HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2017 July 05.

Published in final edited form as:

Biol Psychiatry. 2017 February 01; 81(3): 173–174. doi:10.1016/j.biopsych.2016.10.025.

Protocadherins and the social brain

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Autism Spectrum Disorder is characterized by abnormal or reduced social interactions, language delay and repetitive disorders as well as an increased incidence of intellectual disability and epilepsy. ASD affects males about 4-times as females and is highly genetic (>50%)(1). Thus, a number of recent studies employing human genome and exome sequencing of ASD families have implicated >800 genes in ASD etiology (1). Categorization of these genes implicates several core processes in ASD, chromatin remodeling, transcriptional and translational control, synapse and function. Therefore, mutations or deficits in transcriptional and translational control of genes that regulate synapse and circuit development and/or function are likely lead to ASD-related behaviors. With regard to genes encoding synaptic proteins, there is a prevalence of mutations in the, so-called, synaptic cell adhesion molecules (SCAMS) in ASD, such as the neuroligins, neurexins, contactins, protocadherins and others. SCAMS generally function to connect pre- and postsynaptic sites through homo- or heterophilic interactions of their extracellular domains, and function to scaffold and organize pre- and postsynaptic sites through their intracellular domains, as well as mediate trans-synaptic signaling cascades. Therefore, SCAMS regulate multiple aspects of synapse development, function and plasticity that are essential for the normal development and function of brain circuits (1). Although much work has revealed key roles for some SCAMS (e.g. neuroligins and neurexins) in synapse and circuit function, as well as ASD-related behaviors in rodent models, much less is known for others, such as the protocadherins. Specifically, mutations in the δ family of nonclustered protocadherins, (*Pcdh 8,9,10, &19*) are associated with autism, intellectual disability and epilepsy (*Pcdh19*) (2), while another, *Pcdh17*, is implicated in schizophrenia and language delay (3). While studies have linked *Pcdh8*, *10* and *17* to regulation of synapse function, axon growth and refinement (3), only recently has the δ protocadherins been more directly implicated in ASD-related behaviors.

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Financial Disclosures: None

In this issue of *Biological Psychiatry*, Schoch and colleagues (4) describe that haploinsufficiency of *Pcdh10* in mice leads deficits in social behaviors and communication and implicates *Pcdh10* function in amygdala these behaviors. *Pcdh10*, also known as OL-protocadherin, is highly expressed developing and mature cortex, as well as amygdala and is required for the growth and patterning of specific axons projections as well as the refinement of synaptic connections (3). Schoch et al., discovered that Pcdh10+/− mice displayed two ASD-associated social abnormalities, reduced social approach and increased ultrasonic vocalization, but not increased repetitive behaviors. *Pcdh10*$^{+/-}$ mice exhibited normal exploratory activity and anxiety-related phenotypes, suggesting *Pcdh10* function may be specific to social communication. Of note, the reduced social behaviors were only detected in male mice, revealing a gender-specific interaction with *Pcdh10*. While *Pcdh10* is autosomal, it may be regulated by sex hormones, such as estrogen that protects female mice from *Pcdh10* haploinsufficiency (4). Importantly, the gender bias of the *Pcdh10+/−* social phenotype could be a useful model to study gender/genetic interactions related to ASD.

The authors focused on an analysis of *Pcdh10* function in the amygdala, because of the known role of the amygdala in social behaviors. Interestingly, *Pcdh10*, as well as other *Pcdhs* and some classical cadherins are expressed in localized regions or “patches” of neurons in the developing and mature amygdala (5), many of which are non-overlapping. These results suggest that the (proto) cadherins provide a molecular code for the development of specific amygdala circuits. Within the amygdala, *Pcdh10* is expressed most strongly in the nucleus of the lateral olfactory tract and basal lateral amygdala (5) suggesting that development or connectivity within these amygdalar regions are relevant to social behaviors and/or ASD. In an earlier issue of Biological Psychiatry, Bruining et al., (6) using quantitative-trait locus (QTL) mapping and discovered that haploinsufficiency of *Pcdh9* resulted in a long-term social recognition in mice. Although the authors implicated alterations in sensory neocortex in *Pcdh9* function, *Pcdh9* is also expressed in localized patches in amygdala subregions, some that overlap with *Pcdh10* (5). Thus, *Pcdh9* and *Pcdh10* may regulate common amygdala circuits necessary for normal social behavior.

To test a role for *Pcdh10* in regulation of amygdalar circuits, Schoch et al., imaged evoked circuit activity using voltage sensitive dyes in slices of the amygdala and striatum from *Pcdh10* +/− mice. Although the authors found a normal amplitude of evoked activity, amygdala circuits were unable to follow or synchronize in response to high, gamma frequency (40Hz), stimulation of synaptic inputs, as measured by a decrease in the power gamma band activity. Interestingly, evoked gamma activity in nearby striatal circuits was normal in *Pcdh10* +/− slices, indicating a more specific and key role for *Pcdh10* in the amygdala (5). Gamma frequency activity is typically thought to reflect the synchrony of inhibitory circuits, but can also be an indicator of overall circuit activity and synchrony (7). Related to ASD in humans, studies observe reduced power of sensory-evoked gamma band activity in sensory cortices (7), but it is unclear if altered gamma activity occurs in the amygdala, which may be important to examine. A reduced power of gamma band activity indicates less synchronization of amygdala circuits in *Pcdh10* +/− mice in response high frequency inputs. This result supports a view where *Pcdh10* is necessary for development and/or function of specific synaptic connections of amygdala circuits to support optimal synchrony.

A mechanism by which *Pcdh10* may contribute to proper connectivity of circuits is through activity-regulated refinement or elimination of excitatory synapses. *Pcdh10* and its related δ family member, *Pcdh8*, are both transcriptionally-induced in response to neuronal activity, where they eliminate excitatory synaptic connections (8, 9). Such regulation provides a mechanism for activity and experience to refine developing circuits as well as provide a homeostatic mechanism to prevent circuit hyperexcitability. Consistent with a loss of developmental synapse elimination, Schoch and colleagues observed an increase in the density of dendritic spines, the structural correlate of excitatory synapses, in the lateral and basolateral amygdala of *Pcdh10*$^{+/-}$ mice. Interestingly, they observed a higher number of thin, long, filopodial-like spines, similar to immature spines suggesting that abnormal and overconnectivity in the amygdala of *Pcdh10+/−* mice that contributes to the reduced gamma oscillations and social behavior deficits. The prevalence of increased dendritic spines as well as immature spines is reminiscent of other genetic models of ASD, such as Fragile X Syndrome (10). Fragile X Syndrome is caused by loss of function mutations in an RNA binding protein, FMRP. Importantly, FMRP interacts with *Pcdh10* mRNA regulates its translation (9). FMRP is also implicated in activity and experience-dependent synapse elimination in cortical neurons and may do so through regulation of *Pcdh10* (9). An interesting possibility is that *Fmr1*, *Pcdh8* and *Pcdh10* commonly regulate developmental and activity-dependent synapse refinement in the amygdala to mediate proper social behavior.

Another critical finding from Schoch and colleagues is the discovery of lower levels of GluN1 and GluN2A, two major subunits of NMDA receptor (NMDAR), in the post-synaptic density (PSD) fraction of *Pcdh10*$^{+/-}$ mice. Although the molecular basis of this decrease is unknown, a previous study by Tsai and colleagues showed that *Pcdh10* regulates proteasomal deposition of ubiquitinated post-synaptic density protein 95 (PSD-95) (9). PSD-95 interacts with GluN2A/2B and may regulate the development, localization and signaling through NMDARs. It will be important in future studies to understand if and how *Pcdh10* and other related protocadherins regulate function of the NMDAR and other synaptic proteins and if this is via regulation of PSD-95.

Because of the reduction in NMDAR expression, Schoch and colleagues tested whether enhancing NMDAR function by using the NMDAR co-agonist, D-cycloserine (dCS), could reverse the social behavioral deficits in *Pcdh10*$^{+/-}$ mice. Remarkably, acute (30 min) administration of dCS rescued the social approach deficit in *Pcdh10*$^{+/-}$ mice without affecting locomotor activity. This result suggests that the deficit of social approach in *Pcdh10*$^{+/-}$ mice results from altered activity or plasticity of circuits rather than an abnormal development of circuit connectivity. However, dCS did not rescue the reduced gamma power in amygdala slices, suggesting that it may function in other circuits *in vivo* or affect other aspects of amygdala circuit function that are not captured by measuring gamma band activity. Open label clinical trials with dCS in ASD population have yielded some positive results and this new work by Schoch and colleagues (4) suggests dCS as a therapy for ASD in individuals with mutations or altered expression of δ protocadherins. Furthermore, this study may guide future investigations of other δ family protocadherins in the pathogenesis of ASDs.

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