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Abnormal Synaptic Properties in Down Syndrome: Lessons from Mouse Models

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Overview

With the advent of mouse models of Down syndrome (DS) the possibilities to further explore and understand the dysfunctions associated with DS expands. In particular, the basic and cellular neurophysiology can now be established in mice, which was not previously possible in human DS, so that specific DS dysfunctions can now be separated from the overall disorder and examined in a manner which may provide interventions that directly address particular abnormalities. The function of well defined regions and even certain genes within the triplicated chromosome are being understood with greater clarity to the extent that some DS specific phenotypes could be therapeutically ameliorated in the future.

Introduction

Mental retardation can be attributed to improper neural functioning caused by a broad spectrum of abnormalities that disrupt central nervous system (CNS) function. The cognitive deficits associated with DS are the result of expression of extra gene copies from chromosome (Chr.) 21 affecting CNS function. Mental retardation in DS is characterized by memory deficits, developmental delays, and other cognitive abnormalities. Neurophysiological information is needed to understand the mechanisms causing the mental retardation in DS. Cognitive impairment is one of three phenotypes, including early onset of Alzheimer disease neuropathology and muscle hypotonia, that affect nearly all DS individuals.

In 1866 the English physician, John Langdon Down, first illustrated the characteristic features of individuals, which we now associate with DS (Down, 1866). In 1959, the French geneticist, Jerome Lejeune, showed that DS is caused by chromosomal abnormalities related to the presence of an extra whole or part of Chr. 21, which was termed trisomy 21 (Ts21, Lejeune, 1959; Antonarakis *et al*., 1985; Korenberg *et al*., 1990). There are more than 200 known genes on Chr. 21 (Hattori *et al*., 2000), which can contribute to the numerous DS phenotypic abnormalities. A chromosomal critical region (DSCR) for many of the neurological features such as mental retardation has been hypothesized to be localized between the carbonyl reductase (CBR) and transcriptional regulator *ets*-related gene (ERG) loci (Delabar *et al*., 1993; Dahmane *et al*., 1995; Toyoda *et al*., 2002). However, genes outside the DSCR also can be involved in the DS phenotype (Korenberg *et al*., 1994) and recently the concept and existence of the DSCR has been challenged (Olson *et al*., 2004).

Trisomy mouse models provide insight into the molecular and genetic effects that abnormal chromosome number has upon neurophysiological profiles. The distal segment of mouse Chr. 16 is homologous to nearly the entire long arm of human Chr. 21 (Figure 1). Therefore, mice with full or segmental trisomy 16 (Ts65Dn, Ts16Cje

and Ts1Rhr) are considered genetic animal models of DS. Ts65Dn and Ts1Cje mice demonstrate impaired learning in spatial tests and abnormalities in hippocampal synaptic plasticity, which mirrors deficits seen in DS individuals. Mice in which only the DSCR is triplicated (Ts1Rhr) show no abnormalities related to craniofacial features (Olson *et al*., 2004). Recently an aneuploid mouse strain carrying ~92% of human Chr. 21 (Hsa21) has been developed (Tc1). Although chimeric for Hsa. 21 (Figure 1), these mice show many phenotypes consistent with DS and DS mouse models, such as spatial learning and memory deficits, abnormal synaptic plasticity, decrease in cerebellar granule cell populations, developmental heart problems and decreased mandibular size (O'Doherty *et al*., 2005). In all, these trisomic mouse models provide excellent tools by which to elucidate dysfunctions found in DS individuals.

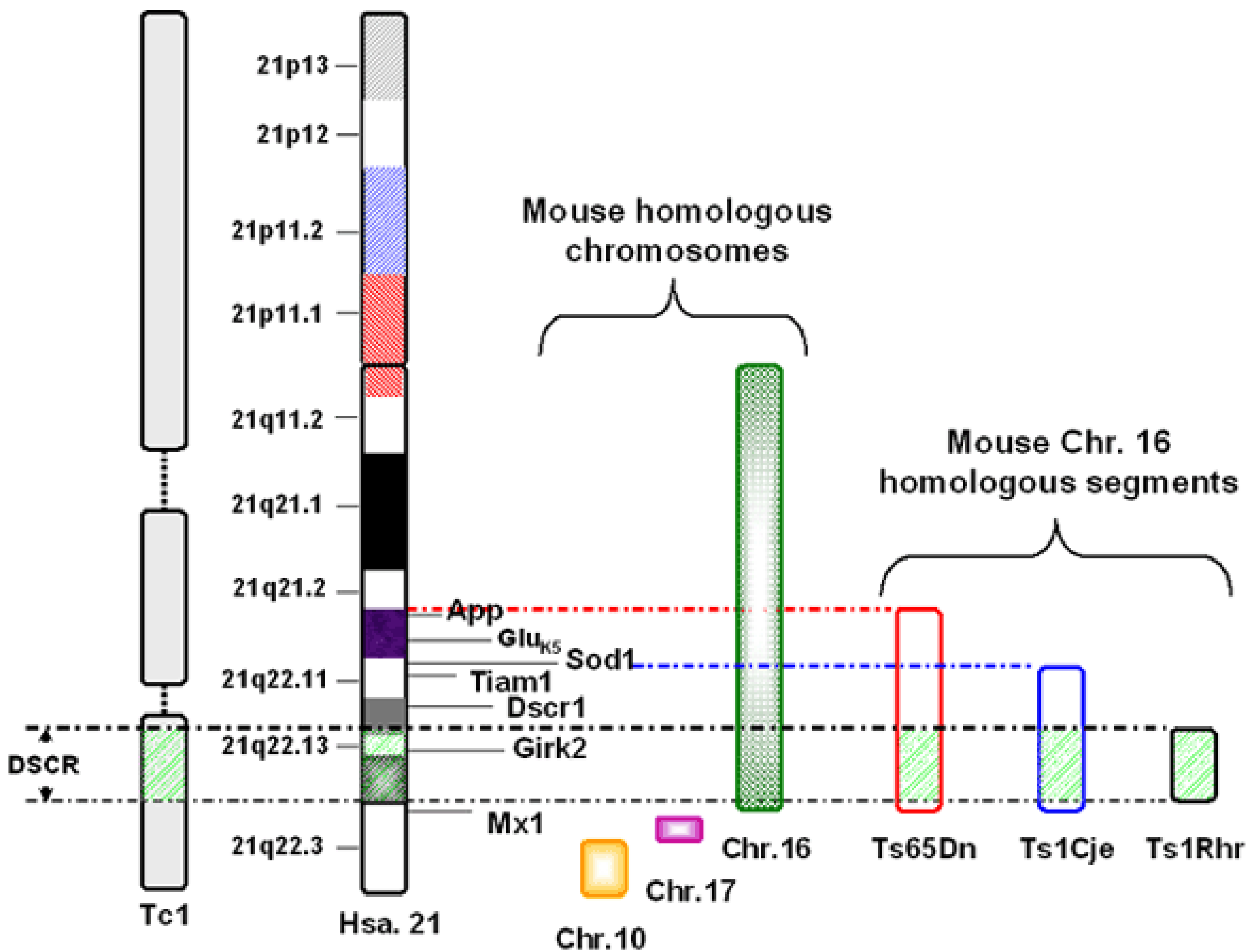

Figure 1. Human chromosome 21 (Hsa. 21) map showing the Down syndrome critical region (DSCR) and relationship of various genes to the trisomy mouse model chromosome segments. Homologous segments of mouse chromosomes 10, 16 and 17 are also represented corresponding to analogous portions of Hsa. 21. *Noted Genes*: amyloid precursor protein (App), glutamate receptor subunit-5 kainate subtype (GluK5), superoxide dismutase-1 (Sod1), T-lymphoma invasion and metastasis-1(Tiam1), Down syndrome candidate region-1 (Dscr1), G-protein coupled inward rectifying potassium channel subunit-2 (Girk2), myxovirus (influenza virus) resistance-1 (Mx1).

We hypothesize that overexpression of genes from Chr. 21 disrupts homeostasis in the DS brain such that mechanisms underlying development, structure and plasticity of neuronal networks are

compromised to the extent that the interaction between them and normal functioning is severely affected.

Abnormal synaptic plasticity in DS mouse models

The hippocampus is part of the limbic system and plays an important role in learning and memory. It is a site for long-term synaptic plasticity that appears to be critical to memory formation, consolidation and retrieval, and therefore has been extensively studied in the modeling of learning and memory. Brief high-frequency activation of specific inputs causes a persistent increase in synaptic responsiveness (an increase in the excitatory postsynaptic potentials termed long-term potentiation (LTP)) that under certain circumstances can last for hours, days or weeks (Bliss & Collingridge, 1993). We investigated the phenomenon of LTP in the CA1 region of hippocampi from Ts65Dn mice (Figure 2 insets) and found there to be reduced LTP over a period of 60 min compared to that of age-matched diploid-controls (Siarey *et al.*, 1997). No significant difference between Ts65Dn and diploid controls was revealed in a paired pulse protocol, suggesting that presynaptic plastic mechanisms are similar. In another set of experiments sequential LTP and long-term depression (LTD) were evoked from Ts65Dn hippocampi (Siarey *et al.*, 1999). Both forms of use-dependent synaptic plasticity were abnormal in Ts65Dn compared to the diploid-controls; with LTP decreased, and LTD increased. We suggest that there may be a shift in the dynamic range of synaptic plasticity within the Ts65Dn hippocampus (Figure 2). These findings may explain the reported spatial behavioral and learning impairments that are persistent throughout the life of the Ts65Dn mouse (Holtzman *et al.*, 1996).

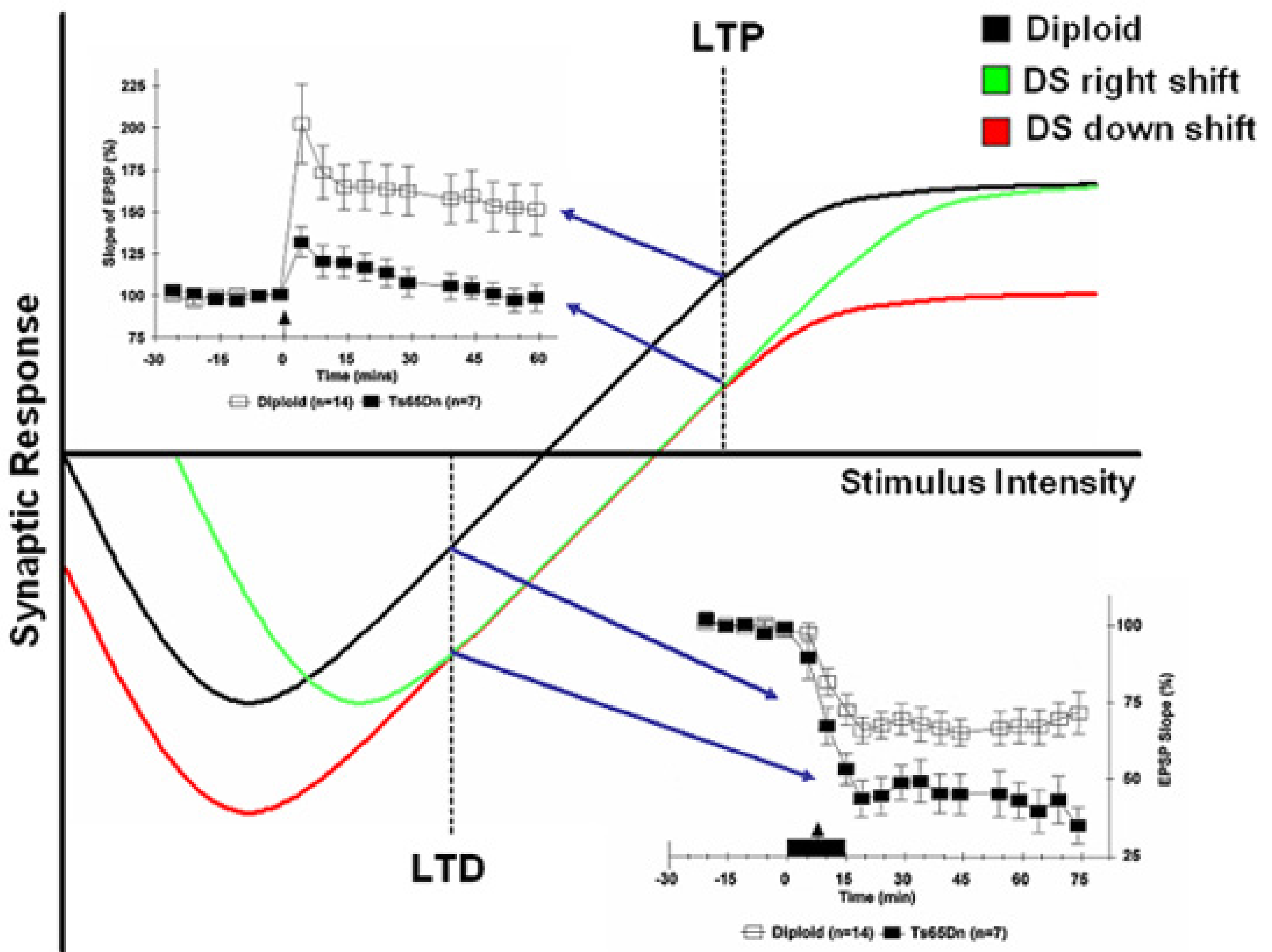

Figure 2. Possible shifts of the stimulus response curve for hippocampal synapses within trisomy mouse models of DS. Stimulus protocols that elicit LTP or LTD are represented by vertical dashed lines and corresponding points along the diploid (black), right (green) or down (red) shifted curves are represented by levels of potentiation or depression from representative responses of Siarey *et al*., (1999). The direction of shift is unknown (both right and downward shifts are possible with the known data) and further experiments are needed to determine saturation and relative levels of potentiation and depression.

In recent months LTP from the Tc1 mouse dentate gyrus was investigated and also found to be impaired, while baseline and short term plasticity were unchanged (O'Doherty *et al*., 2005). These data parallel findings from the other DS mouse models. Behavioral tests of

Tc1 mice correlate with the synaptic plasticity data, in that short-term memory was intact in the alternating T-maze, but long-term memory was impaired as evidenced by the novel-object recognition task. If mice that contain only triplicated DSCR (Ts1Rhr) reveal no changes in behavioral and physiological parameters then we may assume that compensatory mechanisms are sufficient to overcome the consequences of the extra chromosome segment restricted to the DSCR. Whereas, mice such as Tc1, Ts65Dn and Ts1Cje, which contain more than just the DSCR, are not capable of overcoming the consequences of the extra genetic material. This work is in progress.

Mechanisms that explain the deficits in LTP from these mice are unclear; however, recently deficits in LTP of Ts65Dn hippocampus were described by an increase in GABAergic tone. Deficits in LTP from the dentate gyrus of the Ts65Dn mouse were reversed when GABAergic inhibitory neurotransmission was blocked by 100 μM picrotoxin (Kleschevnikov *et al*., 2004). Likewise Ts65Dn dentate neurons showed an increased frequency of miniature inhibitory postsynaptic currents (mIPSCs) and a decrease in paired pulse facilitation (PPF), findings consistent with an increase in GABA release probability. In another study, 10 μM picrotoxin eliminated a deficit in theta burst stimulus (TBS) induced LTP in Ts65Dn CA1 hippocampal region (Costa and Grybko, 2005). These data suggest that an increased inhibitory tone explains the diminished LTP of Ts65Dn hippocampus. Since basal excitatory synaptic transmission measured by extracellular recording electrodes appeared normal in these studies and in all of ours, we hypothesize that compensatory mechanisms to establish normal excitatory transmission do so at the expense of plasticity mechanisms.

Genetic contributions to abnormal synaptic plasticity

The contribution of the many trisomic genes to the deficits in synaptic plasticity remain unclear, however the use of DS mouse models that contain different (e.g. smaller) trisomic segments can clarify which

genes are involved in the dysfunction. For example, the Ts1Cje mouse which contains a smaller triplicated segment than the Ts65Dn mouse (Figure 1). Studies examining the behavior of Ts1Cje mice reveal cognitive and behavioral abnormalities including low levels of locomotion, decrease in exploratory behavior, and impairment in spatial learning in the hidden platform and reverse hidden platform tasks in the Morris water maze (Sago 1998; Sago 2000). Comparisons with the Ts65Dn mouse show that, although the Ts1Cje mouse had similar spatial learning deficits, these deficits were less severe than those found in the Ts65Dn mouse (Sago 2000).

LTP and LTD in the isolated hippocampus of Ts1Cje mice are abnormal compared to diploid controls. LTP was reduced and LTD was augmented in comparison to diploid controls (Siarey *et al.*, 2005) findings that parallel data from Ts65Dn hippocampus (Siarey *et al.*, 1999). These changes are significant, but are less dramatic than were seen in Ts65Dn mice. Although the genetic backgrounds of Ts1Cje and Ts65Dn mice were similar, the two strains of mice were not produced in the same mating scheme, as was the case in Sago *et al*. (2000). Therefore, direct comparisons of the relative changes between them must be interpreted very cautiously. Behavioral studies performed on Ts65Dn and Ts1Cje littermates (derived from the same mating scheme, thus carrying identical genetic background) demonstrated abnormalities in behavior, with the degree of impairment in Ts1Cje mice being more subtle than in Ts65Dn mice (Sago *et al*., 2000).

There is currently no reported evidence to link triplication of any single gene to a specific DS feature and it is unlikely that the overexpression of a single gene is responsible for the neurophysiological impairments in DS brain. Nevertheless, alterations in the expression levels of single genes can cause significant changes in phenotype, behavior and physiology as evidenced by the multitude of knock-out (knock-in) mice and the effects of the genetic manipulations. In order to characterize the effect of individual genes within the milieu of overexpressed genes in

DS, the use of segmental trisomy mice crossed with knockout mice targeted for particular genes on the triplicated chromosomes segment would offer a strategy which can pinpoint the relationship of individual gene overexpression to those of the entire overexpressed segment. (This approach was reported in regards to the App gene in Ts65Dn mice (Cataldo *et al*., 2003)).

There are a number of genes on the extra segment of Hsa. 21 and likewise mouse Chr. 16 that may be involved in abnormal plasticity in the DS mouse models, however, we will limit our discussion to the *App*, *Sod1*, Glu_{K5} and *Girk2* genes. Amyloid precursor protein (APP) is involved in the formation of amyloid plaques in Alzheimer disease and studies investigating the effects of App on LTP produced mixed results. An increase in LTP has been shown in a mouse that harbors a double human APP mutation (Jolas *et al*., 2002); this is in contrast to a study with an APP-null mutant mouse that showed a decrease in LTP (Dawson *et al*., 1999). Interestingly the decrease in LTP in the APP-null mouse could be reversed in the absence of GABAergic inhibition (Fitzjohn *et al*., 2001).

Superoxide dismutase 1 (SOD1) is an important enzyme that regulates oxygen metabolism and levels of free radicals in the brain. Mice that overexpress SOD1 demonstrate impaired LTP and deficient spatial memory (Gahtan *et al*., 1998; Levkovitz *et al*., 1999; Thiels *et al*., 2000; Kamsler and Segal, 2003). Remarkably, blockade of $GABA_A$ activity rescued the LTP deficits similar to that seen in Ts65Dn mice (Levkovitz *et al*., 1999; Kleschevnikov *et al*., 2004; Costa and Grybko, 2005). Contrary to these reports, a more recent study found that SOD1 overexpression resulted in augmented LTP and in enhanced performance of spatial memory tasks (Spalloni *et al*., 2006).

Kainate receptors are a subtype of the excitatory glutamate receptor family. One subunit of these receptors, Glu_{K5} has been shown to be overexpressed and an increase in binding of the kainate receptor

specific ligand $[^3H]$(2S,4R)-4-methylglutamate ($[^3H]$SYM 2081, KlineBurgess *et al*., 2001; Galdzicki and Siarey, 2003) has been demonstrated in the hippocampus of the Ts65Dn mouse. Kainate receptors have been reported to be expressed by hippocampal interneurons (Mulle *et al*., 2000) and their activity increases interneuron firing rates while paradoxically reducing GABA-mediated synaptic inhibition (Christensen *et al*., 2004; Maingret *et al*., 2005). Hence it is possible that overexpression of *Gluκ5* subunits contributes to an increase in GABAergic interneuron excitability but may reduce GABAergic inhibition in the Ts65Dn mouse.

However we suggest that overexpression of App and *Gluκ5* genes alone cannot directly account for the neuroplasticity impairments in the Ts65Dn mouse, since they are not on the Ts1Cje segment (see Figure 1). The Ts1Cje mouse is trisomic for a region of Chr. 16 that incorporates all the genes in the DSCR and spans between *Sod1* and *Znf295* (zinc finger protein 295), and thus lacks triplication of *App* and *Gluκ5* genes and overexpression of these gene products (Amano *et al*., 2004; Olson *et al*., 2004). Synaptic impairments in Ts1Cje mouse should also not be attributed to Sod1 since there is a normal expression of *Sod1* in the brain of these mice (Sago *et al*., 1998; Amano *et al*., 2004). Therefore, since both the Ts65Dn and Ts1Cje mice show impaired synaptic plasticity, genes from within the common trisomic segment most likely cause the abnormal plasticity. One such gene could be *Girk2*. G-protein coupled inward rectifying potassium (GIRK) channels contribute to neuronal resting potential, excitability and firing properties. We have shown that GIRK2 protein is overexpressed ~1.5 fold in Ts65Dn hippocampus (Harashima *et al*., 2006) and is likely to be overexpressed in Ts1Cje as well. In GIRK2 knockout mice, LTP and LTD are also abnormal (Adeniji-Adele, 2004) but in the opposite direction from the DS mouse models, suggesting that the level of GIRK2 expression correlates to the level of potentiation or depression of hippocampal synapses.

Given the limited dynamic range of Schaffer-collateral/CA1 synapses (Savicc *et al*., 2003), a shift in the baseline synaptic strength could explain both a decrease in LTP and an increase in LTD for the Ts65Dn and Ts1Cje mouse models (Figure 2). The expression level of GIRK2 could effectively change the dynamic range of hippocampal synapses. Multiple G-protein coupled receptors, including the metabotropic GABAB receptor activate GIRK currents. GIRK channels have been shown to be highly expressed and constitutively active in CA1 pyramidal cell dendrites (Chen and Johnston, 2005; Koyrakh *et al*., 2005) and therefore likely to dramatically influence synaptic function when overexpressed. GABAB-mediated slow IPSCs are sufficient to inhibit NMDA receptor-mediated excitatory postsynaptic currents (EPSCs) in dentate molecular layer interneurons (Mott *et al*., 1999). These slow IPSCs also block action potentials evoked by weak but not strong depolarizations (Mott *et al*., 1999). Furthermore, overexpression and activation of GIRK channels in cultured rat hippocampal neurons resulted in hyperpolarization of 11-14 mV and depleted action potential (AP) firing by increasing AP threshold 2- to 3-fold (Ehrengruber *et al*., 1997).

Abnormal changes in dendrites, synapses and spines

Changes in dendrite and dendritic spine structure and morphology have been reported in almost all forms of mental retardation (Marin-Padilla, 1972; Ferrer and Gullotta, 1990; Wisniewski, 1990; Kamei *et al*., 1992). Within DS brain, reports indicate reduced spine number along apical dendrites of pyramidal neurons from hippocampus and cingulate gyrus (Ferrer and Gullotta, 1990). Shorter basilar dendrites, altered morphology and defective cortical layering were also found in DS infants and newborns (Takashima *et al*., 1981). Dendritic branching in DS infants (<6 mo) was reported to be greater than normal but declined with age so that by 2 years branching was significantly less than in normal children (Becker *et al*., 1986). Neuronal number may be normal during gestation but markers for dendritic spines and synapses are

significantly reduced in brains from DS fetuses (Weitzdoerfer *et al*., 2001). Cortical lamination is also delayed and disorganized in DS individuals and may indicate disruption in axonal and dendritic connectional and functional units (Golden and Hyman, 1994).

Similar dendritic malformations have been identified in Ts65Dn mice. Ts65Dn hippocampi show significantly less synapse to neuron ratio in DG, CA3 and CA1 compared to diploid controls. This deficit was shown to be predominantly due to decreases in asymmetric (presumably excitatory) synapses in all hippocampal regions (Ayberk Kurt *et al*., 2004). Likewise, the temporal cortex of Ts65Dn mice was shown to have 30% fewer asymmetric synapses but no difference in symmetric synapses (Kurt *et al*., 2000). Layer III pyramidal neurons from Ts65Dn cortex are smaller, less branched and demonstrate a marked reduction in spine density (24%) than diploid neurons (Dierssen *et al*., 2003). Deficits in spine density also have been confirmed in other brain regions including fascia dentata, motor, somatosensory and entorhinal cortices (Belichenko *et al*., 2004). Interestingly, significant increase in spine density of basal CA1 dendrites from 6 month old Ts65Dn mice compared to diploid controls (Belichenko *et al*., 2004).

Both pre- and postsynaptic elements were significantly enlarged throughout Ts65Dn brain (Belichenko *et al*., 2004). In Ts65Dn hippocampus, there was an increase in area of synaptophysin signal, a marker for presynaptic terminals, by 145%, 139% and 131% in the fascia dentata, CA3 and CA1 regions, respectively. Specifically, within the fascia dentata and layers II-III of cortex there were significant decreases in the number of smaller (0.24-2.4 μm^2) synaptophysin positive puncta and significant increases in puncta >4.8 μm^2. Postsynaptic spines were similarly enlarged to the extent that >10% were larger than 0.5 μm^2 (where no spines larger than 0.5 μm^2 were found in diploid neurons) and many showed large irregular shapes, large vacuoles and laminar bodies. No changes were identified in dendritic shaft size. Synaptic apposition zone length (zone where pre-

and post-synaptic membrane is in direct apposition) was significantly greater in asymmetric (presumably excitatory) synapses of Ts65Dn CA1 (Ayberk Kurt *et al*., 2004). There also appears to be a shift in the distribution of inhibitory synapses in Ts65Dn fascia dentata. Inhibitory contacts localized at spine heads remained unchanged, but inhibitory contacts onto dendritic shafts was decreased with a equivalent increase at spine necks by ~17% (Belichenko *et al*., 2004). In a separate trisomy mouse model, Ts2Cje (genetically matches the Ts1Cje segment), similar dendritic anomalies were identified. Decreases in spine density and enlarged dendritic spine were found in dentate granule cells compared to diploid controls (Villar *et al*., 2005). This suggests that these abnormalities are not restricted merely to the Ts65Dn mouse but may be a common feature of these mouse models. Analysis of synapse architecture in other trisomy mouse models, such as Ts1Cje and Ts1Rhr will help clarify the genetic contributions to dendritic anomalies in DS.

Genetic contributions to spine dysgenesis

Several other genes located on Chr. 21 could be involved in DS abnormalities, as many of genes on the triplicated segment play roles in neuronal activity and dendritic spine morphology (see Galdzicki and Siarey 2003). We will focus on three candidate genes Tiam1, Dscr1 and S100b.

The Rac1 specific guanine nucleotide exchange factor (GTPase), Tiam1, illustrates how disruptions in signaling could mediate abnormal synaptic morphology and plasticity. Rac1 and other GTPases modulate spine morphology and regulate actin cytoskeletal elements involved in plasticity mechanisms (Newey *et al*., 2005). Since Tiam1 activates Rac1 through its GTPase activity an overexpression of Tiam1 would raise Rac1 activity levels. Overexpression of constitutively activated Rac1 leads to enlarged spine heads (Tashiro and Yuste, 2004) and also induced the clustering of AMPA receptors and increased the amplitude of miniature EPSCs (Wiens *et al*., 2005). The NMDA receptor plays an

important role in the activity-dependent structural remodeling of dendrites by activation Tiam1 (Tolias *et al*., 2005). Tiam1 is phosphorylated by CAMKII (Fleming *et al*., 1999), a kinase crucial for spatial memory and hippocampal synaptic plasticity (Silva, 2003). Furthermore, phosphatidylinositol-3,4,5-trisphosphate binds to Tiam1 promoting Tiam1 membrane localization (Sander *et al*., 1998), hence implicating PI3K and its downstream signaling cascades. Therefore overexpression of Tiam1 in Ts65Dn mice may be important to the disruptions in synaptic plasticity mechanisms as well as contributing to the structural abnormalities in dendritic spines. Tiam1 may directly account for the increased size of spine heads seen in Ts65Dn mice and indirectly the reduction in dendritic spines. If spines are abnormally large to start with, because of too much Rac1 activation, compensatory mechanisms may reduce the number of spines. Nevertheless, Tiam1 gene is not located on the Ts1Cje segment and therefore deficits in synaptic plasticity, spine density and spine malformations cannot be a result of its overexpression in Ts1Cje (Ts2Cje) mice.

Another Chr. 21 gene, DSCR1, is implicated in disrupted neuronal functioning. A peptide fragment of DSCR1, calcipressin 1, directly binds and inhibits the phosphatase calcineurin (Chan *et al*., 2005), a protein involved in the regulation of transcription factors. The DSCR1 gene is suggested to have a role in learning defects in the Drosophila that is attributed to biochemical perturbations (Chang *et al*., 2003). The Drosophila homolog of DSCR1 specifically affects the mitochondrial functioning, in that it regulates the activity of the ADP/ATP translocator (Chang and Min, 2005). Mitochondria are localized in high density at synapses and their functioning is critical to dendritic spine formation and synaptic plasticity (Li *et al*., 2004). Thus DSCR1 may influence neuronal functioning through both mitochondrial activity and calcineurin phosphatase signaling cascades.

On human chromosome 21 there are also genes not orthologous to mouse chromosome 16 that have been suggested to contribute to DS

neurological phenotypes. Calcium-binding protein S100B (localized to mouse chromosome 10, Figure 1) have been found to exert a spectrum of neurodegenerative activities with potential impact on neuronal cytoskeleton and have been suggested to play role in DS and AD (Shapiro *et al*., 2004). New mouse models that carry triplication of fragments of mouse chromosome 10 and 17 that are orthologous to human chromosome 21 with and without Ts65Dn fragment have to be created to address their role in DS (Vacik *et al*., 2005, Yu *et al*. 2005).

Synapse dysgenesis correlated to electrophysiological data

All reports examining synaptic plasticity in Ts65Dn, Ts1Cje and Tc1 indicate that basal excitatory stimulus response is normal (Siarey *et al*., 1997; Siarey *et al*., 1999; Kleschevnikov *et al*., 2004; Costa & Grybko, 2005; O'Doherty *et al*., 2005; Siarey *et al*., 2005). This is surprising considering the abnormal spine density and increases in the size of pre- and postsynaptic elements. Compensatory changes may be involved that establish normal synaptic activity of integrated signals. The relative decreases in excitatory synapses may be compensated by redistribution of inhibitory inputs or changes in glutamatergic receptor number and/or distribution. More sensitive experiments are needed to determine whether changes in spine morphology and density correlate with changes in basal activity at the single neuron level. Failures analysis or examining spontaneous events under whole-cell recordings as Kleschevnikov *et al*., (2004), who showed there to be an increased frequency of mIPSCs in the Ts65Dn dentate gyrus, are warranted.

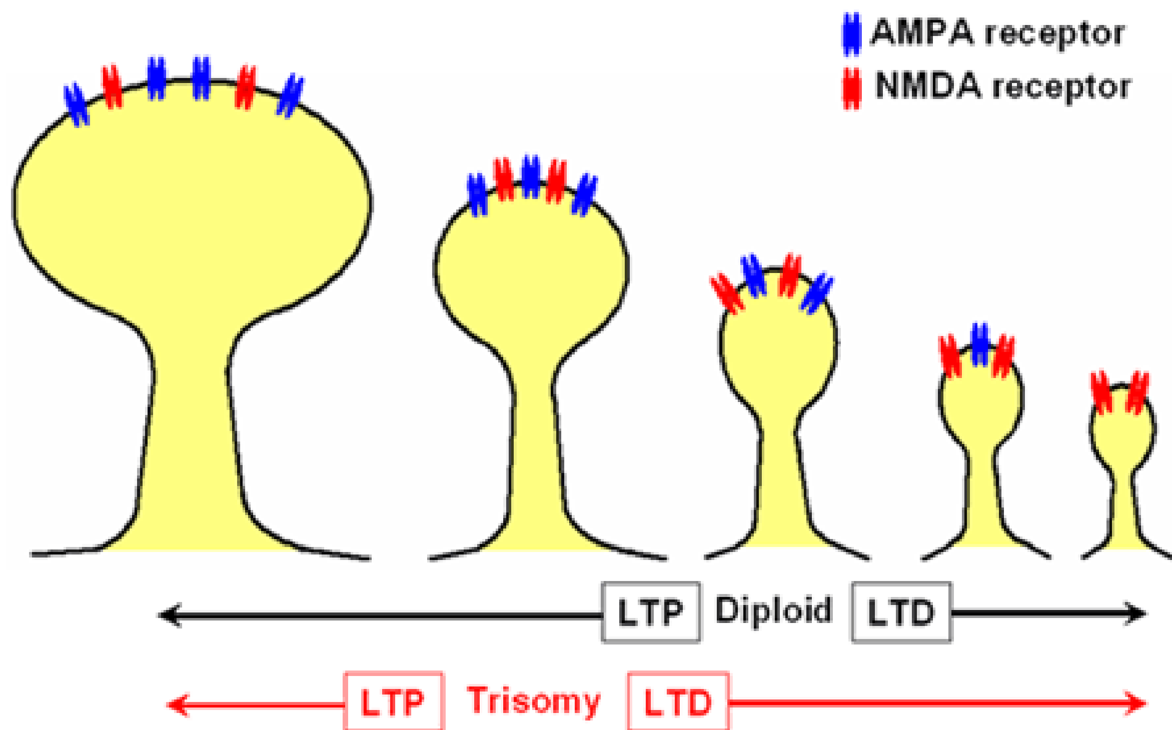

Figure 3. Hypothetical model relating dendritic spine size to probabilities of potentiation and depression of synapses. Baseline for synapses in diploid/control mice are represented as medium sized spines prior to synaptic activation by tetanus that can be enlarged (LTP) or diminished (LTD) with equal magnitude. Spines from trisomy mice are, under basal conditions, enlarged already and therefore the opportunity to undergo further enhancement is diminished. By contrast enlarged spines have an enhanced ability to undergo LTD due to the potential for greater size reduction.

The changes in synapse dysgenesis are consistent with results of synaptic plasticity paradigms. Large dendritic spines are considered less plastic and permanent fixtures of neuronal transmission, whereas smaller spines are more immature and are amenable to plastic changes. Protocols that induce LTP have been shown to correlate with formation of new spines and enlargement of existing ones (Matsuzaki *et al*., 2004). Conversely LTD has been associated with decreases in spine size of hippocampal synapses (Zhou *et al*., 2004; Tada and Sheng, 2005). As mentioned above, LTP is decreased and LTD is enhanced in Ts65Dn and Ts1Cje hippocampus. If spines from these DS mouse models are enlarged under basal condition, then such may preclude

potentiation of stimulated pathways, such that potentiation has reached plateau. Similarly the enhanced LTD may be explained in that the enlarged spine heads are better able to diminish in size compared to smaller spine heads found in diploid mice (Figure 3). This simple model does not take into account the reduction in the length of spine neck that was reported in Ts65Dn dentate gyrus neurons (Belichenko *et al.*, 2004).

Future

An important and far reaching goal in studies of DS mice is to design rational therapy that may be used to alleviate certain neurological phenotypes. Such an approach has been recently successful with a mouse model of neurofibromatosis (NF1). NF1 is a neurological disorder caused by mutations in the gene encoding neurofibromin, where increases in p21Ras activity is a key biochemical marker related to the pathophysiology in both human and mouse model (Li *et al.*, 2005). Pharmacological treatment reversed the biochemical, electrophysiological, and cognitive deficits in an adult mouse model of NF1. This provides hope that a potential treatment of cognitive impairments in people with NF1 is possible (Li *et al.*, 2005).

Although the genetic picture of DS is more complicated that NF1 and its strong developmental component creates additional challenges, a pharmacological goal to ameliorate some of the phenotypes of DS is the most important target for DS patients and their families.

Summary

The mouse models of DS provide a powerful tool to elucidate the mechanisms underlying suboptimal neural functioning in Down syndrome individuals at the neuronal level and then affecting simple and complex neuronal networks. We hypothesize that overexpression of genes from chromosome 21 shifts biological homeostasis in the Down

syndrome brain to a new less functional state. In this altered steady state, mechanisms of development, structure and plasticity malfunction due to compromises caused by the neurophysiological impact of overexpressed genes from trisomy 21.

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