that Reelin 410 and 180 kDa species are significantly reduced in cerebellum of subjects with bipolar disorder (with and without psychosis) versus normal controls. Moreover, bipolar subjects also demonstrated significant deficits in glutamic-acid decarboxylase proteins of 65 and 67 kDa (GAD 65 & GAD67) versus normal controls (Fatemi, Sary, Earle, Araghi-Niknam & Egan, unpublished observations). In contrast, reelin deficiency was limited to the 180 kDa species in the schizophrenic cerebella. All schizophrenic and depressed subjects also showed significant reductions in GAD 65 & 67 proteins versus controls. These results confirm a recent report by Benes and colleagues (Heckers et al., 2002) showing a global deficit in levels of GAD65 & 67 in hippocampus of subjects with bipolar disorder. Interestingly, some brain GABAergic interneurons share the synthetic machinery for production of reelin and GAD65&67 proteins (Pesold et al., 1998) and appear to be dysfunctional in bipolar subjects. Finally, deficits in

hippocampal and cerebellar reelin levels in bipolar subjects (Fatemi et al., 2000; Guidotti et al., 2000; Fatemi, Stry, Earle, Araghi-Niknam & Egan, unpublished observations) correlate well with decreases in levels of blood reelin in patients with bipolar disorder (Fatemi et al., 2001a).

Future larger studies should correlate the extent of reelin deficiency observed in hippocampus and cerebellum of subjects with bipolar disorder with blood and CSF levels of the same protein in order to better define the role of reelin in etiology of bipolar disorder and other neurodevelopmental disorders such as schizophrenia and autism.

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