Supplementary Material

1. Characteristics of Select Proteins Identified in the Immunopurified PAZ from Olfactory Bulb, Hippocampus and Cerebellum

The proteins (highlighted in bold) were selected from the data shown in the VENN diagram of Figure 4. To briefly portray individual proteins major characteristics reported in the literature are listed.

2. Constituents of the PAZ Derived from Olfactory Bulb

Purkinje cell protein 4, also called brain-specific polypeptide 19, is a neurospecific, small calmodulin binding protein, both calcium-free and calcium-bound, that regulates calmodulin-mediated signals [1]. Immunocytochemistry demonstrated that PCP4 is expressed predominantly in the cerebellum, especially Purkinje cells, piriform cortex, thalamic nuclei, caudate nucleus, putamen, cortex and hippocampus [2,3]. PEP-19 appears during the final stages of maturation of Purkinje cells. PCP4 promotes neurotransmitter release by activating calmodulin function and regulates calmodulin-dependent protein kinase II (CaMKII). Peptide antagonists of calmodulin (camstatins) based upon a conserved structural motif in PEP19, neurogranin, and neuromodulin block LTP and increases calcium extrusion in hippocampal CA1 neurons [4,5].

A proteome profile of the mature rat olfactory bulb identifies neuromodulin (NeuM, GAP-43, B-50) [6]. Immunocytochemistry reveals that neuromodulin is predominantly present in neuronal growth cones and preterminal axons [7]. It has been associated with neurite outgrowth [8,9], neurotransmitter release [10], and synaptic plasticity [11].

Stathmin-1 is a ubiquitous cytosolic phosphoprotein highly expressed in the developing nervous system and is maintained in some regions of the adult central nervous system. Immunohistochemistry revealed the presence in cells of the rostral migratory stream indicating an expression of stathmin in regions of the adult nervous system characterized by striking structural plasticity and cell renewal, suggesting that this protein could play a role in the differentiation of newly generated cell populations [12]. Stathmin-1 is related to the neuron-specific membrane-associated stathmin-2 (SCG10). Phosphorylation of both proteins negatively regulate the stability of microtubules in growth cones and act as cellular mediator of microtubule dynamics [13] and their upregulation play a role in axonal regeneration in the adulthood [14,15]. Whereas stathmin-2 is restricted to immature olfactory neurons stathmin-1 is also expressed in basal cells. Proteomic and immunochemical analysis postulated a role for stathmin in adult neurogenesis [16]. Stathmin interacts with tubulin, leading to microtubule destabilization [17]. In adults, stathmin is prominently expressed in neurogenesis pathways including the subgranular zone of dentate gyrus, subventricular zone, rostral migratory stream, and olfactory bulb [12,18].

Olfactory marker protein (OMP) immunohistochemistry identifies olfactory receptor cell axons in the olfactory bulb [19]. OMP is present only in mature neurons [20]. Double labeling demonstrated that OMP and the microtubule-associated MAP2 are distributed in distinct areas within the glomerulus revealing the compartmental nature of subglomerular organization. Axonal areas, identified by dense OMP-immunoreactivity, are found adjacent to areas devoid of OMP. The synaptic vesicle protein synaptophysin strongly co-localized with OMP [21]. OMP knock-out pups fail to show preference between their biological mothers and another unfamiliar lactating female [22].

Intracellular calcium, important in a variety of second messenger cascades, is regulated in part by 5 EF hand calcium-binding proteins such as calretinin, parvalbumin, calbindin, cal-modulin and neurocalcin in developing olfactory bulb [23,24]. These proteins were highly concentrated in the rat main olfactory bulb and were localized in distinct neuronal populations [25]. In adult olfactory bulb calretinin has been localized in mitral cells and interneurons [26]. The axons and especially the axon terminals of mitral cells are calretinin-immunoreactive [27]. The subventricular zone (SVZ) is known to be the major source of neural stem cells in the adult brain. In rodents and non-human primates, many neuroblasts generated in the SVZ migrate in chains along the rostral migratory stream to populate the olfactory bulb with new granular and periglomerular interneurons [28]. Most granular cells in the olfactory bulb are GABAergic and the vast majority of the granular cells that are generated during adulthood in rodents expressed a GABAergic phenotype [29]. GABA appears to be the major transmitter used by periglomerular neurons. A significant number of these neurons also contained the calcium-binding protein calretinin, whereas a smaller number expressed tyrosine hydroxylase, a reliable marker for dopaminergic neurons in the olfactory bulb [30]. Neurons containing parvalbumin, a calcium-binding protein often associated with GABA [31,32], were also detected in adult human olfactory bulb and their distribution overlapped that of the GABAergic neurons.

The lipid-anchored paralemmin is highly expressed in neuronal plasma membrane and has been implicated as a potent modulator of cellular cAMP signaling within the brain [33]. The olfactory neuron specific alpha subunit G(olf) of the trimeric G-proteins [34] involved in odorant sensing and signal transduction is located predominantly in the posterior subdivision of the accessory olfactory bulb [35,36].

3. Constituents of the PAZ Derived from Hippocampus

The dynamin superfamily member atlastin-1, an oligomeric GTPase, is enriched in pyramidal neurons in the cerebral cortex and hippocampus [37]. Atlastin-1 exists as an oligomer, most likely a tetramer, and is highly enriched in vesicular structures within axonal growth cones and variocosities as well as axonal branch points indicating a functional role of atlastin-1 during axonal development regarding axon formation and elongation [38].

Contactin-1 (F3) is a GPI-anchored neuronal cell surface adhesion molecule modulating interactions in developmental and regenerative processes. Contactin-1 is expressed at CA1 synapses, where it is selectively required for paired-pulse facilitation and NMDA receptor mediated long-term depression [39,40]. Contactin-1 assembles in a complex on the synaptic plasma membrane that regulates intercellular interactions necessary for specific modifications in synaptic stress. Contactin-1 plays a selective role in synaptic plasticity [39] and promotes adult hippocampal neurogenesis [41]. Overexpression of contactin-1 leads to increased CA1 long-term potentiation and improved spatial and object recognition memory [41].

Prominent expression of the neuron specific neurochondrin (Norbin – neurite-outgrowth re-lated rat brain protein) in adult brain was observed in hippocampus, amygdala, septum, and nucleus accumbens with moderate expression in the dorsal striatum [42,43]. Neurochondrin was originally discovered as a protein that induces neurite outgrowth [44]. A synaptosome fraction purified from mouse brain contained both neurochondrin and mGluR5 [43]. Neurochondrin knockout attenuated mGluR5-dependent stable changes in synaptic function—LTP and LTD—in the hippocampus [43]. Neurochondrin is a negative regulator of calcium/calmodulin-dependent protein kinase II phosphorylation and essential for the

spatial learning process [45]. Neurochondrin knockout led to a behavioral phenotype associated with an animal model for schizophrenia, as indexed by alterations both in sensomotoric gating and psychotomimetic-induced locomotor activity [43].

PP2A is a trimeric serine/threonine protein phosphatase composed of a scaffold subunit that is associated with a catalytic subunit and an additional, more variable, regulatory subunit that is expressed in a cell- and tissue-specific manner [46]. Long-term depression in the hippocampus was associated with an increase in the activity of PP1 and PP2A [47] that could be blocked by inhibitors of PP1 and PP2A [48]. These protein phosphatases could reduce extracellular signal-regulated kinase 2 (ERK2) in the adult hippocampus during LTD but not ERK1 [49]. PP2A is associated with Alzheimer neurofibrillary pathology. Phosphorylated tyrosine (Y307) in the catalytic subunit inactivated PP2A that was then unable to dephosphorylate tau [50]. The counter player the glycogen synthase kinase-3 inhibited PP2A and phosphorylated tau [50]. PP2A mRNA expression was quantitatively decreased in Alzheimer's disease hippocampus [51]. Over activation of PP2A was involved in lead-induced deficits in learning and memory [52].

The name septins was chosen to reflect the role of these proteins in separation of mother and daughter cells [53]. The septins 3/5/7 and septin 11 belong to a family of proteins with GTPase activity that form heterooligomeric filaments and ring-like structures that act as diffusion barriers and scaffolds.

Septins are involved in cytokinesis, positioning of the mitotic spindle, cellular morphology, vesicle trafficking, apoptosis, neurodegeneration, and neoplasia [54–56]. In mammals, 14 septin genes have been identified. Each septin gene is expressed in several spliced forms. Although most septins are highly expressed in the brain [57], only recently their role in neuronal function [58] and in neuropathological diseases such as Alzheimer`s disease [57], Parkison disease [59,60] and hereditary neuralgic amyotrophy [61] is beginning to be addressed. Septins can associate both with actin filaments and microtubules. Septins 3, 5, and 7 were localized in the presynaptic terminals, frequently associated with synaptic vesicles [57,62–65] and the presynaptic active zone [66,67]. Septin 3 was particularly abundant in mossy fiber nerve terminals in the hippocampus where it strongly co-localizes with synaptophysin and dynamin-1 [65]. In neurons, septin 11 forms heterooligomeric complexes with septin 5 and septin 7. Septins 3/5/7/11 exhibited an increase in expression from embryonic day 15 to postnatal day 70, and were abundantly expressed in axons and growth cones of developing hippocampal neurons, and were present in presynaptic terminals of mature synapses indicating a functional role within the presynapse. Knockdown of septin 5 or septin 1 in developing hippocampal neurons impaired axon growth [68].

Dihydropyrimidinase-related protein 2 has been identified as a constituent of the rat brain hippocampus proteome [69]. The function of dihydropyriminidase-related proteins 1 and 2 is not resolved yet, however both proteins have been implicated in axon growth and guidance [70]. Dihydropyrimidinase-2 regulated axon extensions [71] and neurogenesis [72]. Dihydropyrimidinase-related protein-2 demonstrated changes in protein abundance in a variety of neurological disorders such as Alzheimer`s disease [70,73], phenylketonuria mouse model [74], methamphetamine exposure [75], depression [71,72], kainite-induced pathology [76], and cellular nitrating conditions [77]. Dihydropyrimidinase-related protein 2 has been observed in an axogliasomal fraction [78] and has been linked to spatial memory formation [79]. The neurotrophin BDNF induced dihydropyrimidinase-related protein 2 expression changes in hippocampal neurons [80].

4. Constituents of the PAZ Derived from Cerebellum

Calbindin, named calbindin D-28k due to its vitamin D dependence and its apparent molecular mass, belongs to the large family of EF-hand calcium-binding proteins characterized by well conserved helix-loop-helix motives that bind calcium ions with high affinity [81]. Calbindin is enriched in Purkinje cerebellar neurons [81,82]. Cells which displayed calbindin during brain development were also calbindin positive in the adult animal. Positive cells represented 74% of the Purkinje cells from the cerebellar cortex, whereas less than 1% of the neurons in the frontal cortex were immunopositive [83]. Adult expression pattern developed steadily in cerebellum [84]. In mature Purkinje cells calbindin contributed about 15% of total cellular protein [85]. Selective deletion of calbindin from cerebellar Purkinje cells resulted in distinctly different cellular and behavioral alterations with permanent deficits of motor coordination and sensory processing [86]. Calbindin-deficient mice developed normally without upregulation of related calcium-binding proteins. However, when challenged in tests of movement coordination, severe ataxia became evident [87].

Dipeptidyl peptidase-like protein 6 (DPP6, also known as DPPX) is a type II membrane glycoprotein with a large extracellular C-terminal domain and a single transmembrane that revealed no enzyme activity domain [88,89]. DPP6 was expressed in cerebellar granule cells where it regulated resting membrane potential and input resistance [90] suggesting a role for DPP6 in sculpting the high frequency excitability of cerebellar granule cells [91]. DPP6 is an integral auxiliary subunit of the Kv4.2 potassium ion channel complex that is crucial in the regulation of firing frequency and synaptic plasticity [88,90,92,93]. Interaction of DPP6 with the permeation and gating modules of the KV4 channels facilitated inactivation [94,95].

The neuronal membrane glycoprotein M6-a (M6a) is a 278-amino acid transmembrane glycoprotein with four transmembrane domains with one intracellular and two extracellular loops and the N- and C-termini located in the cytoplasm [96]. It is the only member of the proteolipid protein family of tetraspan proteins to be expressed exclusively in the central nervous system [97]. M6a expression was particularly strong in unmyelinated axonal fibers such as cerebellar parallel fibers [98]. M6a has been suspected to play a role in the formation of nerve cell processes since in cultured cerebellar neurons treated with monoclonal M6a antibody, neurite formation was severely impaired [99]. Strong labeling for M6a was observed in the cerebellar molecular layer corresponding to heavily stained axon terminals originating from granule cells. As observed by immune electron microscopy M6a was present only on the cytoplasmic side of the presynaptic membrane and on the membrane of synaptic vesicles [100]. M6a has been allocated to the leading edge of growth cones in cultured cerebellar neurons [101] and in lipid rafts in membrane microdomains where it induced filopodia formation [102].

Proline-rich transmembrane protein 2 (PRRT2) is a largely uncharacterized protein. It is expressed in the brain and has been demonstrated to interact with SNAP-25, a component of the molecular machinery involved in the release of neurotransmitters at the presynaptic plasma membrane [103]. PRRT2 has been described to play a role in Paroxysmal Kinesigenic Dyskenia, a dominant movement disorder [104], as well as in other neurological disorders [105].

The function of *N*-myc downstream-regulated gene 2 (NDRG2) protein is unknown, however it is believed to be involved in cell growth events [106]. Using subtractive cloning technology it was shown that the A/B-hydrolase fold protein gene NDRG2 (NDRG family member 2) was upregulated at both the

RNA and protein levels in Alzheimer´s disease brains. Expression of NDRG2 in affected brains was revealed in cortical pyramidal neurons, senile plaques and cellular processes of dystrophic neurons [107].

The inositol 1,4,5-trisphosphate receptor type 1, also named Purkinje cell protein 1, is a ubiquitous 250 kDa major phosphorylated glycoprotein especially abundant in cerebellar Purkinje cells at the plasma membrane [108–111]. Intracranial injection of 14C-leucine, revealed that inositol 1,4,5-trisphosphate receptor type 1 was one of the dominant proteins in the cerebellum. In Purkinje cell deleted mutant mice no inositol 1,4,5-trisphosphate receptor type 1 was present [111].

Phosphatidylethanolamine-binding protein 1 (PEBP-1) is largely undescribed. It has been involved in the function of presynaptic cholinergic neurons of the central nervous system in respect of learning and memory [71].

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