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Review

Cadherins and neuropsychiatric disorders

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ABSTRACT

Cadherins mediate cell–cell adhesion but are also involved in intracellular signaling pathways associated with neuropsychiatric disease. Most of the ~100 cadherins that are expressed in the brain exhibit characteristic spatiotemporal expression profiles. Cadherins have been shown to regulate neural tube regionalization, neuronal migration, gray matter differentiation, neural circuit formation, spine morphology, synapse formation and synaptic remodeling. The dysfunction of the cadherin-based adhesive system may alter functional connectivity and coherent information processing in the human brain in neuropsychiatric disease. Several neuropsychiatric disorders, such as epilepsy/mental retardation, autism, bipolar disease and schizophrenia, have been associated with cadherins, mostly by genome-wide association studies. For example, CDH15 and PCDH19 are associated with cognitive impairment; CDH5, CDH8, CDH9, CDH10, CDH13, CDH15, PCDH10, PCDH19 and PCDHb4 with autism; CDH7, CDH12, CDH18, PCDH12 and FAT with bipolar disease and schizophrenia; and CDH11, CDH12 and CDH13 with methamphetamine and alcohol dependency. To date, disease-causing mutations are established for PCDH19 in patients with epilepsy, cognitive impairment and/or autistic features. In conclusion, genes encoding members of the cadherin superfamily are of special interest in the pathogenesis of neuropsychiatric disease because cadherins play a pivotal role in the development of the neural circuitry as well as in mature synaptic function.

Contents

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1. Introduction

Several candidate genes have been associated with neuropsychiatric disorders in recent years, such as epilepsy/mental retardation, autism, bipolar disease and schizophrenia (see articles in Wildenauer, 2009). In view of the strong evidence for a genetic and developmental component in these disorders, genes that regulate neural development as well as mature brain function are of particular interest. In the present review, we discuss recent evidence that several neuropsychiatric disorders are linked to cadherins (El-Amraoui and Petit, 2010; Hirano and Takeichi, 2012), a large family of cell adhesion molecules that regulate morphogenesis by mediating cell–cell adhesion and are involved in intracellular signaling pathways (Hirano et al., 2003; Halbleib and Nelson, 2006; Takeichi, 2007; Hirano and Takeichi, 2012).

Cadherins are glycosylated transmembrane proteins that appeared with the transition from unicellular to multicellular organisms during evolution (Hulpiau and van Roy, 2011). The extracellular cadherin repeats confer binding specificity to cadherins. The binding depends on calcium ions that attach to highly conserved motifs in the extracellular domain. Typically, cadherin-mediated binding is preferentially homotypic, i.e. a cadherin type adheres more strongly to the same cadherin type than to other cadherin types. This binding specificity provides a basis for the specific adhesion of opposing cell surface membranes, thereby regulating morphogenetic processes (Brigidi and Bamji, 2011; Halbleib and Nelson, 2006; Redies, 2000; Hirano and Takeichi, 2012).

The molecular hallmark of cadherins are so-called cadherin repeats in the extracellular domain that are each about 100 amino acids long. In humans, more than 100 cadherin-related genes exist. Many of the genes of the cadherin superfamily are organized in clusters, which have been mapped to human chromosomes 5p14–15, 5q13–15, 5q31–32, 13q14.3–21.1, 16q22.1, 16q24.1 and 18q12.1. There are several subfamilies of cadherins that share specific structural features and sequence motifs, especially in their cytoplasmic domain, which interacts with signaling molecules (Hulpiau and van Roy, 2011; Hirano and Takeichi, 2012). Because of these shared features, it is likely that gene duplication, reverse transcription and gene translocation contributed to the diversity of the cadherin superfamily (Hulpiau and van Roy, 2009). The present review focuses on two cadherin families, the classic cadherins and protocadherins, that have been particularly well studied in the mammalian nervous system (Table 1; for reviews, see Redies, 2000; Hirano et al., 2003; Redies et al., 2011; Hirano and Takeichi, 2012). Other cadherins, which have also been associated with neuropsychiatric disorders, such as Fat and T-cadherin (cadherin-13), will also be mentioned. Each of these (sub-)families is characterized by conserved cytoplasmic motifs, suggesting different roles in cell adhesion and signal transduction (Hulpiau and van Roy, 2011; Hirano and Takeichi, 2012). Cadherin (sub-)families not implicated in neuropsychiatric disorders so far, including desmosomal cadherins, calsyntenins and flamingo cadherins (CELSRs), are outside the scope of this review (for a complete overview of the cadherin superfamily, see Hulpiau and van Roy, 2011; Hirano and Takeichi, 2012).

The association of cadherins with neuropsychiatric disorders prompts the question whether cadherins possess special neurobiological features that predispose them toward this association. Surprisingly, the answer is more clearly affirmative than for some of the intracellular signaling molecules that have previously been linked to neuropsychiatric disorders. Members of the cadherin superfamily share general expression profiles and have distinct functions in brain development and mature brain function. These features make a causative role of cadherins in neuropsychiatric disorders plausible, as outlined in the following sections.

In the nervous system, cadherins play critical roles in neural tube regionalization, neuronal migration, gray matter differentiation, neural circuit formation, spine morphology, and synapse formation and remodeling (Hirano et al., 2003; Redies, 2000; Takeichi, 2007; Hirano and Takeichi, 2012). Apart from disease-causing mutations, sequence variants within or near cadherin genes have been associated with an increased risk for neuropsychiatric disorders.

In the present review, we will first discuss the evidence for multiple roles of cadherins in brain development and mature brain function. Secondly, we will summarize recent genetic studies suggesting an association between cadherins with neuropsychiatric disorders. The involvement of cadherins in cell signaling pathways that have been implicated in these diseases, mostly relating to their adhesive functions, will also be reviewed (for a comprehensive survey of other downstream signaling pathways, see Hirano and Takeichi, 2012).

2. Expression and role of cadherins in CNS development

Cadherins play a role during morphogenesis of most, if not all tissues and organs in multicellular organisms (Halbleib and Nelson, 2006). In the vertebrate embryo, cadherin deficits are