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Heparanase-inhibiting marine polysaccharides in Sanfilippo syndrome (MPSIIIA)

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BACKGROUND

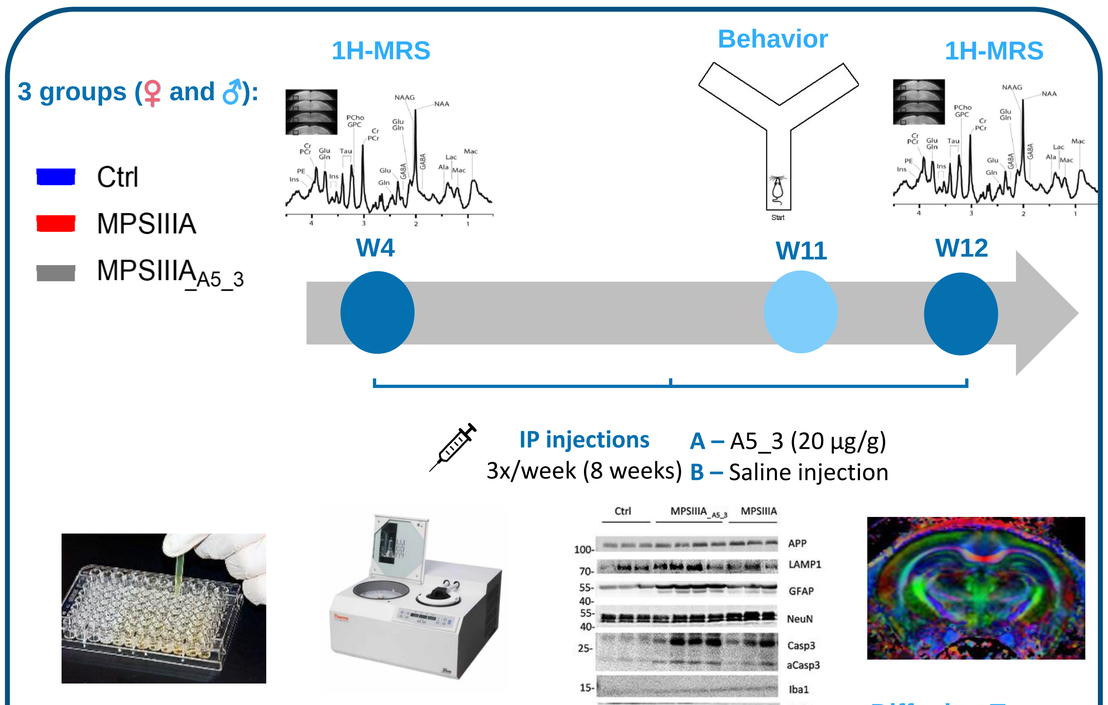
Mucopolysaccharidosis IIIA (Sanfilippo syndrome) is a hereditary disease caused by mutations in enzymes responsible for the catabolism of heparan sulfate (HS), leading to HS fragment accumulation, multisystemic failure and premature death. Available strategies do not provide cure and therapies based on renewable sources are a growing field. We showed that treatment of a MPSIIIA cell line with two marine polysaccharides (A5_3 and A5_4) caused limited degradation of intracellular HS, thus affecting its turnover. For this reason, we decided to test the effect of treatment on a mouse model of MPSIIIA (Sgsh^{D31N}).

AIMS

To evaluate early and late brain metabolic alterations by Magnetic Resonance Spectroscopy (MRS), behavioral outcomes and neuroinflammation following treatment with A5_3 (from 4 to 12 weeks of life), with the final aim of obtaining a first *in vivo* indication of protective effects of A5_3 for the treatment of Sanfilippo syndrome.

METHODS

- MRS: Mice were continuously anesthetized under a flow of 1.5-2% isoflurane in oxygen for the duration of the experiments. The body temperature was maintained at 37°C using a thermoregulated water circulation system placed on the back of the mouse. MRS experiments were performed on a 9.4-T/31-cm magnet (Magnex Scientific, Abington, UK) connected to Direct Drive console (Varian, Palo Alto, CA) equipped with 12-cm gradient coils (400 mT/m, 120 msec). A Fast Spin Echo T2W image was performed to position ^{1}H-MRS voxels of interest. ^{1}H-MRS spectra acquisition were performed on the cortex and hippocampus using an ultrashort echo time (TE/TR=2.7/4000 ms) SPECIAL spectroscopy method (*Magn Reson Med* 2006; 56: 965-970).
- Diffusion Tensor Imaging (DTI): Ex vivo MRI experiments were performed on a 14.1T magnet (Bruker) with a homemade saddle coil of 2 cm diameter. A multi-b-value shell protocol was acquired using a spin-echo sequence (FOV = 21 × 16 mm2, matrix size = 128 × 92, 12 slices of 0.6mm, 3 averages with TE/TR = 45/2,000ms).
- Behavior tests: Open Field test. Animals were individually placed in the center of an arena (43 x 50 cm, white Plexiglas) divided into central and peripheral areas and left to explore freely for a total of 10 min, of which the first 5 minutes were used for analysis. ANY-MAZE Video Tracking System version 7.10 (Stoelting Europe) was used to assess motor activity, exploratory drive and anxiety. Beam balance test. During training, animals were encouraged to cross two wooden beams elevated 30 cm above the ground, until reaching a familiar item from their housing box on the other end of the beam.



RESULTS

Brain metabolism is altered in the brains of MPSIIIA mice at 4 and 12 weeks of age, partially reversed upon treatment

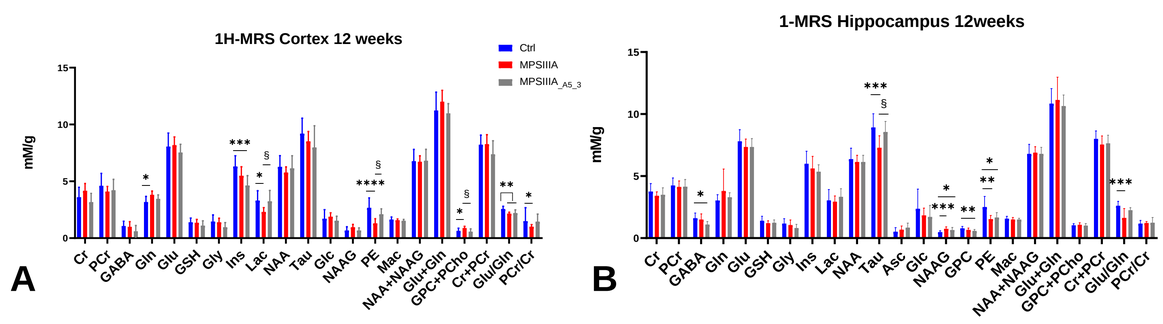


Figure 1: ^{1}H-MRS metabolite quantification from cortex (A) and hippocampus (B) at 12 weeks. * = p < 0.05, ** = p < 0.01.

MPSIIIA animals have decreased exploratory activity and incoordination, with no memory or muscle strength impairments at 11 weeks. A5_3 improved beam balance performance in MPSIIIA mice.

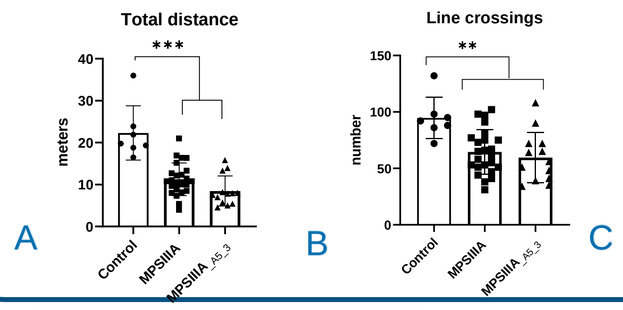
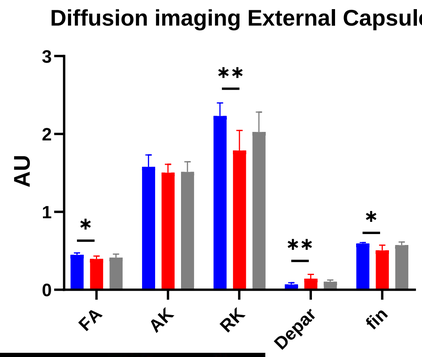


Figure 2 - Open Field - total distance travelled **(A)**, total number of line crossings **(B).** Average of time to cross beam in the balance test **(C)**. * = p < 0.05, ** = p < 0.01, *** = p < 0.001.

White matter integrity is affected in the brains of MPSIIIA animals, with reversal upon treatment with A5_3



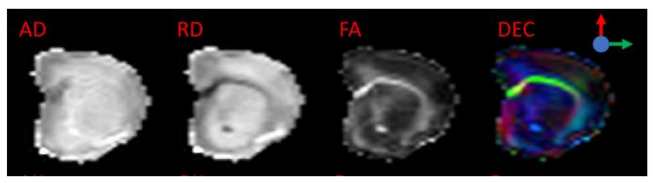
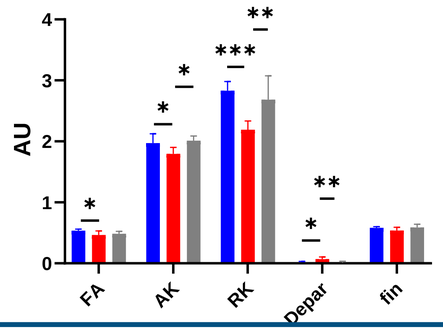


Figure 3: MRI derived diffusion imaging parameters on external capsule and cingular white matter medial region. Axial diffusivity (AD), Radial diffusivity (RD), Fractional anisotropy (FD), axial (AK) and radial (RK) kurtosis, axial diffusivity in the extra axonal space (Depar), intra-axonal volume fraction (fin). * = p < 0.05, ** = p < 0.01, *** = p < 0.001.



CONCLUSION

In this study, we demonstrate alterations in the brain of MPSIIA mice in energetic metabolism, namely regarding neurotransmission and cell integrity, white matter damage and the presence of markers of neuroinflammation and apoptosis, as well as lysosomal enlargement and decreased deambulation in the open field. The treatment with A5_3 was able to revert the alterations in some of the parameters assessed, but the administration route should be changed in order to grant more bioavailability of A5-3 to the brain. MRS showed to be a powerful technique to detect early metabolism alterations in MPSIIIA mice.

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