

The use of mouse models to understand and improve cognitive deficits in Down syndrome

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Remarkable advances have been made in recent years towards therapeutics for cognitive impairment in individuals with Down syndrome (DS) by using mouse models. In this review, we briefly describe the phenotypes of mouse models that represent outcome targets for drug testing, the behavioral tests used to assess impairments in cognition and the known mechanisms of action of several drugs that are being used in preclinical studies or are likely to be tested in clinical trials. Overlaps in the distribution of targets and in the pathways that are affected by these diverse drugs in the trisomic brain suggest new avenues for DS research and drug development.

Introduction

Trisomy 21 (Ts21) is among the most complex genetic conditions compatible with human survival past term. Ts21 results in Down syndrome (DS), which is the most common genetic cause for cognitive impairment, occurring at a frequency of ~1 in 700 live births (Parker et al., 2010). Dosage imbalance of more than 300 genes (Hattori et al., 2000) that are present on the extra copy of chromosome 21 results in a wide range of clinical features, including hypotonia, speech and language impairment, congenital heart defects, and craniofacial dysmorphology (Delabar et al., 2006). Achieving improvements in cognitive ability that would expand the potential of people with DS to live more independently has been the goal of decades of research in the field.

Because of the inherent complexity of the genetic perturbation represented by Ts21, the availability of animal models that replicate some aspects of the condition has been pivotal to obtaining an increased understanding of the neurophysiological outcomes of trisomy. In this Perspective, we discuss the cognitive phenotypes of several mouse models, including Ts65Dn, Ts1Cje, Ts1Rhr, the recently described Ts1Yey, Ts2Yey and Ts3Yey strains, the 'triple trisomy' model (Ts1Yey;Ts2Yey;Ts3Yey) and Ts1Yah. We also describe the most widely used behavioral tests to measure cognitive traits in these models. Most, if not all, pending pharmacotherapies for DS have been tested in the Ts65Dn strain, which is often referred to as the 'Down syndrome' mouse. We discuss the mechanism of action of recently tested drugs that improve cognition in mouse models, including some that will soon enter clinical trials to test their ability to improve cognition in individuals with DS (Reeves and Garner, 2007).

Mouse models of DS

Mouse models of DS are based on conserved synteny between human chromosome 21 (Hsa21) and mouse chromosomes 16 (Mmu16), Mmu17 and Mmu10 (Pletcher et al., 2001). This relationship was revealed during the course of 20 years of mapping studies, culminating in comparative sequencing (Hattori et al., 2000; Francke et al., 1982; Lin et al., 1980; Waterston et al., 2002). A number of sequence analyses have been presented that approach a consensus in finding ~175 genes that are highly conserved between Hsa21 and the mouse genome. The maps for frequently used models are shown in Fig. 1. As depicted, the Ts65Dn, Ts1Yey, Ts1Cje and Ts1Rhr strains are trisomic for segments of Mmu16 that are homologous to Hsa21, whereas Ts2Yey and Ts3Yah strains are trisomic for Mmu10 segments that are homologous to Hsa21, and Ts3Yey and Ts1Yah strains are trisomic for segments of Mmu17. Ts65Dn is the most widely studied mouse model and recapitulates some aspects of brain morphology and behavioral phenotypes observed in people with DS (Reeves et al., 1995). Ts1Cje and Ts1Rhr strains also show impairment in learning and memory, but phenotypes in these mice (which have fewer genes in trisomy) are generally less severe than in the Ts65Dn strain (Olson et al., 2007; Belichenko et al., 2009; Sago et al., 1998). Ts3Yey and Ts1Yah strains, which have triplicated regions of Mmu17, show some learning impairment, but their brain morphology has not been characterized (Yu et al., 2010b). Ts2Yey, which contains the Mmu10 region in triplicate, does not show impairment in the learning and memory tests assessed to date (Yu et al., 2010a). However, Ts1Yey;Ts2Yey;Ts3Yey ('triple trisomy') mice do recapitulate most of the behavioral features of the Ts65Dn strain (Yu et al., 2010a). Tc1 mice are transchromosomal (have one or more chromosomes or fragments transferred from a different species; in the case of Tc1 mice, this is Hsa21) and are mosaic for Hsa21-carrying cells – that is, the human chromosome is lost in a subset of cells from all tissues. They show mild learning impairment (O'Doherty et al., 2005). All cells in the Tc1 zygote are trisomic, and the exact point in lineage when a given cell or its neighbors become euploid cannot be determined. The percent of mosaicism varies from mouse to mouse, and among tissues in the same mouse. Several recent reviews describe mouse models of DS in detail (Brault et al., 2007; Gardiner, 2010; Kahlem et al., 2004; Moore and Roper, 2007).

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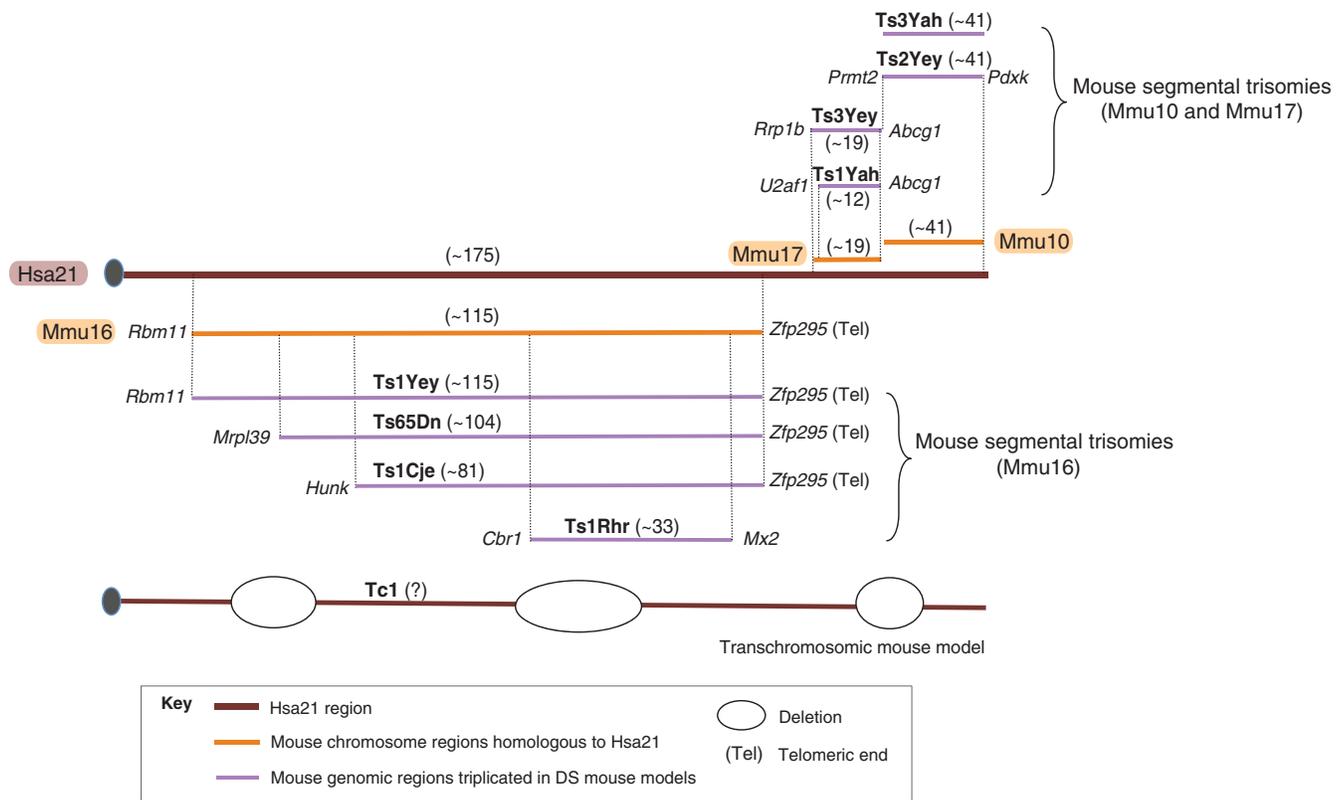


Fig. 1. Mouse models of Down syndrome (DS). Mouse orthologous regions to Hsa21 that are present on Mmu16, Mmu17 and Mmu10 are represented above and below Hsa21. The flanking genes found at the boundaries of the triplicated region in each model are depicted in italics; the approximate number of Hsa21 orthologous genes is shown in parentheses (not yet reported for the Tc1 strain). Mmu16 has the largest region of homology with Hsa21, and the Ts1Yey mouse [Dp(16Lipi-Zfp295)1Yey] contains the entire homologous region in trisomy. Ts65Dn, Ts1Cje and Ts1Rhr mice are segmental trisomies containing partial segments of Mmu16. The more recently developed segmental trisomic mouse strains Ts1Yah and Ts3Yey [Dp(17Abcg1-Rrp1b)1Yey] have three copies of the Hsa21-orthologous region of Mmu17, whereas Ts2Yey mice [Dp(10Prmt2-Pdxx)1Yey] and Ts3Yah mice duplicate the region on Mmu10. Tc1 is a transchromosomal mouse model bearing a mostly intact copy of Hsa21, producing trisomy for about 80% of the genes on that chromosome. Ts2Yey is the official alternate name for Dp(10Prmt2-Pdxx)1Yey on the MGI database, but has been referred to as Ts1Yey in print (Yu et al., 2010b). Combining the triplicated regions of Ts1Yey, Ts2Yey and Ts3Yey produces the triple trisomy model that is trisomic for all mouse orthologs of Hsa21 genes.

Strain background is an important consideration in the use of these models. Although most can be (and have been) completely inbred, the most widely used model, Ts65Dn, cannot be. Ts65Dn mice are maintained as an advanced intercross between C57BL/6 and C3H strains – that is, they have an average of 50% B6 alleles and 50% C3H alleles. One key difference is at the *Pde6b* (*rd1*) locus. C3H carries a common mutation in this gene that causes retinal degeneration in *rd1/rd1* mice, resulting in blindness by ~1 month of age (Keeler, 1924). A congenic C3H strain carrying only wild-type *Pde6b* alleles has been developed, and there is a simple molecular screen for homozygotes. Obviously, it is essential not to mix blind mice into experiments involving cognitive tests (Pittler and Baehr, 1991).

The availability of mice that are trisomic for different subsets of Hsa21-orthologous genes provides a powerful system to identify which genes contribute most to cognitive phenotypes (Lana-Elola et al., 2011). Because many of these complex phenotypes derive from the effects of multiple genes, one powerful approach is to ‘subtract’ the third copy by crossing a trisomic mouse to a genetically engineered strain that carries a null allele for the gene of interest (Salehi et al., 2006; Sussan et al., 2008) or even for a smaller

segmental monosomy (Olson et al., 2004; Olson et al., 2007), thereby returning dosage for those genes to the normal two copies in the presence of the remaining trisomy. This allows a description of genes that are necessary and/or sufficient to produce a phenotype, as opposed to attempts to claim that a single gene ‘causes’ a complex phenotype of DS (Roper and Reeves, 2006).

Aspects of brain function that map to different brain regions have been tested in these mouse models using a variety of tests. Some of the defects detected have parallels with cognitive phenotypes of DS. A common finding is the presence of impaired learning and memory. Synaptic plasticity, which is commonly measured by inducing long-term potentiation (LTP) in the hippocampus, is conventionally believed to be the physiological mechanism that underlies learning and memory. Many mouse DS models show reduced hippocampal LTP (Box 1).

Cognitive deficits in DS can be artificially conceptualized into those that are a product of development that result in functional, learning and memory deficits from birth, and those that are a function of age-related degenerative processes. The latter are accelerated in people with DS compared with the general population, especially the formation of the histopathological

Box 1. Electrophysiological measurements in the trisomic hippocampus

Synaptic plasticity is the physiological response to neural activity, measured as changes in synaptic efficacy and excitability between presynaptic and postsynaptic neurons. Changes in synaptic strength can be triggered in vitro in brain slices with appropriate electrical stimulation of presynaptic neurons, which is converted to detectable electrophysiological or potentiation changes in postsynaptic neurons. Enhancement in potentiation that persists for long periods of time is called long-term potentiation (LTP) and can last for several minutes in a brain slice. Conversely, a persistent decrease in potentiation, or depression, is called long-term depression (LTD) (Martin et al., 2000; Neves et al., 2008). Most forms of LTP and LTD are glutamatergic and involve the activation of postsynaptic N-methyl-D-aspartate (NMDA) channels, but NMDA-independent mechanisms are also known (Katsuki et al., 1991; MacDonald et al., 2006).

LTP and LTD are thought to be the physiological basis for learning and memory. They conform to Hebbian rules – that is, the strength of the connection between pre- and post-synaptic neurons depends on their levels of activity. Synaptic connections can strengthen (when LTP is stimulated) or weaken (when LTD occurs) when the same type of stimulation is repeated; in other words, the synaptic connection recapitulates the original response following a particular stimulus (Hebb et al., 1994). The exact role of these conditions in learning or memory is a subject of ongoing investigation (Neves et al., 2008).

Given their proposed role in learning and memory, hippocampal LTP and LTD have been measured in many mouse models of DS, with contradictory findings by different groups. The method used to stimulate LTP gives variable results in trisomic mice, so equating the changes is not always justified (Costa and Grybko, 2005). LTP stimulation by theta burst stimulation (TBS) has been shown to be deficient in hippocampal slices from Ts65Dn mice, whereas there are contradictory reports about the results using high frequency stimulation (HFS). For example, Costa and Grybko did not find a deficit in LTP using HFS (Costa and Grybko, 2005), whereas others have reported a deficit using the technique (Siarey et al., 1999). The table below summarizes electrophysiological findings in the hippocampal regions of mouse models of DS. ↓, reduced; ↑, increased; ↔, similar, compared with euploid controls; ND, not determined.

Mouse model	LTP			LTD
	CA1	CA3	DG	CA1
Ts65Dn	↓ (Siarey et al., 1997)	↔ (Hanson et al., 2007) ^a	↓ (Kleschevnikov et al., 2004)	↑ (Siarey et al., 1999)
Ts1Cje	↓ (Siarey et al., 2005)	ND	↓ (Belichenko et al., 2007)	ND
Ts1Rhr	↔ (Olson et al., 2007)	ND	↓ (Belichenko et al., 2009)	ND
Ts1Yey	↓ (Yu et al., 2010a)	ND	ND	ND
Ts2Yey	↔ (Yu et al., 2010a)	ND	ND	ND
Ts3Yey	↑ (Yu et al., 2010a)	ND	ND	ND
Ts1Yey;Ts2Yey;Ts3Yey	↓ (Yu et al., 2010b)	ND	ND	ND
Ts1Yah	↑ (Pereira et al., 2009)	ND	ND	ND

^aThe study by Hanson et al. (Hanson et al., 2007) reported a significant impairment in excitatory and inhibitory synaptic transmission in the CA3 region of Ts65Dn mice.

stigmata of Alzheimer's disease (AD). Neurofibrillary tangles and plaques are evident in essentially every person with DS by the fourth decade of life, although a substantial fraction of people do not show a corresponding cognitive decline. In this review, we concentrate primarily on the changes that are evident early in life.

Behavioral tests

Behavioral tests can be used to assess defects in the function of specific brain regions, given their attributed roles in performing certain types of tasks (Table 1). Spatial and recognition learning and memory have been the most widely assessed in trisomic mice, using a variety of tasks that have differences in the degree of aversiveness. These tests have helped to define the brain regions that are especially affected in Ts65Dn mice and other models of DS, and in some cases have been successfully translated into behavioral tests that can be performed on people with DS. For example, behavioral tests in Ts65Dn mice originally pointed to deficits in hippocampal function that were subsequently implicated in children with DS (Edgin et al., 2010; Moran et al., 1996; Pennington et al., 2003; Reeves et al., 1995). Such tests can also be used to assess the efficacy of candidate drugs for DS (see later). Several important behavioral tests are described below.

Novel object recognition or object-in-place (context) test

The novel object recognition task (NORT) is a non-aversive test, meaning that it is not associated with a punishment for failing nor conducted under stress-inducing conditions. NORT is based on

the innate tendency of rodents to prefer exploring novel objects over familiar ones. Mice are initially given an opportunity to habituate to an open arena, which later contains the objects that they are expected to explore. Habituation reduces the novelty of the arena compared with the objects. Mice are presented with two objects and allowed to explore for a short time. 24 hours later, one of the two familiar objects is replaced with a new object and the mice are again allowed to explore them. Normal mice tend to spend more time exploring a novel object compared with a familiar object, but mice with impaired recognition memory cannot discriminate between the two. Normal mice also remember if a familiar object has been moved to new position, which can be tested using the object-in-place test (Fernandez et al., 2007).

Ts65Dn and Ts1Rhr mice show impaired NORT performance in multiple versions of the test, whereas Ts1Cje mice can discriminate novel objects from familiar ones (Fernandez et al., 2007) (Table 1). These results are not readily explained by the genes that are triplicated in each model: Ts1Cje mice are trisomic for 80% of the genes in Ts65Dn mice and all genes in Ts1Rhr mice, yet Ts1Cje mice show no deficit in NORT. Ts1Yah mice, which have only 12 Hsa21 orthologous genes in triplicate, are impaired in NORT (Pereira et al., 2009). Tc1 mice, by contrast, are similar to euploid controls in the standard NORT paradigm (Morice et al., 2008).

Object recognition has been attributed to the dentate gyrus (DG) and to the CA1-CA3 regions of the hippocampus (Fernandez et al., 2007). However, the role of the hippocampus in recognition memory

Table 1. Behavioral tasks used on mouse models of DS, indicating brain regions involved in the learning and memory of each task

Behavioral task	Brain regions associated with task	DS mouse models tested in task	
		Impaired	Normal
Novel object recognition test (NORT)	Perirhinal cortex, postrhinal cortex, medial prefrontal cortex, hippocampus, insular cortex	Ts65Dn (Fernandez et al., 2007); Ts1Rhr (Belichenko et al., 2009); Ts1Yah (Pereira et al., 2009)	Ts65Dn (Hyde and Crnic, 2002); Tc1 (long-term) (O'Doherty et al., 2005); Ts1Cje (Fernandez et al., 2007)
Object-in-place (context) test	Hippocampus, medial prefrontal cortex, perirhinal cortex, postrhinal cortex	–	Ts1Cje (Fernandez and Garner, 2007); Ts65Dn (Fernandez and Garner, 2008)
Spontaneous alternation test	Hippocampus, septum, mammillary bodies (hypothalamus), thalamus, prefrontal cortex, vestibular system, cerebellum, raphe nuclei, striatum (caudate nucleus)	Ts65Dn (Fernandez et al., 2007); Ts1Cje (Belichenko et al., 2007); Ts1Rhr (Belichenko et al., 2009); Ts1Yah (Pereira et al., 2009)	Ts65Dn (Demas et al., 1996); Tc1 (O'Doherty et al., 2005)
Morris water maze (MWM) – cued or visible platform test	Superior colliculus, basal ganglia, striatum, parietal cortex	Ts65Dn (Reeves et al., 1995; Netzer et al., 2010)	Ts65Dn (Escorihuela et al., 1998; Sago et al., 2000); Ts1Cje (Sago et al., 1998); Ts1Rhr (Olson et al., 2007); Tc1 (Morice et al., 2008); Ts1Yey (Yu et al., 2010a); Ts2Yey (Yu et al., 2010a); Ts3Yey (Yu et al., 2010a); Ts1Yey;Ts2Yey;Ts3Yey (Yu et al., 2010b); Ts1Yah (Pereira et al., 2009)
Morris water maze (MWM) – hidden platform test	Hippocampus, locus coeruleus (pontine nuclei), thalamus, striatum, septum, entorhinal cortex, subicular complex, posterior parietal cortex, posterior cingulate cortex, fimbria and fornix	Ts65Dn (Reeves et al., 1995; Sago et al., 2000); Ts1Cje (Sago et al., 1998); Ts1Yey (Yu et al., 2010a); Ts1Yey;Ts2Yey;Ts3Yey (Yu et al., 2010b)	Ts1Rhr (Olson et al., 2007); Tc1 (Morice et al., 2008); Ts1Yah (Pereira et al., 2009); Ts2Yey (Yu et al., 2010a); Ts3Yey (Yu et al., 2010a)
Acoustic or tone conditioning	Amygdala, perirhinal and entorhinal cortex, cerebellum, thalamus	–	Ts65Dn (Salehi et al., 2009)
Contextual fear conditioning	Amygdala, hippocampus, subicular complex, perirhinal cortex, entorhinal cortex, nucleus accumbens, insular cortex, locus coeruleus, cerebellum	Ts65Dn (Costa et al., 2008; Salehi et al., 2009); Ts1Yey (Yu et al., 2010a); Ts1Yey;Ts2Yey;Ts3Yey (Yu et al., 2010b)	Ts2Yey (Yu et al., 2010a); Ts3Yey (Yu et al., 2010a)

is controversial, and it is thought that the role of the hippocampus is in learning the context in which the objects are placed. This suggests that the hippocampus is necessary for a 'what-where-when' scenario or the object-in-place task, but not for NORT (Balderas et al., 2008). Interestingly, Ts65Dn mice perform normally in the object-in-place task (Fernandez and Garner, 2008). Furthermore, an earlier report using 10- to 12-month-old Ts65Dn mice found them to be normal in the object-in-place task and NORT (Hyde and Crnic, 2002). Perirhinal and insular cortices located in the temporal lobe and cerebral cortex of the brain, respectively, might make important contributions to NORT deficits in Ts65Dn mice for which the underlying mechanisms remain to be elucidated (Bermudez-Rattoni et al., 2005; Winters and Bussey, 2005).

Spontaneous alternation

Spontaneous alternation assesses a form of short-term working memory. In this test, mice are allowed to explore a T-shaped or Y-shaped maze. As in NORT, there are many variations of this test, and different variations might emphasize function of different brain regions. Also similar to NORT, free exploration versions of the test are based on the innate tendency of rodents to explore novelty, by visiting a different arm of the maze than the one just visited. Outcomes are measured as the percentage of times the mouse chooses to enter a different arm than the one it recently visited (alternations), divided by the possible number of alternations it could have made in the task. Among mouse models of DS, Ts65Dn, Ts1Cje, Ts1Rhr and Ts1Yah strains are most impaired, showing lower spontaneous alternation (50-60%) compared with control euploid mice (70-80%) (Belichenko et al., 2007; Fernandez et al., 2007; Pereira et al., 2009). Tc1 transchromosomal mice show comparable rates of alternation to euploid control mice (O'Doherty et al., 2005).

Morris water maze

Experiments involving some variation of the Morris water maze (MWM) test have been the most frequently used behavioral assessments of learning and memory in Ts65Dn mice. Significant differences in the performance of Ts65Dn mice compared with euploids in the MWM have been reported many times by many laboratories, lending credence to the conclusion that the mice are truly impaired.

The test is performed in a circular water tank of 90-150 cm in diameter, filled with water that has been made opaque by adding milk or non-toxic white paint. A transparent platform is submerged ~2 cm below the water surface. A cued (visible) platform task, where mice learn to find the platform with a visible cue (such as a flag), is usually carried out as a control experiment to rule out factors that might affect results for reasons not involving visuospatial integration. The cued platform task can be solved by combining praxic and taxic strategies, for which mice learn a sequence of movements in response to a stimulus or a proximal cue (Fraenkel and Gunn, 1961). In the next phase (the hidden-platform task), the platform is not visibly tagged, and a complex spatial mapping strategy or locale strategy must be learned to find the platform (Morris, 1981; Redish and Touretzky, 1998). This requires the use of extra- and intra-maze cues to define the coordinates of the platform, the position of which is kept constant, while the starting position of the mice is changed in each trial to reduce taxic and/or praxic learning (Vorhees and Williams, 2006). Learning is evaluated using the latency time to find the platform, path length and/or type of trajectories (Morris, 1981; Petrosini et al., 1998; Vorhees and Williams, 2006).

A probe trial, in which the platform is removed and mice are allowed to explore the water maze for 1-3 minutes, is generally carried out a day after the last hidden-platform session. Normal mice spend a higher percentage of time in the quadrant that

formerly contained the platform (Vorhees and Williams, 2006), compared with mice that have impaired learning and memory.

Most contemporary reports concur that trisomic mice are similar to euploid mice in the cued task (Bimonte-Nelson et al., 2003; Escorihuela et al., 1998; Rueda et al., 2008; Sago et al., 2000), but Ts65Dn, Ts1Cje and Ts1Yey mice show impaired learning and memory in the hidden-platform task (Table 1) (Li et al., 2007; Reeves et al., 1995; Sago et al., 1998). Ts1Rhr mice do not show impairment in the MWM in either cued or hidden-platform tasks (Olson et al., 2007). Mice in which all Hsa21 orthologous genes are trisomic (i.e. 'triple trisomy' mice) show impaired performance in the MWM (Yu et al., 2010a), but trisomy for only the Mmu10 or Mmu17 segments (Fig. 1) does not result in impairment in this task. In fact, Ts1Yah mice performed better in the hidden platform task than their euploid littermates (Pereira et al., 2009; Yu et al., 2010b). Surprisingly, Tc1 transchromosomal mice were also reported to do as well as euploid controls in a standard MWM paradigm (Morice et al., 2008). However, as mentioned earlier, the human transchromosome is lost in a substantial fraction of cells in Tc1 mice, and half or more euploid neurons might provide compensation for impairments in trisomic neurons (O'Doherty et al., 2005).

Stasko and Costa found that increasing stress causes deterioration in the performance of Ts65Dn mice in the MWM (Stasko and Costa, 2004). Differences in MWM results have been reported between sexes as well. In this regard, it is interesting to note that environmental enrichment, where mice are housed with toys and running wheels etc., has been shown to improve learning in female but not male Ts65Dn mice (Martinez-Cue et al., 2002).

Fear conditioning

In fear conditioning, a conditioned stimulus (CS) such as a tone and/or context is paired with an unconditioned stimulus (US), such as an electric shock that naturally generates a freezing response (i.e. fearful behavior). The CS can then induce a freezing response in the absence of the US, because normal mice remember and associate the two stimuli (Phillips and LeDoux, 1992; Wehner and Radcliffe, 2004). In this test, mice are habituated in a chamber for 3-5 minutes before being exposed to a tone, at the end of which they receive a mild foot shock (the US). A day later, the mice are tested separately for tone conditioning, in a different chamber (novel context) and exposed to the tone without receiving the shock. The following day, the mice are tested for contextual conditioning by being reintroduced to the initial chamber (conditioned context) and being exposed to the tone, again without receiving the shock. The freezing response on hearing the tone is evaluated in both the novel and conditioned context (Salehi et al., 2009). Both the tone and the context form components of the CS, but the association of each one with the US relies on different regions of the brain (Table 1). Acoustic (tone) fear conditioning is primarily dependent on the amygdala, with a lesser contribution by perirhinal, entorhinal and postrhinal cortices, and the thalamus (Campeau and Davis, 1995; Goosens and Maren, 2001; Kholodar-Smith et al., 2008). It has been proposed that the hippocampus has a more pronounced role in contextual discrimination, with important input from the cerebellum (Anagnostaras et al., 2001; Biedenkapp and Rudy, 2009; Sacchetti et al., 2002). However, the precise role of the

hippocampus in fear conditioning is unresolved (Frankland et al., 1998).

Ts1Yey, Ts65Dn and triple trisomy mice (Ts1Yey;Ts2Yey;Ts3Yey) all show a reduced freezing response when reintroduced to the conditioned context compared with euploid littermates (Table 1) (Hyde and Crnic, 2001; Salehi et al., 2009; Yu et al., 2010a; Yu et al., 2010b). The Mmu10 and Mmu17 segmental trisomies, Ts2Yey and Ts3Yey, each show a normal response (Yu et al., 2010b). Ts65Dn mice do remember the association between the tone and the shock, and show a normal freezing response to acoustic conditioning (Salehi et al., 2009; Turner et al., 2001). This indicates that the amygdala function of pairing acoustic CS to the US is intact in Ts65Dn mice, whereas the function of pairing contextual CS to the US is not. However, whether the latter is a result of dysfunction in one or all of the brain regions – such as the hippocampus, entorhinal and perirhinal cortices, etc. – involved in the task is unclear from the present data (see Table 1).

Candidate drugs for DS

The identification of brain regions affected by trisomy in mice has been instrumental in the development of pharmacological approaches to correct underlying imbalances that disrupt cognitive functions in DS. In cases in which candidate drugs improve performance in the tests described above, mouse models provide the opportunity to assess physiological, molecular and structural changes that result from the treatment. In this way, mouse models remain a fundamental tool to rationalize the basis for treatment in humans. Indeed, essentially every proposed treatment for people has developed from results in Ts65Dn mice using the tasks described above. In this section, we review studies that have shed light on drug candidates for DS, discussing those that have effects on brain physiology, biochemistry and morphology, and briefly mention the drugs that will soon advance into clinical trials.

Drugs that influence synaptic plasticity

Several drugs have been tested on the basis of their remedial effects on synaptic plasticity, assessed by correction in LTP (Table 2). LTP is reduced in the CA1 and DG in hippocampal slices from Ts65Dn mice (Box 1). A key finding in this area was the demonstration that this reduced LTP occurred in part owing to an imbalance between excitatory and inhibitory inputs to the hippocampus. The balance could be returned to normal by the addition of drugs that inhibit γ -aminobutyric acid A (GABA_A) receptors (which respond to the inhibitory neurotransmitter GABA) in both Ts65Dn and Ts1Cje mice (Belichenko et al., 2007; Hanson et al., 2007; Kleschevnikov et al., 2004). On the basis of these observations, drugs that inhibit GABA_A receptors were tested for their ability to improve cognition. Picrotoxin (PTX) and pentylentetrazol (PTZ) are antagonists that bind non-competitively to these receptors. In one study, Ts65Dn mice were treated for ~2 weeks before cognitive testing in a modified NORT paradigm (Fernandez et al., 2007). Treatment with either PTX or PTZ completely reversed the NORT deficit observed in untreated Ts65Dn mice (Fernandez et al., 2007), and was subsequently demonstrated to overcome learning and memory deficits observed in the MWM test as well (Rueda et al., 2008). Remarkably, some cognitive improvement and even improved LTP was demonstrable for more than 2 months after the treatment

Table 2. Overview of drugs tested for improving cognition, their biological targets and the behavioral tasks used to assess drug efficacy in Ts65Dn mice

Drug	Biological target and drug action	Target distribution in the brain	In vivo studies			Results and cognitive tests conducted after treatment (Ts65Dn)
			Reference	Dose	Regimen	
DAPT	Inhibits γ -secretase	Hippocampus (CA1-3, DG), parietal cortex, olfactory nuclei, amygdala, basal ganglia, superior and inferior colliculi, striatum, thalamus, hypothalamus, cerebellum (Siman and Salidas, 2004)	Netzer et al., 2010	3 mg/kg (total)	S.c. injections, twice daily for 15 days; age: 4 months (females)	Improvement: MWM (hidden and visible platform)
Fluoxetine	Upregulates serotonin receptor 5HT1A (Bianchi et al., 2010); increases neurogenesis (Malberg et al., 2000); inhibits KCNJ6 current (Kobayashi et al., 2003)	Hippocampus (DG) (neurogenesis) (Malberg et al., 2000)	Bianchi et al., 2010	5 mg/kg	Daily s.c. injection from P3-P15; age: P43 (males and females)	Improvement: contextual fear conditioning; seen 28 days after stopping treatment; no effect in MWM (Moran et al., 2002)
L-DOPS with carbidopa	Adrenergic receptors in the brain; converted to norepinephrine	Whole brain: cerebral cortex (EC, PRH), CA1-CA3, DG, cerebellum, thalamus, raphe nuclei, amygdala, olfactory bulb, inferior olivary nucleus, striatum, subiculum (Duncan et al., 1991)	Salehi et al., 2009	L-DOPS 1 mg/g with carbidopa 0.125 mg/g	S.c. injection 5 hours before testing each day for 3 days; age: 4-6 months	Improvement: contextual fear conditioning; benefits disappear 2 weeks after termination of treatment
Memantine	NMDA open channel antagonist (Johnson and Kotermanski, 2006); reduces oxidative damage (Dias et al., 2007); upregulates BDNF (Marvanova et al., 2001); non-competitive inhibitor of serotonin receptor 5HT ₃ (Rammes et al., 2001)	Whole brain (Wenzel et al., 1997)	Costa et al., 2008	5 mg/kg	Two regimens tested: (1) dosed on day 1 and 2 of testing, 15 minutes prior to testing, i.p.; age: 4-6 months and 10-14 months. (2) Dosed on day 1 or day 2, 15 minutes prior to testing; age: 4-6 months	Improvement: contextual fear conditioning
			Lockrow et al., 2010	20 mg/kg or 10 mg/kg	Two regimens tested: (1) long-term treatment: started at 4 months of age, continued for 6 months, daily p.o. of 20 mg/kg. (2) Short-term treatment: day 1 and day 2 of NORT, 30 minutes prior to testing, i.p. 10 mg/kg; age: 8 months	Improvement: novel object recognition, radial arm maze; attributed to acute treatment, not long-term treatment
			Rueda et al., 2010	30 mg/kg	9 weeks, p.o.; aged Ts65Dn mice	Improvement: MWM
Pentylenetetrazol (PTZ)	Non-competitive inhibitor of GABA _A receptor	Whole brain: supramammillary nucleus, cerebral cortex layers I-VI (EC, PRH), hippocampus (CA1-CA3, DG), cerebellum (ML, GCL, Purkinje cells and cerebellar nuclei), thalamus, subiculum, striatum, basal forebrain etc. (Walsh et al., 1999)	Fernandez et al., 2007	3 mg/kg	17 days, p.o.; age: 3-4 months	Improvement: novel object recognition and spontaneous alternation; improvement lasts 2 months after termination of treatment
			Rueda et al., 2008	3 mg/kg	7 weeks p.o.; started 4 weeks before the testing and continued for 3 weeks of testing; age: 4 months	Improvement: MWM (no probe trial); short term spatial memory
Picrotoxin (PTX)	Non-competitive inhibitor of GABA _A receptor	Whole brain: supramammillary nucleus, cerebral cortex layers I-VI (EC, PRH), hippocampus (CA1-CA3, DG), cerebellum (ML, GCL, Purkinje cells and cerebellar nuclei), thalamus, subiculum, striatum, basal forebrain etc. (Walsh et al., 1999)	Fernandez et al., 2007	1 mg/kg	4 weeks cross longitudinal, i.p.; age: 3-4 months	Improvement: novel object recognition; improvement lasts at least 2 weeks after stopping treatment
SAG 1.1	Activates sonic hedgehog pathway	Cerebellum, hippocampus (DG) (Frank-Kamenetsky et al., 2002)	Roper et al., 2006	20 μ g/g	P0, single s.c. injection	Complete restoration of cerebellar morphology
Xamoterol	β_1 -receptor-specific agonist	Whole brain: cerebral cortex, hippocampus, cerebellum, thalamus, striatum, subiculum, etc. (Palacios and Kuhar, 1982)	Salehi et al., 2009	3 mg/kg	S.c. injection 5 hours before testing each day for 3 days; age: 4-6 months	Improvement: contextual fear conditioning

EC, entorhinal cortex; DM, dentate gyrus; GCL, granule cell layer; i.p., intraperitoneal; ML, molecular layer; PRH, perirhinal cortex; p.o., by mouth; s.c. subcutaneous.

was stopped (Fernandez et al., 2007). Several compounds that inhibit GABA_A receptors are being developed for clinical trials.

Memantine is an open-channel antagonist of N-methyl D-aspartate (NMDA) receptors (Table 2) (Chen and Lipton, 2005) that has been reported to alleviate some of the symptoms of AD (Ferris, 2003). Ts65Dn mice show some sequelae of AD, including degeneration of forebrain cholinergic neurons and degeneration of norepinephrine (NE) inputs to hippocampus from locus coeruleus (LC) (Casanova et al., 1985; Salehi et al., 2006; Salehi et al., 2009; Weinshenker, 2008). Several groups have tested the efficacy of memantine in improving cognition in young adult Ts65Dn mice. Acute treatment prior to behavioral testing can improve learning in contextual fear conditioning (Costa et al., 2008) and NORT (Lockrow et al., 2010). However, Lockrow et al. reported that acute treatment on the day of testing is required even after long-term dosing (Table 2). Although known to be neuroprotective, memantine does not seem to protect against the age-related neurodegeneration in the basal forebrain and LC in Ts65Dn mice; however, treatment led to increased production of brain-derived neurotrophic factor (BDNF), as reported previously (Lockrow et al., 2010; Marvanova et al., 2001; Salehi et al., 2009). Extended treatment of aged mice with memantine improved their performance in the MWM, but whether acute treatment influences performance in this behavioral task has not been tested (Rueda et al., 2010).

Drugs that act on brain biochemistry

Humans with DS exhibit age-related neurodegeneration in many regions of the brain, including the LC and the basal forebrain (Casanova et al., 1985; Mann et al., 1985; Schochet et al., 1973). This results in a deficiency of important neurotransmitters such as NE and acetylcholine (ACh). Additionally, the increase in the expression of amyloid precursor protein (APP), which is present in three copies in both humans with DS and in Ts65Dn mice, causes a concomitant increase in APP-derived amyloid- β (A β) peptides, which form the most important component of amyloid plaques in AD (Dalakas et al., 1984; Glenner and Wong, 1984). A β might contribute to cognitive decline in DS by inducing synaptic depression in neurons that overexpress APP (i.e. all neurons in Ts65Dn mice) (Kamenetz et al., 2003) or oxidative-stress-induced neurotoxicity (Butterfield, 2002). Similarly to mouse models of AD, age-related degeneration of the LC and reduction of NE levels is seen in Ts65Dn mice, along with increased production of APP (Netzer et al., 2010; Salehi et al., 2009). However, Ts65Dn mice do not show neuritic plaques and neurofibrillary tangles (Reeves et al., 1995). Drug candidates that rescue NE deficiency or that target increased levels of APP have shown promising results in mouse models of DS.

L-threo-dihydroxyphenylserine (L-DOPS) corrects the deficiency in the production of NE in Ts65Dn mice (Table 2) (Salehi et al., 2009). L-DOPS is converted to NE by the enzyme aromatic L-amino acid decarboxylase (AAAD). Treatment with L-DOPS, when administered together with carbidopa, an inhibitor of peripheral AAAD activity that cannot cross the blood brain barrier, restores learning and memory in contextual fear conditioning tests in Ts65Dn mice. This improvement in cognition has been attributed to corrected NE-modulated adrenergic activation in the hippocampus; however, the enzyme AAAD is present in many brain regions in which the NE activity could affect cognition. Also, the

LC is the source of NE for many other brain regions, including the cerebellum and the neocortex, which might also contribute to improved cognition in the presence of L-DOPS (Loughlin et al., 1986). A second drug that targets NE deficiency, xamoterol, specifically activates β_1 adrenergic receptors (although NE activates all types of adrenergic receptors). Treatment with xamoterol also improves learning and memory in contextual fear conditioning in Ts65Dn mice (Salehi et al., 2009).

N-[(3, Difluorophenyl)acetyl]-L-alanyl-2-phenylglycine-1,1-dimethylethyl ester (DAPT) is an inhibitor of γ -secretase, the enzyme that cleaves APP (an important step in generating A β peptides). DAPT can reduce the production of A β peptides from APP in mice (Dovey et al., 2001). Treatment with DAPT reduces levels of A β peptides 40 and 42 in Ts65Dn mice, as well as reducing the amount of C-terminal fragments of APP. In line with the theory that increased levels of A β peptides contribute to cognitive decline in DS (Kamenetz et al., 2003), DAPT treatment also normalizes learning and memory in the MWM in female Ts65Dn mice (Netzer et al., 2010).

Degeneration of basal forebrain cholinergic neurons (BFCNs) has been also found in Ts65Dn mice (Holtzman et al., 1996), which is correlated with deficient ACh release in the hippocampus during spontaneous alternation testing (Chang and Gold, 2008). To compensate for reduced ACh levels, mice were treated with physostigmine, an inhibitor of acetylcholine esterase that breaks down ACh. Acute treatment with physostigmine (50 μ g/kg) 10 minutes prior to testing reverses deficits in 4-month-old Ts65Dn mice, but not in 10-month-old mice (Chang and Gold, 2008). This drug has not been tested for long-term effects or in other behavioral tasks.

Drugs that affect brain morphology

Parallels between the morphology of the trisomic brain in humans with DS and Ts65Dn mice include reduced cell number and volume in the hippocampal DG (Lorenzi and Reeves, 2006) and the notable decrease in overall size of the cerebellum along with a reduction in the number and density of its granule cell neurons (Baxter et al., 2000). As mentioned earlier, the number and size of BFCNs is also reduced in Ts65Dn mice (Holtzman et al., 1996). A final group of potential drugs consists of those that have effects on these morphological characteristics of the trisomic brain, usually by stimulating proliferation of neuronal populations that are depauperate. Fluoxetine (Prozac), injected daily from postnatal day 3 (P3) to P15, was shown to increase neurogenesis in the DG of male and female Ts65Dn mice by P15 (Bianchi et al., 2010). 28 days after stopping the treatment, providing time for the newly generated neurons to become incorporated in the circuitry, the treated mice showed improvement in contextual fear conditioning. Other molecular markers in the hippocampus that are known to be abnormal in Ts65Dn mice, such as the 5-hydroxytryptamine 1A (5HT1A) receptors, were also normalized to euploid levels following this treatment (Bianchi et al., 2010).

The cerebellum is smaller in Ts65Dn mice compared with euploid mice, reflecting observations in humans with DS. In Ts65Dn mice, a single dose of a sonic hedgehog agonist SAG 1.1 on the day of birth normalized the cerebellar volume and the deficit in granule cell number to the level observed in euploid littermate controls by P6 (Roper et al., 2006). We have found that the

corrections mediated by SAG 1.1 persist into adulthood; however, we did not find any change in neuronal number in the DG following SAG treatment (I.D. and R.H.R., unpublished results).

Finally, the levels of nerve growth factor (NGF) in Ts65Dn mice were reduced in the medial septal region, which contains the BFCNs, because of a deficiency in retrograde transport of NGF to this region from the hippocampus (which is one of the sites of production). As a way to reverse or reduce the degeneration of BFCNs, NGF was administered intracerebroventricularly. This treatment reversed abnormalities in BFCN size and number as well as in cholinergic innervation (Cooper et al., 2001). However, behavioral effects of such a treatment have not yet been demonstrated.

Drugs that are likely to enter clinical trials

Several pharmaceuticals, including PTZ, L-DOPS and memantine, are in or will soon be in clinical trials to test their ability to improve cognition in people with DS. Some of these are true double-blinded placebo-controlled cross-over trials with sufficient numbers of participants to provide the statistical power to draw conclusions about efficacy. Others are pilot studies that should give an indication of efficacy to encourage the initiation of a fully powered trial. Notably, memantine has been approved by the European Union and by the U.S. Food and Drug Administration for the treatment of AD, and is the subject of a pilot study for DS currently (<http://clinicaltrials.gov/ct2/results?term=costa+and+down+syndrome>). If it is found to be safe in the DS population, it can be expected that memantine will be a prescribed drug for DS in the near future.

Perspective

Understanding the bases for differences in cognitive impairment among different mouse models of DS will guide mechanism-based drug design. These models can be assessed using behavioral tests to detect specific deficits that implicate specific brain regions that should be tested in humans. There is a clear correlation between the number of genes that are orthologous to Hsa21 and the degree of behavioral abnormalities observed in mouse models (Table 1). For example, Ts1Cje mice are less affected than Ts65Dn mice, in that Ts1Cje mice have normal recognition memory and seem to be better at spatial tasks (Fernandez and Garner, 2007; Sago et al., 2000). However, these differences in behavior are related to specific genes: Ts1Rhr mice have impaired object recognition but normal spatial learning and memory, despite the fact that they are trisomic for about half the genes that are triplicated in Ts1Cje mice (Belichenko et al., 2009; Olson et al., 2007). Tc1 transchromosomal mice, which are trisomic for the majority of human genes from Hsa21, show normal spatial and recognition learning and memory, and are therefore dissimilar to Ts65Dn mice or to triple trisomy mice (Morice et al., 2008; O'Doherty et al., 2005; Yu et al., 2010a). Overall, it is important to note that the strength of these studies is not to compare human and mouse behavior, but to map affected brain regions by comparable trisomy in the two species.

Different subregions of the hippocampus have been attributed specific roles in different forms of spatial learning (Kesner et al., 2004; McHugh et al., 2007; Tsien et al., 1996). The normal performance of Ts65Dn mice in the object-in-place task demonstrates that some form of hippocampal function is intact in these mice (Fernandez and Garner, 2008). The behavioral

phenotype of Ts1Yah mice is interesting because they perform normally in the complicated MWM task but are impaired in NORT, both of which require hippocampal contribution (Pereira et al., 2009). However, all of these tasks depend to some extent on multiple brain regions, and therefore the contribution of the hippocampus cannot be completely segregated from that of other regions in the final outcome. Therefore, regions such as the entorhinal and perirhinal cortices, the striatum and the cerebellum need to be studied in further detail to determine their contribution to the learning deficits in trisomy.

Basic research in this field is being translated into rational pharmacotherapies that aim to facilitate cognitive processes and expand life opportunities for people with DS. Although the known targets of the different classes of drugs discussed here are expressed in different regions of the trisomic brain, it is possible that different drugs act on some of the same pathways of learning, owing to interactions between target pathways. For example, PTZ, which binds non-competitively to GABA_A receptors, can induce seizures in NE-deficient mice because NE normally modifies the activity of GABA_A receptors through specific interactions. This indicates that GABA and NE activities have some form of feedback regulation whereby the deficiency of one can be compensated to some extent by the other. Indeed, NE-deficient mice do not normally have seizures but display seizures upon the addition of a strong epileptic, such as PTZ, which does not markedly affect normal mice (Szot et al., 1999; Tully et al., 2007; Weinshenker et al., 2001). In addition, memantine and DAPT might act by reducing excitotoxicity or abnormal currents through NMDA receptors that are caused by increased A β levels. A detailed electrophysiological study performed on Ts65Dn mice demonstrated a reduction in the efficacy of both inhibitory and excitatory connections in the hippocampal CA3 region (Hanson et al., 2007). Therefore, even drugs with seemingly diametrically opposed effects, such as reducing inhibitory connections (PTZ) or reducing excitatory connections (memantine), can improve cognition in Ts65Dn mice.

It might be appropriate to differentiate drug candidates for DS on the basis of short-term efficacy (i.e. corrections of physiologically stable states are achieved in the presence of drugs in the bloodstream) or long-term efficacy (i.e. treatment achieves close to a normal homeostatic steady state). In addition, correction of developmental processes, such as cerebellar cell number and volume, can also result in normalization that persists long after treatment. SAG 1.1, fluoxetine and possibly other neuroprotective drugs might also function in this manner.

A new era in the field of DS research and therapeutics is unfolding. Clinical trials to test drugs that aim to improve cognitive impairment – the most significant barrier to a normal lifestyle for people with DS – will commence soon. Studies of Ts65Dn mice have made an enormous contribution to the field, providing the basis for many potential treatments. The availability of additional genetic models of DS that more closely reflect the gene dosage in people is enabling us to refine our understanding of morphological, physiological or developmental deficiencies that lead to cognitive impairment in DS. Because the range of intellectual disability in people with DS varies from just below normal to significantly impaired and might encompass many different aspects of cognitive function and adaptive behavior, it is unlikely that a single drug will normalize brain function in all individuals. New mouse models with

an expanded representation of the genetic basis for DS will open up new avenues for understanding the molecular basis of the various clinical features of DS. Trisomic mice will continue to be an essential tool for understanding and developing therapies to ameliorate disadvantageous features of DS.

ACKNOWLEDGEMENTS

This work was supported in part by a grant from the Down Syndrome Research and Treatment Foundation and by Award Number R01HD038384 from the National Institute of Child Health & Human Development (R.H.R.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Child Health & Human Development or the National Institutes of Health.

COMPETING INTERESTS

The authors declare that they have no competing or financial interests.

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