Developmental and epileptic encephalopathies (DEE) are early-life onset syndromes characterized by drug-resistant epilepsy and cognitive impairment. The GluN2A(N615S)-mutated mice carry a mutation in the Grin2a gene coding for the GluN2A subunit of the NMDA glutamate receptor and display symptoms similar to those described in human patients, representing a valuable murine model for GRIN-related DEEs. We investigated the effects of a ketogenic diet (KD) on the epileptic phenotype and behavior in the GluN2A(N615S) model. After behavioral and seizure testing, mice were sacrificed and several tissues were collected. Brains slices were stained for different markers such as WFA for perineuronal nets (PNNs), parvalbumin (PV) for PV+ interneurons (PV+ INs) and Iba1 for microglia.

Results of behavioral tests: KD influences activities of daily living, reduces hyperactivity, improves spatial learning and memory (in male mice) and protects against AGS in mutated mice.

Results of IHC analysis: preliminary data show a reduced neuroinflammation (Iba1+ microglial cells) and an increase in PV+ INs and PNNs in the hippocampus of KD-fed Grin2a<sup>ΔSh</sup> mice.

Conclusions: we confirmed previous data indicating several deficits and impairments in Grin2a<sup>ΔSh</sup> mice – consistent with DEE phenotypes in patients – and proved here that some of them overall improve with KD, such as nest building performance and hyperactivity, whereas memory and learning ameliorate in a sex-based manner (males). We demonstrated for the first time in this DEE model that KD is effective in reducing susceptibility to AGS: preliminary IHC data show that this achievement could be mediated by an increase in inhibitory activity through PV+ INs and PNNs, and by a reduced neuroinflammation.

References: Bertocchi I. et al., Comm Biol, 2021; Bertocchi I., Cifarelli L. et al., Br J Pharmacol, 2024