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CONTENTS

LATENT MUSCULAR DYSTROPHY IN GENOTYPICALLY DYSTROPHIC-DWARF MICE

Tsuyoshi Totsuka, Kimi Watanabe, and Sigehiro Kiyono

Department of Physiology, Institute for Developmental Research, Aichi Prefectural Colony, Aichi

We have proposed a working hypothesis for the development of murine muscular dystrophy, as summarized in Fig. 1. This is based on the following experimental results. In muscular dystrophic mice (dy/dy; strain C57BL/6J-dy), the forelegs seemed to function almost normally even at 3 months of age, whereas the hindlegs showed characteristic signs of the disease at an early age (about 2 weeks), suggesting that comparative studies on the fore- and hindleg muscles might yield clues clarifying the mechanism involved in the development of murine muscular dystrophy. However, the forelegs of dystrophic mice were also found to be affected by the disease at least by 1 month of age. Thus, the endurance of the forelegs was much less than that in normal mice[1)]. Moreover, it was found that the foreleg muscles, as well as the hindleg muscles[2),3)], were abnormal in collagen content[4)], in the level of protease activities[5)], and in the histological images (unpublished results from our laboratory). Also, the growth of the fore- and hindleg muscles was arrested at about 1 month of age. From a biochemical study of the hindleg muscles, the drastic increase in the apparent volume per muscle cell which occurs on and after 10 days of age in normal development was not observable in dystrophic mice[6)]. Findings thus far showed that there was no remarkable difference to explain the variation in the degree of apparent severity of the fore- and hindleg involvement in any feature of the muscles but rather the difference was in the growth of the bones[7)]. The growth (lengthening) of the foreleg bones was much smaller and slower than that of the hindleg bones during the period from 10 to 20 days of age in muscular dystrophic mice as well as in normal mice. It is noteworthy that the onset of the disease observable in the hindlegs (about 14 days of age) occurred in this period.

According to our working hypothesis, the clinical signs of the disease must be alleviated in dystrophic mice in which growth, including bone-lengthening, was arrested. To investigate this, a few effective methods are available at present, such as hypophysectomy and genetic methods. Genes bm (brachymorphic), bp

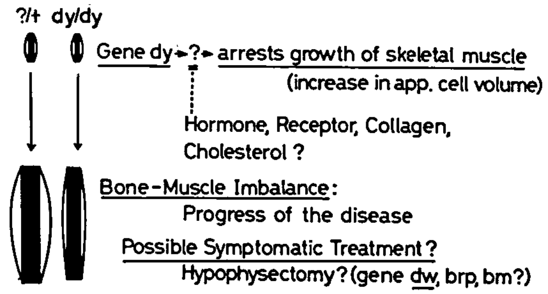

Fig. 1

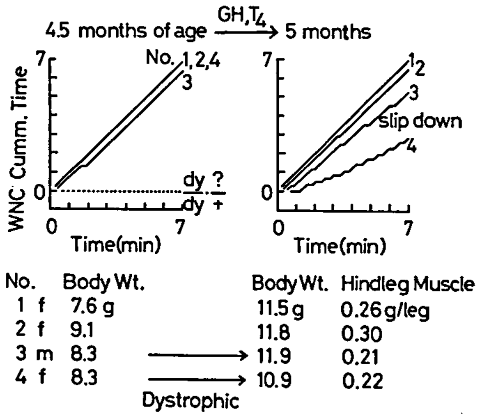

Fig. 2

Fig. 1. A working hypothesis for the development of murine muscular dystrophy.

Fig. 2. Latent muscular dystrophy in genotypically dystrophic-dwarf mice. The genotypically dystrophic-dwarf mice (Nos. 3 and 4) were not dystrophic till they were treated with GH and T_4. f, m: female, male, respectively.

(brachypod), brp (another brachypod), and dw (pituitary dwarf) may be suitable for the purpose. We have already succeeded in producing genotypically dystrophic-brachymorphic (dy/dy•bm/bm), dystrophic-brachypod (dy/dy•brp/brp), and dystrophic-dwarf (dy/dy•dw/dw) mice. In the present study, results for dystrophic-dwarf mice are reported. In order to obtain dystrophic-dwarf mice, crosses were performed between F1 hybrid carriers (dy/+•dw/+), which were produced by crossing C57BL/6J-dystrophic carriers (dy/+•+/+) with DW/J-dwarf⁸⁾ carriers (+/+•dw/+; purchased from the Jackson Laboratory). In the F2 hybrid mice, phenotypically normal, dystrophic, and dwarf mice were observed but not the dystrophic-dwarf type. All the mice tested in our wire-net-climbing (WNC) apparatus⁹⁾, except for the dystrophic ones which continually dragged their hindlegs after about 3 months of age, showed almost normal locomotive activities even at 4.5 months of age (Fig. 2). Some of the phenotypically dwarf mice, however, began to manifest an abnormal sign in their eyes with age, which is a characteristic of murine muscular dystrophy. From this and the theoretical expectation (*i.e.*, one-sixteenth of the F2 hybrid mice should be genotypically dystrophic-dwarf mice), it was suggested that the dystrophic-dwarf mice were latent in the phenotypically dwarf ones. In fact, this was demonstrated by the following experiments.

F2 hybrid dwarf mice were injected intraperitoneally with bovine growth hormone (GH) and thyroxine (T_4). As the phenotypically dwarf mice grew with the GH-T_4-treatment (100 μg GH and 10 μg T_4/day¹⁰⁾, every other day for about 15 days), some of them began to exhibit the characteristic clinical signs of muscular dystrophy (sometimes dragging their hindlegs and revealing depressed activity in the WNC apparatus). Thus, genotypically dystrophic-dwarf mice could be identified. These dystrophic-dwarf mice had less muscle in their hindlegs than the nondystrophic dwarf mice which had been raised with GH-T_4-treatment. Five dystrophic-dwarf mice have been observed thus far.

From the present findings, it was concluded that muscular dystrophy was latent in genotypically dystrophic-dwarf (dy/dy•dw/dw) mice in which growth had been arrested by the gene dw. This suggests that hypophysectomy may be an effective symptomatic treatment for murine muscular dystrophy.

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