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Research Report

# Long-term memory for aversive training is impaired in *Idua*$^{-/-}$ mice, a genetic model of mucopolysaccharidosis type I

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ABSTRACT

Mucopolysaccharidosis type I (MPS I) is a lysosomal storage disease that leads to neurodegeneration and neurological deficits, among other pathological and clinical consequences. The aim of the present study was to evaluate neurobehavioral parameters in a genetic mouse model of mucopolysaccharidosis type I (MPS I). During exploration of an open field, adult MPS I (*Idua*$^{-/-}$) mice showed normal locomotion and anxiety but reduced number of rearings. *Idua*$^{-/-}$ mice performed normally in a novel object recognition memory task and showed normal short-term retention of inhibitory avoidance training. By contrast, long-term retention of inhibitory avoidance was impaired in *Idua*$^{-/-}$ mice. The deficit in inhibitory avoidance memory could not be attributed to reduced footshock reactivity. The results indicate that *Idua*$^{-/-}$ mice present deficits in long-term memory for aversive training and reduced exploratory behavior.

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## 1. Introduction

Mucopolysaccharidosis type I (MPS I) is a heritable lysosomal storage disease resulting from a deficiency of alpha-L-iduronidase, the enzyme required for degradation of glycosaminoglycans (GAGs) dermatan sulfate and heparin sulfate. In affected children, mutations in the *IDUA* gene lead to GAG accumulation in lysosomes, tissue pathology, and severe clinical features including growth delay, altered facial features, skeletal abnormalities, hepatosplenomegaly, and central nervous system (CNS) deficits (Scriver, 2001). Neurodegeneration, severe mental retardation and death in childhood are seen in the most severe phenotype of MPS I, Hurler syndrome, which results from homozygosity for some mutations in the *IDUA* gene (Scott et al., 1995; Scriver, 2001).

The availability of a genetic mouse model of MPS I (*Idua*$^{-/-}$) makes it possible to investigate the neurological deficits associated with MPS I (Clarke et al., 1997; Ohmi et al., 2003; Hartung et al., 2004). A previous study has suggested that *Idua*$^{-/-}$ mice show impaired memory assessed in an open field

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habituation paradigm (Hartung et al., 2004). In addition, cognitive deficits have been observed in mouse models of other types of lysosomal storage disease. For instance, MPS VII show impaired spatial memory (Chang et al., 1993; Frisella et al., 2001). However, a detailed behavioral analysis of *Idua*$^{-/-}$ mice has not been previously reported. In the present study, we investigated open field behavior, memory for aversive training, and recognition memory in *Idua*$^{-/-}$ mice. Developmental and metabolic features of *Idua*$^{-/-}$ mice have been described elsewhere (Hartung et al., 2004).

## 2. Results

### 2.1. *Open field behavior*

Results for open field behavior are shown in Fig. 1. There were no significant differences between groups in the latency to start locomotion ($P = 0.93$; Fig. 1A), number of crossings performed ($P = 0.24$; Fig. 1B), or defecation ($P = 0.43$; Fig. 1D) indicating that *Idua*$^{-/-}$ mice showed no alterations in locomotion or anxiety. However, *Idua*$^{-/-}$ mice showed a significantly lower number of rearings, which indicates reduced exploratory behavior, compared to control animals ($P < 0.05$; Fig. 1C).

### 2.2. *Novel object recognition*

In the recognition memory task, there was no difference between groups in the total time spent exploring both objects during the training trial, indicating that both groups showed similar locomotion and motivation during task acquisition. Mean ± SE total exploration time (s) was 14.00 ± 3.12 s in control mice and 13.10 ± 1.98 s in *Idua*$^{-/-}$ animals ($P = 0.81$). In addition, there was no significant difference between groups in exploratory preference in the training trial ($P = 0.71$) (Fig. 2A). There were no significant differences between groups in short ($P = 0.55$; Fig. 2B)- or long-term ($P = 0.66$; Fig. 2C) memory retention of the object recognition task. Both groups showed significant preference towards the novel object during both the short- and long-term retention test trials (both $Ps < 0.01$ in the short-term retention test trial and both $Ps < 0.05$ in the long-term retention test trial). These findings indicate that *Idua*$^{-/-}$ mice showed no alterations in novel object recognition memory.

### 2.3. *Inhibitory avoidance*

Results for inhibitory avoidance are shown in Fig. 3. There were no significant differences between groups in training trial performances ($P = 0.75$; mean ± SE overall training trial step-down latencies was 9.04 ± 4.01 s). There was no significant difference between groups in short-term inhibitory avoidance retention ($P = 0.96$) (Fig. 3A). However, *Idua*$^{-/-}$ mice showed impaired long-term retention when compared to the control group ($P < 0.01$) (Fig. 3B). These results indicate that *Idua*$^{-/-}$ mice showed impaired long-term memory for inhibitory avoidance training.

### 2.4. *Footshock reactivity*

There was no significant difference between groups in reactivity to the footshock assessed by flinch (Fig. 4A) and jump (Fig. 4B) thresholds ($Ps = 1.00$ and 0.11 for flinch and jump thresholds respectively), indicating that *Idua*$^{-/-}$ mice showed no alterations in nociception.

## 3. Discussion

The main result of the present study is that *Idua*$^{-/-}$ mice, a mouse model of MPS I, showed impaired long-term memory of inhibitory avoidance, a type of single-trial aversively motivated conditioning, whereas no alterations were observed in

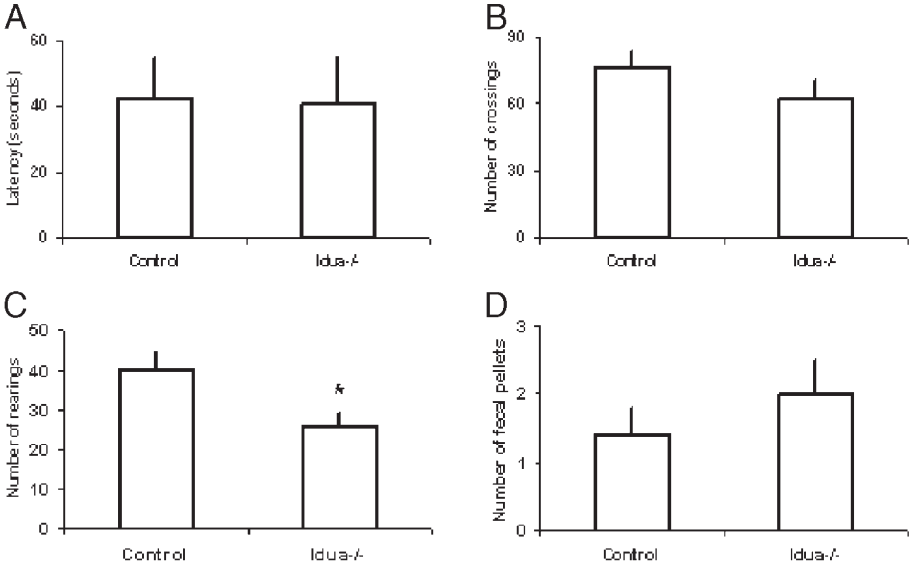


**Fig. 1 – Open field behavior in *Idua*$^{-/-}$ and control mice. Animals were left to freely explore the arena for 5 min. Data are mean ± SE (A) latency to start locomotion (s), (B) number of crossings, (C) number of rearings, and (D) number of fecal pellets. $N = 9$ animals in the control group and 11 animals in the *Idua*$^{-/-}$ group. *Significant difference from the control group ($P < 0.05$).**

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