Synapsin III: Role in Neuronal Plasticity and Disease

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Abstract

Synapsin III was discovered in 1998, more than two decades after the first two synapsins (synapsins I and II) were identified. Although the biology of synapsin III is not as well understood as synapsins I and II, this gene is emerging as an important factor in the regulation of the early stages of neurodevelopment and dopaminergic neurotransmission, and in certain neuropsychiatric illnesses. Molecular genetic and clinical studies of synapsin III have determined that its neurodevelopmental effects are exerted at the levels of neurogenesis and axonogenesis. *In vitro* voltammetry studies have shown that synapsin III can control dopamine release in the striatum. Since dopaminergic dysfunction is implicated in many neuropsychiatric conditions, one may anticipate that polymorphisms in synapsin III can exert pervasive effects, especially since it is localized to extrasynaptic sites. Indeed, mutations in this gene have been identified in individuals diagnosed with schizophrenia, bipolar disorder and multiple sclerosis. These and other findings indicate that the roles of synapsin III differ significantly from those of synapsins I and II. Here, we focus on the unique roles of the newest synapsin, and where relevant, compare and contrast these with the actions of synapsins I and II.

Keywords

phosphoprotein; neurogenesis; axon formation; dopamine; schizophrenia; polymorphism

1. Introduction

Synapsins are a family of three neuron-specific genes – designated synapsins I, II and III– which encode phosphoproteins that play crucial roles in the regulation of neurotransmission

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and neurodevelopment [1, 2]. Synapsins I and II were identified in the late 1970s [3, 4], and have since been studied intensively as regulators of synaptic function. Synapsin III, which is the subject of this review, was discovered in 1998 as a result of early work on the human genome project [5, 6]. The human synapsin III gene was identified via homologous sequences on chromosome 22 that were different from synapsin I (localized to chromosome X) or synapsin II (localized to chromosome 3). Synapsin III shares structural and functional properties with synapsins I and II, but also possesses unique features as described below.

The human synapsin III gene spans an unusually large region within the genome (494,000 bases) compared to synapsin I (48,000 bases) or synapsin II (43,500 bases). Despite this difference, the gene possesses a conserved intron-exon structure very similar to those of synapsins I and II [6]. The full-length synapsin III protein (isoform IIIa) exhibits protein homology with the other two synapsins: they share conserved domains A, C and E. Domain B is not conserved among the synapsins, and synapsin III possesses a unique region termed domain J (Fig. 1). Like the other two synapsins, synapsin III is also an avid substrate for several protein kinases [7].

Although the synapsins share similar domain structures and sequence homologies, synapsin III has a unique transcriptional profile with respect to alternative splicing [8]. Six different mRNAs (IIIa to IIIf) are transcribed from the synapsin III gene, whereas only two spliced isoforms are known to arise from the synapsin I (Ia and Ib) and II (IIa and IIb) genes. The synapsin III mRNAs exhibit differential tissue- and developmental stage-specific expression. Three of the neuronal transcripts are detected in fetal and to a lesser extent adult brain (IIIa–IIIc), whereas one (IIId) is detected only in fetal brain. Additionally, two transcripts (IIIe and IIIf) are detected only in nonneuronal tissues. Parenthetically, a putative second promoter, which is contained within an intron in the synapsin III gene locus, appears to generate the nonneuronal synapsin IIIe and IIIf transcripts [8]. This level of transcriptional complexity is far greater than that described previously for the synapsin I and II genes, and suggests that synapsin III may have functions distinct from those ascribed to synapsins I and II [8].

Structural studies also imply a distinct role for synapsin III. For instance, the C domains of synapsins are structurally homologous to a family of ATP-utilizing enzymes [9]. Consistent with this observation, synapsins were shown to bind to ATP with a high affinity and to ADP with a low affinity, suggesting that synapsins might also be ATP-utilizing enzymes [5, 9, 10]. Curiously, calcium inhibited the binding of ATP to synapsin III, activated the binding of ATP to synapsin I, but did not affect the binding of ATP to synapsin II [5]. This intriguing data suggests a biological rationale for the existence of three synapsins, but to date, the significance of these findings have yet to be determined.

The expression profile of synapsin III also suggests a function distinct from the other two synapsins. In the adult brain, synapsin III expression is much lower than that of synapsins I or II [6], and it is developmentally regulated in a manner that differs from that of the other two synapsins [11]. Although synapsin III, like synapsins I and II, is localized to the synapse [6], the synapsin III protein is primarily localized to regions outside of the synapse in the adult brain [11]. Thus, the subcellular localization of synapsin III includes extrasynaptic sites, such as the cell body and growth cones [11], whereas synapsins I and II are almost exclusively localized at synaptic sites [11]. These findings suggested that unlike synapsins I and II, synapsin III does not play a major role in synaptic activity, but rather, in early neural development. Despite these dissimilarities, synapsin III does not function in isolation – all synapsins form hetero-and homodimers, and therefore the function of synapsin III is entwined with the other synapsins [12]. Here, we present our current understanding of the newest member of the synapsin gene family, synapsin III, with regards to its relationship

with the other synapsins, its role in neurodevelopment and neurotransmission, and its potential relevance to human illness.

2. Neurotransmission

2.1 Kinetics

A role for synapsins in the regulation of neurotransmitter release was first reported more than two decades ago [13]. The creation of mice bearing homozygous deletions of individual synapsins of all three synapsin genes (triple knockout or TKO) has proven to be invaluable tools in deciphering the precise mechanisms by which synapsins exert their physiological actions.

Initial experiments with mice bearing a homozygous deletion of the synapsin III gene (synapsin III knockout mice) revealed subtle changes in neurotransmission. Superficially, synapsin III knockout mice do not display neurological abnormalities such as seizures or motor disturbances [14]. This contrasts strongly with synapsin I and II knockout mice, which exhibit seizures after 1–2 months of age [15, 16]. In both synapsin I and II knockout mice, there is depletion in the reserve pool of synaptic vesicles [15–17], which results in a rapid decrease of neurotransmission after repeated stimulation. This presumably accounts for the seizure phenotype in synapsin I and II knockout mice. However, in mice lacking synapsin III, the size of the recycling pool is actually increased, but release kinetics is slower [14]. Consequently, the number of vesicles released per action potential is similar between synapsin III knockout and wild-type mice. Consistent with this observation, the density and distribution of synaptic vesicles in synapsin III knockout mice does not differ from those of the wild-type controls [14].

While there were no major changes in the reserve pool of synaptic vesicles, a significant reduction in inhibitory postsynaptic currents was observed in synapsin III-deficient neurons [14]. Synaptic depression was also substantially reduced at strong synapses. In this context, synapsin III appears to act as a negative regulator while synapsins I and II act as positive regulators of neurotransmission.

2.2 Specificity for Dopamine Release

Investigations of the role for synapsins in neurotransmission revealed that synapsin I is primarily responsible for maintaining the pool of GABAergic vesicles [18, 19] while synapsin IIa maintains glutamatergic synaptic vesicles [20]. Nevertheless, synapsins do not appear to be involved in the release of serotonin in the substantia nigra [21] or acetylcholine at neuromuscular junctions [22].

Recently, it was demonstrated that synapsin III is specifically involved in the release of dopamine in the striatum [21]. Initially, this observation was made using substantia nigra pars reticulata slices prepared from TKO mice. Release of dopamine in response to electrical stimulation was approximately doubled, both *in vivo* and in striatal slices from TKO mice, compared to wild-type controls [21]. A similar magnitude of dopamine release was also observed in slices derived from synapsin III knockout mice, suggesting that synapsin III is primarily responsible for the regulation of dopamine release in the striatum. It should be emphasized that dopamine is a neurotransmitter that is clinically important in many neuropsychiatric disorders, and this finding has potentially significant implications for synapsin III in brain disorders, as described below.

3. Neurodevelopment

3.1 Neurogenesis

Synapsin III protein is enriched in young neuronal precursor cells of the hippocampal dentate gyrus [23], a region of the brain where neurogenesis is known to persist well into adulthood (reviewed in [24]). In synapsin III knockout mice [14], neurogenesis was markedly altered, suggesting a direct link between synapsin III and neurogenesis. Since neurogenesis consists of a number of stages of development, proliferation, survival, and differentiation of neural progenitor cells were systematically quantitated in the hippocampal dentate gyrus of adult synapsin III knockout and wild-type mice [25]. A 30% decrease in proliferation and a 55% increase in survival of neural progenitor cells were observed in synapsin III knockout mice. No difference in the volume of the dentate gyrus was noted between synapsin III knockout and wild-type mice, suggesting that the decrease in proliferation was compensated by the increased survival of neural progenitor cells [25]. A 6% increase in the number of neural progenitor cells that differentiated into neurons was also observed. Immunocytochemistry of the adult hippocampal dentate gyrus revealed that synapsin III co-localizes with markers of neural progenitor cell development (i.e. Nestin, PSA-NCAM, NeuN, and Tuj1), but synapsin III immunoreactivity did not co-localize with markers of mitosis (i.e. Ki67 and PCNA) (Fig. 2). These results suggest a complex role for synapsin III during this stage of neurodevelopment, because deletion of synapsin III affects each step during the process of neurogenesis in the hippocampal dentate gyrus.

As will be discussed later, there is increasing evidence that adult neurogenesis is highly relevant to psychiatric illness. For instance neurogenesis in the hippocampal dentate gyrus is associated with facilitated learning and memory [26], is disrupted by depression and stress [27, 28], but is stimulated by some antidepressants [29, 30], lithium [31, 32] and certain antipsychotic drugs [33–38].

3.2 Axonogenesis

To determine if synapsin III has a role in the morphological development of neurons, the hippocampal culture system, in which morphological stages of neuronal development are well-established [39, 40], was employed [11]. These experiments demonstrated that synapsin III protein is expressed at an earlier developmental time-frame than synapsins I and II [11]. Remarkably, immunohistochemical experiments revealed that, in contrast to synapsins I and II, synapsin III failed to co-localize at synaptic sites with synaptic markers (e.g. synaptophysin). In contrast, synapsin III was concentrated in all cell bodies and most growth cones, suggesting a prominent role in axon growth. In support of this notion, depletion of synapsin III by either antisense oligonucleotides [11] or genetic ablation [14] led to hypertrophied growth cones and stunted axons. Depleting synapsin III after axons had formed did not appear to have subsequent effects on neuronal maturation [11]. The results indicate a distinct role for synapsin III in axonogenesis.

Significantly, specific stages of neurodevelopment are not affected by depletion of individual synapsin genes. For instance, depletion of synapsin III has no effect on synapse formation or maintenance, processes that are regulated both by synapsin I [41] and synapsin II [42]. Conversely, the lack of synapsin I and II immunoreactivity in neural progenitor cells [23] suggests that these synapsins are not involved in neurogenesis. These observations indicate that synapsin III plays a much earlier role in neurodevelopment, which contrasts with the later roles of synapsins I and II in the formation and maintenance of synapses.

4. Neuropsychiatric Disorders

4.1 Importance of Neurotransmission

Since the advent of psychopharmacology in the 1950s and 1960s, it has been recognized that specific neurotransmitters play an integral role in the pathophysiology of various neuropsychiatric disorders. It is well established that most antidepressants in current use enhance serotonin and/or noradrenaline accumulation at the synapse [43]. Typical antipsychotic drugs are all selective antagonists of the dopamine D2 receptor, and their potency at this receptor is directly correlated with clinical efficacy [44]. Conversely, reagents that increase synaptic dopamine (e.g. antagonists of the dopamine transporter such as cocaine and amphetamines) exacerbate psychosis [45]. These observations led to the formulation of the dopamine hypothesis of schizophrenia [46]. While the mechanism of action of lithium in the treatment of bipolar disorder remains poorly understood, most of the newer treatments for this disorder are anticonvulsants, suggesting a generalized dysfunction of neurotransmission in this condition [47]. Since synapsin III is involved in dopamine release, its dysfunction fits well with a potential role in psychosis.

Although dysfunctions in specific neurotransmitters such as the serotonin, noradrenaline and dopamine systems are often viewed as potential players in susceptibility to mental illness, the etiology of psychiatric disorders remains poorly understood. Indeed, many investigators have raised the possibility that abnormal neurotransmission may not be the primary locus of dysfunction in mental disorders. As will be discussed in the next section, growing evidence suggests that neurodevelopmental abnormalities may underlie the pathogenesis of some psychiatric disorders.

4.2 Importance of Neurodevelopment

There is increasing evidence that neurodevelopmental abnormalities may underlie major psychiatric disorders such as schizophrenia [48, 49], bipolar disorder [50] and depression [51]. The evidence is strongest for schizophrenia, where data from childhood and adolescent observations [52, 53], postmortem analyses (for review see [54]), and neuroimaging studies [55] suggest this progressive brain disorder originates early in life.

At a cellular level, postmortem analyses of brains from individuals with schizophrenia have demonstrated the existence of a malformed cytoarchitecture [56], dendritic abnormalities [57], decreased dendritic spine densities [58], reduced neuropil [59] and cell body sizes [60], and decreased expression of synaptic proteins [61] and mRNA [62], suggesting disrupted synaptic connections in this disorder. Although there is a wide range of cellular abnormalities, they encompass the types of abnormalities that have been observed in synapsin III knockout mice, including aberrations in axon outgrowth.

Recently, abnormalities of neurogenesis in the adult have been investigated as a potential major contributor to mental illness (for review see [63]). The existence of adult neurogenesis was debated for many years after it was first described [64]. It is now accepted that limited neurogenesis occurs in all adult mammalian brains, primarily at two sites: the subgranular zone of the hippocampal dentate gyrus [64, 65], and the subventricular zone which gives rise to neurons in the rostral migratory stream and olfactory bulb [66–68]. Studies have shown that stem cells responsible for adult neurogenesis are functional and contribute to cognition [26, 69, 70]. The enrichment of synapsin III in neural progenitor cells in precisely these same regions, and its effects on various neurogenic stages and behavior when depleted, implies that synapsin III exerts a functional role in neurogenesis, which may have broad implications for neuropsychiatric disorders [25].

4.3 Behavioral Studies

Although psychiatric disorders are difficult to study in rodents, over the years a number of different behavioral tests have been developed that may have face, predictive, and construct validity. One such neurophysiological correlate is prepulse inhibition (PPI), a phenomenon in which a weak stimulus (the prepulse) preceding a stronger stimulus inhibits a startle response. Patients with schizophrenia and some other neuropsychiatric disorders have impaired PPI (reviewed in [71]). Impaired PPI in these patient populations is thought to reflect dysfunctional sensorimotor gating mechanisms, and similar deficits in PPI are produced in rats by pharmacological or developmental manipulations, and in mice by pharmacological and genetic manipulations.

Cognitive impairments have also been reported in major depression [72], bipolar disorder [73] and schizophrenia [74]. Domains of cognition that are disrupted significantly in schizophrenia include attention, executive function, verbal and visual-spatial working memory [74]. Impairments of working and semantic memory are primarily due to dysfunction of the frontal cortex, temporal cortex and hippocampus.

A neurophysiological screen was initially conducted to exclude gross deficits in the synapsin III knockout mice [75]. No abnormalities were detected in anxiety- or depressive-like responses, or in gross sensory or motor function; however, synapsin III knockout mice increased their exploratory activities when placed into a novel environment [76]. Hippocampal function was examined using the Morris water maze [77], novel object recognition [78] and social transmission of food preference tests [79, 80]. Synapsin III knockout mice did not display abnormalities in the Morris water maze test, but showed deficits in the novel object recognition and social transmission of food preference tests. Both the object recognition and social transmission tasks require an intact hippocampus, and successful performance on the tests relies upon somewhat different brain circuits and areas [79, 81–83]. Hence, synapsin III may play a selective role in learning and memory functions where spatial learning and memory are largely intact, while processes underlying explicit memory are affected [76]. Synapsin III knockout mice were also examined in tests of conditioned fear, a type of emotional memory that requires an intact hippocampus and amygdala, the latter is a brain region implicated in paranoia [84, 85], a form of psychosis seen in subtypes of schizophrenia. Synapsin III knockout mice displayed abnormalities in both contextual and cued fear conditioning [76] suggesting that depletion of synapsin III has widespread behavioral consequences involving connections between the amygdala, hippocampus and frontal cortex. The amygdala deficits in the synapsin III knockouts were further supported by abnormalities in fear-potentiated startle.

Sensorimotor gating was also evaluated in synapsin III knockout mice using auditory PPI, and by challenging these mice with drugs that are typically used to treat individuals with schizophrenia. Synapsin III knockout mice are deficient in PPI and fail to show prepulse-dependency of the response (Fig. 3). Clozapine, an atypical antipsychotic used in the treatment of schizophrenia, restores the PPI performance of synapsin III knockout mice to that of the vehicle-treated wild-type controls (Fig. 3).

Taken together, synapsin III knockout mice demonstrate deficits in cognition, emotional processing and sensorimotor gating. Similar deficits have also been described in patients with psychosis. Thus, synapsin III knockout mice may serve as a useful model system for further investigations of mechanisms underlying this symptom.

4.4 Post-Mortem Studies

Several synaptic proteins are decreased in dorsolateral prefrontal cortex and hippocampus of post-mortem brain, two regions that are implicated in brain disorders (for review see [61]).

These findings are consistent with the hypothesis that neural mis-connectivity contributes to schizophrenia and other neuropsychiatric disorders [86].

The hippocampus is considered to be one region of the brain where a convergence of imaging, postmortem, and functional studies has revealed subtle changes in schizophrenia (for review, see [54]) and bipolar disorder (for reviews see [87, 88]). Synapsin III levels were decreased by 75% in postmortem hippocampi of individuals with bipolar disorder, and decreased by more than 50% decreased in individuals with schizophrenia [89].

Another region implicated in both schizophrenia [90] and bipolar disorder [91] is the dorsolateral prefrontal cortex. At the mRNA level, synapsin II is one of the most consistently down-regulated genes in the prefrontal cortex of individuals with schizophrenia [62]. In agreement with this observation, synapsin III protein levels were also significantly decreased in the prefrontal cortex of individuals with schizophrenia [92].

Curiously, synapsin I levels are not significantly different between schizophrenia and controls in the hippocampus [89] or prefrontal cortex [93], indicating a potential disparity in the involvement of specific synapsins in mental disorders. This result is relevant because synapsins are thought to function together as heterodimers [12]. If confirmed, the involvement of synapsins II and III but not synapsin I in specific mental disorders may be an important clue to investigating molecular mechanisms underlying these conditions.

4.5 Genetic Studies

Early twin and familial studies strongly support the hypothesis that genetics plays a strong role in the susceptibility to schizophrenia [94]. Subsequent studies have shown that genetics also plays a significant role in a variety of other major psychiatric disorders (for review, see [95]), including bipolar disorder, major depression, anxiety disorders and addiction. However, genetic studies have shown that for virtually all these conditions, inheritance of the disorder is complex, and that susceptibility is influenced by environmental factors that have yet to be determined. Thus, in a recent opinion, "high heritability has not … translated into a satisfying search for genetic lesions" [96].

One potential explanation for the difficulty in identifying susceptibility genes for mental disorders is that multiple genes of weak effect may work in concert with environmental factors and/or among themselves to produce susceptibility to major psychiatric illness [95]. The majority of psychiatric genetic studies are not designed to detect such genes of weak effect. Consequently, a recent strategy has emerged in psychiatric genetics where investigators are now seeking rare variants in mental disorders to better understand a biological basis of these conditions [97, 98].

In this regard, synapsin III is located on human chromosome 22q12.3 [6]. Several studies have consistently demonstrated evidence for a susceptibility gene located on chromosome 22q12.3 for schizophrenia [99–101] and bipolar disorder [102, 103]. Indeed, a number of chromosomal loci linked to bipolar disorder are identical to those linked to schizophrenia, raising the possibility of genetic overlap between the two disorders [104–107].

Since the identification of synapsin III, several studies have conducted genetic associations between polymorphisms in the synapsin III gene and schizophrenia [108–113]. In most studies, the polymorphic variations employed were located in introns, and would likely be nonfunctional. In the next section, we describe potentially functional polymorphisms in synapsin III: (1) S470N, which abolishes a functional mitogen-activated protein kinase (MAPK) site in the synapsin III protein that may affect neurotrophic signaling; and (2)

synapsin III promoter mutations, of which one has been shown to alter DNA-protein interactions at a transcription factor binding site.

4.6 Functional Polymorphisms in the Synapsin III Gene

In a search for potentially functional polymorphisms in the synapsin III gene, exons from this gene were sequenced from probands derived from families that displayed linkage to schizophrenia at chromosome 22q12–13 [7]. Two polymorphisms residing on exon 12 were identified: one polymorphism affected the third base of the codon for Leu469, which was silent (L469L), and the other mutation consisted of amino acid 470, that was changed from Ser to Asn (S470N). In this study sample, all individuals that possessed S470N also inherited L469L [7].

Using association analyses, the S470N polymorphism was found to be more frequent in individuals with schizophrenia than in controls [7]. A subsequent follow-up study also found that S470N appeared more frequently in schizophrenia in a Caucasian population [114], but the sample was too small to draw firm conclusions. Curiously, these investigations found a 50-fold increase in the frequency of both the S470N and L469L polymorphisms in the African population. Parenthetically, in this population, both polymorphisms were found more frequently in schizophrenia, with L469L being statistically significant and S470N exhibiting a trend towards significance. S470N was also found more frequently in individuals with schizophrenia in another independent Caucasian population, but the frequency of the polymorphism was too rare to draw conclusions [115].

It is highly unlikely that a single gene can act alone to confer susceptibility to schizophrenia or to other major mental disorders. Moreover, there are very few studies that analyze multiple genes at a time. However, in recent Bayesian analyses of single nucleotide polymorphisms, 30 candidate genes for schizophrenia were studied [115]. These analyses revealed that S470N was one out of six polymorphisms that were considered risk factors for schizophrenia when considered in combination with other mutations [115].

Subsequent studies revealed that S470N might affect neurodevelopment. Synapsin III is predominantly expressed during mouse neonatal development [7], which corresponds to the peak of neurogenesis during brain cortical development [116]. Synapsin III is also a substrate for abundant brain proline-directed kinases, such as cyclin-dependent protein kinase 5 (cdk5) and mitogen-activated protein kinase (MAPK). Ser-470 is an evolutionarily conserved site for the MAPK known as Erk1/2, a downstream effector of neurotrophin action [7]. Further studies have revealed that Ser-470 is phosphorylated by MAPK almost exclusively during neonatal development, and is stimulated by the neurotrophins, NT-3 [7] and BDNF [unpublished observation]. The degree of phosphorylation at Ser-470 parallels the levels of phospho-Erk1/2, suggesting that Ser-470 on synapsin III is a physiological substrate for MAPK and a downstream target of neurotrophins. These observations raise the possibility that S470N could affect neurotrophic signaling.

Taken together, these findings are consistent with the accumulating evidence of a neurodevelopmental defect in schizophrenia. In particular, abnormalities in neurotrophic signaling have been implicated in this disorder. Studies have demonstrated aberrant levels of BDNF [117, 118], NT-3 [119], and their respective cognate receptors, trkB [117, 118, 120] and trkC [120, 121] in this condition. Moreover, there are selective changes in the expression levels of downstream activated MAPK signaling molecules that were observed in postmortem brain from individuals with schizophrenia [122].

Two single nucleotide polymorphisms (SNPs) in the synapsin III promoter have also been investigated by a number of research groups: rs133946 (position -631) and rs133945

(position -196). The SNP rs133945 is potentially functional, because an ATTT motif is located at position -196 that resembles the octamer sequence recognized by members of the POU family of transcription factors [123]. Indeed, the G-allele of this SNP has consistently resulted in greater binding to brain proteins than the A-allele, suggesting that this polymorphism has an effect on DNA-protein complexes [123]. The functional relevance of rs133946 has not been investigated.

Interestingly, no striking differences in the frequencies of these SNPs were observed in schizophrenia [113, 123] or bipolar disorder [123], although there were trends towards significance in some ethnic samples, suggesting that the studies were underpowered. However, there were significant differences in protein-DNA interactions using protein extracts from postmortem brains of individuals with bipolar disorder and synthetic DNA corresponding to alleles of rs133945 [123]. These results suggest that additional variables (e.g.. composition of protein extracts) should be considered when investigating the functional relevance of a polymorphism.

Both rs133946 and rs133945 have also been investigated in the context of multiple sclerosis. An initial report in an Italian cohort showed that the C631/A196 haplotype seems to confer a significant protection against this neurological condition [124]. A subsequent study in a German cohort has failed to find any association between these polymorphisms and multiple sclerosis [125]. However, a recent study in a Spanish Basque cohort has also reported that C631/A196 may be protective factors against multiple sclerosis [126].

5. Conclusions

Synapsin III is emerging as an important regulator of early neurodevelopmental processes as well as dopaminergic neurotransmission. Synapsin III appears to play significant roles during neurogenesis and axon formation, while synapsins I and II are primarily involved in the formation and maintenance of synapses. Synapsin III is involved in slow synaptic transmission, particularly dopamine release [21], whereas synapsins I and II are involved in fast neurotransmitter release (i.e. glutamate and GABA [127]).

These functions of synapsin III are particularly relevant to psychiatric disorders that encompass psychosis, a symptom shared by schizophrenia and bipolar disorder. Schizophrenia is currently believed to have a neurodevelopmental basis [96], and recent experiments posit neurogenesis, which is affected by synapsin III [25], as a stage that is affected in this condition [63]. A role for synapsin III in psychiatric disorders is also supported by postmortem studies [89, 92]. Additionally, support also derives from its role in dopaminergic transmission [21], which is believed to be the site of action of antipsychotic drugs, as well as a behavioral phenotype in synapsin III knockout mice that is consistent with psychosis [76]. Functional polymorphisms in the synapsin III gene may be relevant to schizophrenia, bipolar disorder and possibly multiple sclerosis (Section 5.6.2). The discovery of the synapsin III polymorphism, S470N, is particularly instructive, as it could affect neurotrophic signaling. Taken together, these investigations into synapsin III have provided new insights into mechanisms of neural plasticity as they may relate to a variety of neuropsychiatric disorders.

Acknowledgments

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Here are five bullet points highlighting the core findings of our article:

- We compare the actions of Synapsin III with those of Synapsins I and II.

- Synapsin III is mainly involved in the regulation of neurogenesis and axonogenesis.

- By contrast, Synapsins I and II are involved in synapse formation and maintenance.

- Synapsin III, but not I or II, is implicated in dopamine release in the striatum.

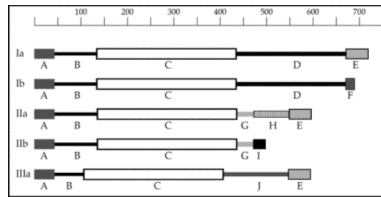- Human genetic and animal studies support a role for synapsin III in psychosis.

Figure 1.
Protein Domain Structure of the Synapsins. Domains are schematically represented and indicated by letters A–J. The length of the polypeptide chains is shown at the top in number of amino acid residues.
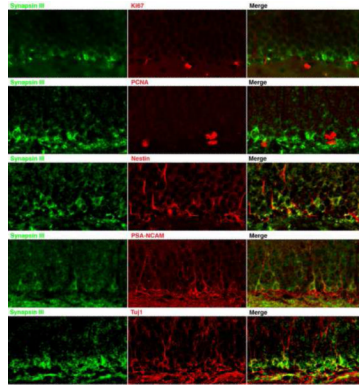
Figure 2.
Synapsin III Co-localizes with Markers of Early Neuronal Development. Sections from the hippocampal dentate gyrus from a wild-type adult mouse were stained with antibodies specific to synapsin III and to the indicated proteins; images were obtained using confocal microscopy. Synapsin III does not co-localize with the mitotic markers Ki67 and PCNA, but it does co-localize with markers of early neuronal development that include Nestin, PSA-NCAM, and Tuj1.
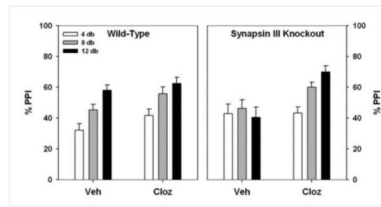
Figure 3.
PPI is Abnormal in Synapsin III Knockout Mice, and is Rescued by an Atypical
Antipsychotic Drug. Wild-type and synapsin III knockout mice were injected with vehicle
saline (Veh) or 1 mg/kg clozapine (intraperitoneal). Wild-type mice show normal responses
in PPI: increasing PPI with increasing prepulse intensity, which is unaffected by clozapine.
By contrast, synapsin III knockout mice have an abnormal response to PPI (vehicle
injection), which is restored when they are treated with clozapine.