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The effects of piracetam on cognitive performance in a mouse model of Down's syndrome

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Abstract

Piracetam is a nootropic agent that has been shown to improve cognitive performance in a number of animal model systems. Piracetam is reported to be used widely as a means of improving cognitive function in children with Down's syndrome (DS). In order to provide a preclinical assessment of the potential efficacy of piracetam, we examined the effects of a dose range of piracetam in the Ts65Dn mouse model of DS. Ts65Dn mice are trisomic for a region of mouse chromosome 16 with homology to human chromosome 21. Daily piracetam treatment at doses of 0, 75, 150, and 300 mg/kg ip was initiated in 6-week-old male Ts65Dn and euploid control mice. Following 4 weeks of treatment, mice were tested in the visible and hidden-platform components of the Morris water maze and were placed overnight in computerized activity chambers to assess effects on overall activity. Piracetam treatment was continued through the 4 weeks of testing. In control mice, 75 and 150 mg/kg/day piracetam improved performance in both the visible- and hidden-platform tasks. Although low doses of piracetam reduced search time in the visible-platform component in Ts65Dn mice, all piracetam doses prevented trial-related improvements in performance in Ts65Dn mice. The 300-mg/kg/day-piracetam dose was associated with a reversal of the nocturnal spontaneous hyperactivity in Ts65Dn. These data do not provide support for piracetam treatment for individuals with DS.
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1. Introduction

Down's syndrome (DS), the most common known genetic cause of mental retardation, is the result of a trisomy of chomosome 21. Although the degree of cognitive impairment in DS can be quite variable, individuals with DS have significantly lower IQs with disproportionately impaired speech and language skills [22] as well as specific difficulties in auditory and visual memory [21]. The mental retardation of DS also is characterized by difficulties in spatial learning and in the acquisition and extinction of conditioned and operant responses [32]. Children with DS also have been noted to have a high incidence of hyperactivity with accompanying attentional deficits [26].

With the notable exceptions of thyroid hormone replacement in congenital hypothyroidism or phenylalanine restriction in phenylketonuria (PKU), there have been few treatment successes for mental retardation. For DS, various hormone therapies (including thyroid, steroid, and growth hormone), glutamic acid, and combinations of vitamins, minerals, amino acids, and other nutritional supplements have been recommended on the basis of perceived or theoretical benefits without documentation of efficacy from double-blind treatment studies [29]. The use of specific pharmacological agents with documented efficacy in animal model systems is largely unexplored.

The development of a segmentally trisomic mouse, Ts(17^{16})65DN (Ts65Dn) from a reciprocal translocation of

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a segment of mouse chromosomes 16 to 17 has been an important breakthrough for modeling some of the behavioral and cognitive deficits of DS [9]. Ts65Dn mice are trisomic for the segment of mouse chromosome 16 that extends from the beta amyloid precursor protein (*App*) gene to the distal telomere [1]. The translocated segment does not contain the chromosomal segment homologous to the region between the centromere of human 21 and the *App* gene. Nor does it carry the distal regions of chromosome 21 that are carried on mouse chromosomes 10 and 17. Behavioral testing in a number of laboratories has demonstrated that young adult Ts65Dn mice have a cognitive performance deficit similar to that of DS. Ts65Dn mice perform poorly in spatial memory paradigms. They have increased escape latencies in both the visible- and the hidden-platform components of the Morris water maze task [12,13,16,27] and make more errors in radial arm mazes [11] than euploid littermate controls. The mice also are hyperactive [7,27] and demonstrate a number of relatively subtle motor deficits [6].

A number of experimental compounds have been developed that result in improved cognitive performance in animal models. One of the most studied of these is piracetam. Drugs of this type were initially classified as nootropic to indicate their cognitive-enhancing potential and as a reflection of the lack of understanding of the physiological or pharmacological basis for this action. A number of putative mechanisms of action for piracetam including enhanced membrane fluidity [24], modulation of AMPA-sensitive ionotropic glutamate receptors [18,25], and increased cholinergic neurotransmission [33] have been proposed.

Piracetam and a number of piracetam derivatives have been demonstrated to result in dose related improvements in cognitive performance in both older [28,30] and in pharmacologically challenged normal animals [5]. The piracetam derivative, oxiracetam, has recently been demonstrated to improve performance of DBA mice in the Morris water maze and in a contextual fear paradigm [14], tests in which this strain otherwise performs poorly.

Results in human clinical trials on the cognitive enhancing effects of piracetam have not been consistent. Piracetam has been demonstrated to have only limited effects in Alzheimer's disease. While cognitive performance was not improved over a 1-year trial, piracetam did appear to slow the progress of cognitive decline while administered [8]. Piracetam has also been tested in a number of childhood neurodevelopmental disorders. Although many of these studies were small and not all were well controlled, several reported significant benefits with minimal side effects (e.g., Ref. [4]) suggesting some therapeutic potential for these compounds in developmental disorders.

Piracetam has attracted great interest within the DS community. Many parents are administering piracetam to children with DS in response to case testimonials about its ability to improve intelligence [20]. There are multiple websites promoting the use of piracetam in DS that also provide opportunities for parents to exchange information about sources of the drug, dosages, and potential side effects. In addition, based on studies in animals demonstrating synergistic effects of combined piracetam/choline treatment [2], this combination treatment is recommended for DS on a number of websites. However, the first formal assessment of the efficacy of piracetam in DS has not been positive. Results from a recently reported double-blind, placebo-controlled, crossover study of the efficacy of piracetam for increasing cognitive functioning in DS have [20] have shown not only that piracetam treatment did not enhance cognitive performance but demonstrated that it also was associated with a number of adverse effects.

In the experiments reported here, we examined the behavioral effects of a range of piracetam doses in Ts65Dn mice to ascertain whether there was a clear preclinical rationale for its use in DS. We specifically evaluated the effects of piracetam on performance in a Morris water maze task and on spontaneous activity as measured in computerized activity chambers. As detailed above, Ts65Dn mice have been demonstrated to show behavioral deficits in both of these paradigms.

2. Methods

Male 5-week-old Ts65Dn ($n = 34$) and euploid littermate control ($n = 36$) mice were obtained from The Jackson Laboratory. Ts65Dn mice were generated by repeated crossings of Ts65Dn females to C57BL/6JEi × C3H/HeSnJ (B6EiCSn) F1 hybrid males. Animals from the same litter were group housed and maintained on a 12–12-hlight–dark schedule. All mice were chromosomally genotyped. Because C3H/HeSnJ mice carry a recessive mutation producing retinal degeneration, all mice were preexamined by individual ophthalmoscopy, and only those mice without signs of retinal disorder were used.

Beginning at 40 days of age, mice received daily injections of one of three dose of piracetam (75, 150, and 300 mg/kg) or saline vehicle (1 ml/100 g body weight). Piracetam treatment continued for 4 weeks prior to and through the 4-week testing period. Testing consisted of assessments of performance on the visible- and hidden-platform components of the Morris maze task and assessment of spontaneous activity within computerized activity chambers.

2.1. Morris water maze

The Morris water maze [23] consists of a circular stainless steel swim tank (72 cm in diameter and 15 cm deep) filled with water made opaque by the addition of nontoxic white latex powder paint. A small platform (5 cm square) was placed into the tank in one of four quadrants. The top of the platform was 1 cm below the surface of the water. The testing had a number of components. The first was a visible-platform task in which the position of the platform was signaled by the presence of a visually conspicuous "flag"

above the platform. To solve this task and swim directly to the platform, an animal needs only to learn that the flag indicates the location of the platform. The platform location varies among four possible positions within each block of trials and animals are tested on three blocks of trials per day (a total of 12 trials) for 2 days. Blocks of trials were separated by 1 h. Animals were placed into the water in the center of the tank. Latency to locate the platform and escape from the water on each trial was the dependent measure. Once the platform was located, mice were allowed to remain on the platform for 30 s before beginning the next trial. Mice were allowed to swim for a maximum of 60 s. Animals that did not find the platform within that time were placed on the platform and allowed to remain there for 30 s.

Twelve days after completion of the visible-platform task, mice were tested on the hidden-platform version of the task. In this version, there was no flag identifying the position of the platform and the escape platform was maintained in a fixed location within the tank. Since there were no immediate platform cues and the animal could not see the platform, the mice needed to acquire a multiple spatial relationship among the patterns around the perimeter of the tank, extra-maze cues, and the position of the platform. Animals received three blocks of trials for three consecutive days on the hidden-platform task. Animals were placed into the tank around the perimeter in one of four start positions that were used in a semirandom fashion throughout the four trials per block. Mice were allowed to search the tank for 60 s and allowed to remain on the platform for 30 s. If the platform was not located within 60 s, they were removed from the water and placed on the platform. Again, escape latencies were the dependent variable.

Data from the visible- and hidden-platform testing were first analyzed using a three-way mixed model ANOVA for factors of genotype, piracetam dose, and blocks of trials. Significant effects were explored further with two-way ANOVAs, analyses of main effects, and paired *t* comparisons.

2.2. Spontaneous activity

During the period between visible- and hidden-platform testing, the spontaneous activity of a subgroup of the Ts65Dn ($n=26$) and control mice ($n=28$) was examined in computerized Digiscan (Omnitech Electronics) activity monitors. The experimental chambers consisted of clear Plexiglas cages measuring 16 × 16 × 12 in. (40 × 40 × 30.5 cm) with a row of infrared monitoring sensors mounted every 5 cm along the perimeter at the base and a second row of sensors mounted at a height of 10 cm. Data were collected and interpreted in hardware by a Digiscan computer connected to a computer for data storage and subsequent analysis. For this experiment, we collected data on horizontal activity expressed as the number of photocell interruptions. Animals were placed into the chambers 2 h prior to lights out and activity was monitored in 2-h intervals for 26 h with food and water present. The first 2-h period was considered a habituation period. Data from the subsequent 12 sampling intervals were analyzed by a mixed model ANOVAs with genotype and piracetam dose as independent variables and sampling interval as a repeated variable. Significant effects were explored further with two-way ANOVAs, analyses of main effects, and paired *t* comparisons.

3. Results

3.1. Morris water maze testing

3.1.1. Visible platform

As shown in Fig. 1, the performance of vehicle-treated control and Ts65Dn mice improved with experience, control mice performed better than Ts65Dn mice and piracetam affected performance in both groups. Overall ANOVA

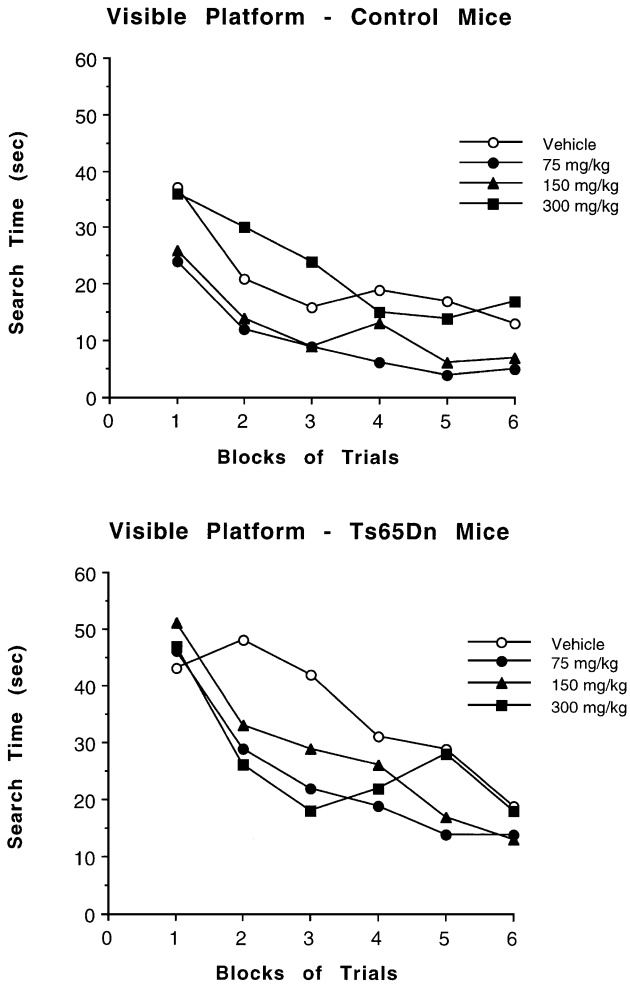

Fig. 1. Search times in the visible-platform component of the Morris water maze task across six blocks of trials. Top panel: performance of control mice receiving daily intraperitoneal injections of vehicle or one of three doses of piracetam ($n=9$ all groups). Bottom panel: performance of Ts65Dn mice receiving daily injections of vehicle or one of three doses of piracetam ($n=8$, vehicle and 150 mg/kg doses; $n=9$, 75- and 300-mg/kg doses).

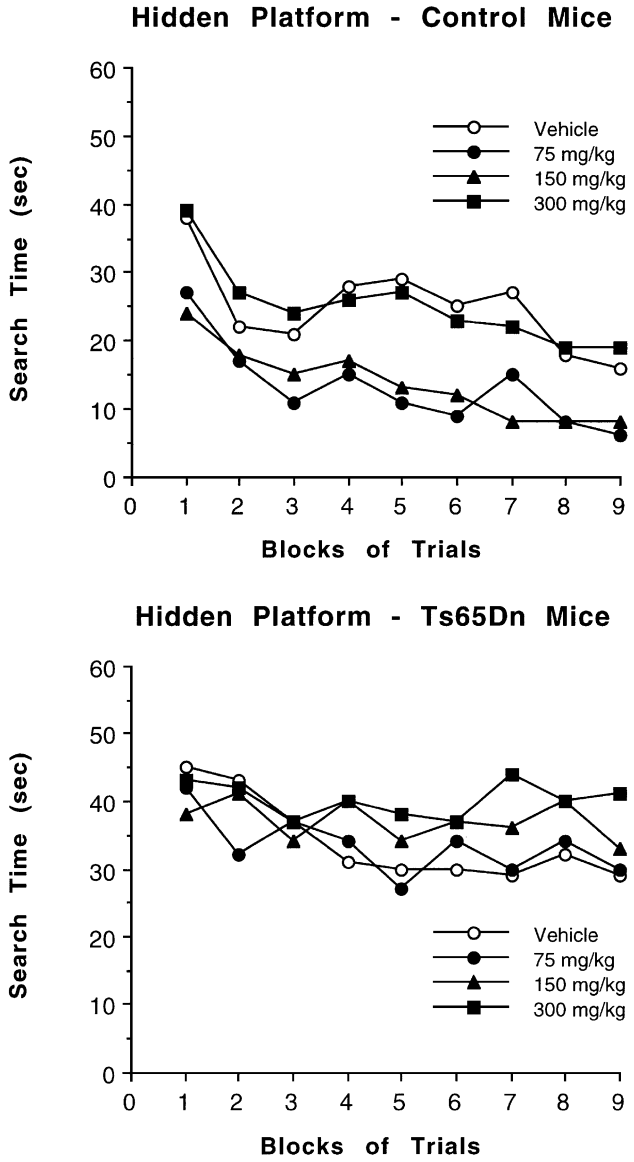

Fig. 2. Search times in the hidden-platform component of the Morris water maze task across nine blocks of trials. Top panel: performance of control mice receiving daily intraperitoneal injections of vehicle or one of three doses of piracetam ($n=9$ all groups). Bottom panel: performance of Ts65Dn mice receiving daily injections of vehicle or one of three doses of piracetam ($n=8$, vehicle and 150 mg/kg doses; $n=9$, 75- and 300-mg/kg doses).

indicated significant effects of genotype, $F(1,62)=32.231$, $P<.0001$, piracetam dose, $F(3,62)=5.057$, $P<.005$, and trial block, $F(5,310)=96.712$, $P<.0001$, on search time in the swim tank. There were also significant Genotype × Trial, $F(5,310)=3.658$, $P<.005$, Dose × Trial, $F(15,310)=1.864$, $P<.05$, and a three-way, Genotype × Dose × Trial interactions, $F(15,310)=4.031$, $P<.0001$.

Piracetam affected performance in controls such that there was a significant dose effect, $F(3,32)=12.706$, $P<.0001$. Search times in the groups receiving either the 75-or 150-mg/kg dose were improved relative to the vehicle group. This effect of piracetam was not evident at the 300-mg/kg dose. In contrast, there was not a significant dose effect in Ts65Dn mice. There was, however, a significant Dose × Trial interaction, $F(15,150)=4.058$, $P<.0001$, reflecting improved performance in later trials at the 75- and 150-mg/kg doses.

3.1.2. Hidden platform

As in the visible-platform task, controls performed better than Ts65Dn in the hidden-platform portion of testing (Fig. 2). Piracetam differentially affected performance depending on dosage and genotype. Overall ANOVA indicated significant effects of genotype, $F(1,62)=30.406$, $P<.0001$, trial block, $F(5,310)=13.344$, $P<.0001$, and a significant Genotype × Trial interaction, $F(5,310)=2.271$, $P<.05$. In control mice, there was a significant piracetam effect, $F(3,32)=4.750$, $P<.01$, such that the 75- and 150-mg/kg doses significantly improved performance. At the 300-mg/kg dose, there was no effect. In contrast, there was no significant piracetam effect in Ts65Dn mice. The overall effect of trial block was significant, $F(5,150)=3.713$, $P<.005$; however, analyses of simple effects indicated that this was evident only in the vehicle-treated mice. Performance did not improve over time in any of the Ts65Dn groups receiving piracetam. This point is emphasized in Fig. 3 by comparing search times in the first and ninth block in Ts65Dn mice at the four doses. There was a significant improvement in search time in the vehicle-treated group ($P<.01$) but not in any of the piracetam groups.

3.2. Activity

As shown in Fig. 4, Ts65Dn mice were hyperactive compared to euploid controls. This hyperactivity was most

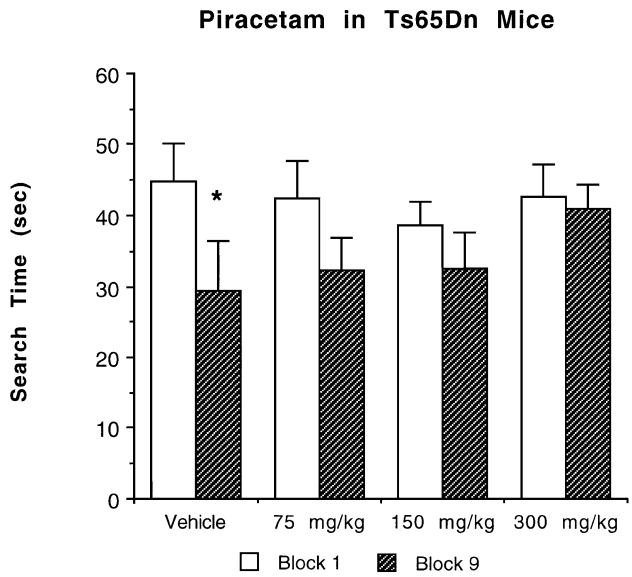

Fig. 3. Comparison of search times in the first and ninth trial blocks in Ts65Dn mice receiving the vehicle or one of the three doses of piracetam. * Significant reduction in search time from Block 1 ($P<.05$).

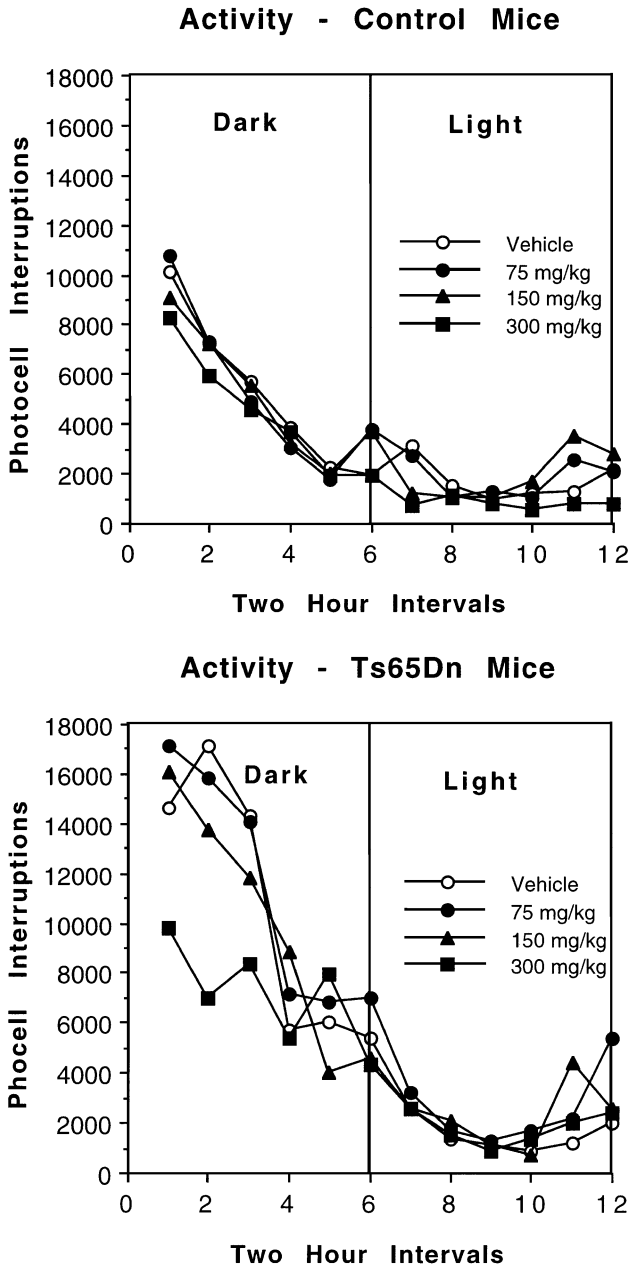

Fig. 4. Activity expressed as photocell interruptions in 2-h time blocks across a 24-h period. Top panel: activity of control mice receiving daily intraperitoneal injections of vehicle or one of three doses of piracetam ($n=6$, vehicle; $n=8$, 75 mg/kg; $n=7$, 150 and 300 mg/kg). Bottom panel: activity of Ts65Dn mice receiving daily injections of vehicle or one of three doses of piracetam vehicle and 150 mg/kg ($n=7$) and 75 and 300 mg/kg ($n=6$).

evident at the beginning of the dark cycle. Piracetam had no effect on activity in controls but had a dose-specific effect on activity in Ts65Dn mice. Overall ANOVA indicated significant effects of genotype, $F(1,46)=24.874$, $P<.0001$, time, $F(11,506)=81.923$, $P<.0001$, and significant Genotype × Time, $F(11,506)=9.402$, $P<.0001$, and Dose × Time interactions, $F(33,506)=1.589$, $P<.05$. Although there was not a significant dose effect in Ts65Dn mice, there was a significant Dose × Time interaction, $F(33,242)=1.877$, $P<.05$. At the 300-mg/kg dose, piracetam blocked the beginning of the dark cycle hyperactivity normally seen in the Ts65Dn mice.

4. Discussion

The data from these experiments demonstrate that the 75- and 150-mg/kg/day-piracetam doses improved performance in both the visual- and hidden-platform components of the Morris maze testing in normal mice. Positive effects of piracetam in Ts65Dn mice were limited to the less demanding visible-platform component of the Morris water maze task. Indeed, in Ts65Dn mice, performance in the hidden-platform task was impaired by all doses of piracetam. At the highest dose (300 mg/kg), piracetam abolished the nocturnal hyperactivity normally found in Ts65Dn mice. Lower piracetam doses had no effect on activity.

Our original behavioral characterization of the Ts65Dn mouse demonstrated performance impairments in the Morris water maze and hyperactivity during the dark phase of the light/dark cycle [27]. The current data in vehicle-treated Ts65Dn mice replicate these findings. Ts65Dn mice had longer search times in both the hidden- and visible-platform phases of the Morris water maze test and were hyperactive in the dark cycle as indicated by significantly more beam interruptions in the early dark period.

The behavioral phenotype of the Ts65Dn model has a number of clear strengths. Similar results have been obtained across different tests aimed at assessing the same processes in a number of laboratories [7,9,10,12,13,16,17]. This consistency of findings demonstrates that the behavioral deficits in the Ts65Dn mice are robust. Furthermore, although differences in sensorimotor skills have been detected early in development in Ts65Dn mice [16], their sensorimotor capabilities as adults are relatively intact [6] and do not preclude testing aimed at identifying learning and memory deficits. Finally, the pattern of findings, including deficits in learning and memory, hyperactivity, and reduced behavioral inhibition [3,7], is consistent with aspects of the mental retardation in DS. Children with DS exhibit clear learning and memory deficits, often evidence hyperactivity and have been described as impulsive [26]. Thus, the Ts65Dn mouse provides a model for preclinical assessment of the efficacy of treatments aimed at cognitive improvement in DS.

The data for these experiments do not provide support for the use of piracetam to produce cognitive enhancement in DS. Although positive effects were found at the two lower doses in the visible-platform portion of Morris water maze testing, piracetam negatively affected performance in the more demanding hidden-platform component of testing. While untreated Ts65Dn mice showed a small but significant improvement in performance over testing in the hidden-platform component, this experience-related improvement did not occur in any of the piracetam-treated Ts65Dn mice.

The piracetam-induced improvement in performance in euploid control mice provides a positive control for the negative Ts65Dn results.

The mechanisms through which piracetam can improve cognitive performance are not clearly delineated. As noted above, piracetam affects both glutamatergic [18,25] and cholinergic [33] neurotransmission and actions on both of these systems have been proposed for piracetams's behavioral effects. Why piracetam should improve performance in euploid mice but impair performance in the Ts65Dn mice is not clear. Relatively little is known about the effects of this segmental trisomy on synaptic neurotransmission. An age-related decline in cholinergic markers [16] and a lower number of cortical synapses [19] in Ts65Dn mice have been noted. However, detailed characterizations of neurochemical indexes in Ts65Dn mice have yet to be reported.

Our findings of a lack of significant overall piracetam-induced improvement in performance in Ts65Dn mice are similar to the results from a recently reported clinical trial of piracetam in children with DS. In a controlled, randomized, double-blind, crossover clinical trial, piracetam failed to significantly improve cognitive functioning in children with DS [20]. Children's performance was assessed on a wide range of cognitive and behavioral measures and on parental and teacher questionnaires. Piracetam in doses of 80–100 mg/kg/day did not significantly improve cognitive performance. Some minor numerical improvements in parental and teacher ratings were found although these were not judged to be clinically significant. Adverse side effects were detected in 7 of the 18 children who completed testing. These adverse effects were associated mainly with central nervous system stimulatory effects and included increased aggressiveness and irritability.

The highest dose of piracetam did ameliorate the nocturnal locomotor hyperactivity in Ts65Dn mice. Piracetam has been previously demonstrated to ameliorate hypoxia-induced open-field hyperactivity in rats [15]. The mechanism underlying these actions is unclear. It is unlikely due to a sedative effect. Extensive characterization of piracetam and other pyrrolidine derivatives have noted that they are relatively side effect-free and without sedative activity [31]. Since the clinical trial with piracetam in DS noted increased stimulatory activity and aggressiveness as side effects [20], it seems unlikely that piracetam would have clinical utility for the hyperactivity often associated with DS.

In summary, these data do not provide support for piracetam therapy to improve cognitive performance in children with DS. Although there was some small improvement in the visible-platform component of the Morris water maze task with low-dose piracetam treatment, piracetam prevented learning in the more complex hidden-platform component. Together with the recent clinical data, these results using a preclinical model with many genetic and behavioral features of DS provide no rationale for piracetam treatment in children with DS.

Acknowledgements

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