mouse models with calpastatin knockout mice to assess its effect not only on huntingtin cleavage and aggregation but also additional molecular markers.
Methods Effects of depleting the endogenous inhibitor of calpains on huntingtin fragmentation and aggregation, as well as on other molecular markers of Huntington disease were investigated via western blotting, filter retardation assays and immunocytochemistry or immunohistochemistry.
Results We demonstrated that reduced or ablated calpastatin expression triggers calpain overactivation and a consequently increased mutant huntingtin cleavage in cells and *in vivo*. These alterations were accompanied by an elevated formation of predominantly cytoplasmic huntingtin aggregates. Conversely, calpastatin overexpression in cells attenuated huntingtin fragmentation and aggregation. In addition, we observed an enhanced cleavage of DARPP-32, p35 and synapsin-1 in neuronal tissue upon calpain overactivation.
Conclusions Our results corroborate the important role of calpains in the molecular pathogenesis of Huntington disease and endorse targeting these proteolytic enzymes as a therapeutic approach.

A24 ABSTRACT NOT PRESENTED

A25 METABOLISM OF SIALO-CONJUGATES IS DEFECTIVE IN PRE-CLINICAL MODELS OF HUNTINGTON'S DISEASE

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Background In the last decade, perturbed metabolism of some sialylated molecules has been described to play an essential role in the pathogenesis of Huntington's disease (HD). In this context, we have contributed to demonstrate that metabolism of sialic-acid containing glycosphingolipids – gangliosides – is impaired in HD and its modulation results therapeutically effective in HD pre-clinical models.

Interestingly, evidence of altered levels of both sialo-glycoproteins and gangliosides suggests an overall perturbed metabolism of sialo-conjugates in HD.
Aims The aim of this study is to investigate whether the metabolism of sialic acid is globally impaired in HD and to identify it as novel potential therapeutic target.
Methods *In vitro* experiments were carried out in immortalized mouse striatal-derived knock-in cells expressing endogenous levels of wild-type (STHdh7/7) or mutant huntingtin (STHdh111/111). All *in vivo* studies were performed in R6/2 HD mice and in age-matched control littermates.
Results Our data demonstrate that expression of a number of enzymes (sialyl-transferases) that are involved in the synthesis of different sialo-conjugates, is significantly impaired in multiple HD pre-clinical models. Preliminary results also indicate that metabolism of sialic acid may be easily modulated *in vitro* and *in vivo* and therefore pharmacologically targeted. More studies are in progress to fully clarify the beneficial effects of such modulation.
Conclusion Collectively, our results indicate that the metabolism of sialo-conjugates is globally affected in HD and may represent a 'druggable' target for developing novel approach for the treatment of the disease.

A26 POLYAMINE METABOLISM IN HUNTINGTON'S DISEASE

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Background N-methyl-d-aspartic acid receptor (NMDA) mediated excitotoxic destruction of striatal neurons is one of the models proposed for the pathogenesis of Huntington's disease. Polyamines (putrescine, spermidine and spermine) may be involved in excitotoxicity by modulating NMDA receptors either in a negative or positive manner.
Aims In the framework of this work, we aimed to investigate the effects of polyamines on the mutant huntingtin mediated excitotoxicity.
Methods HEK293 cells, stably expressing mutant or normal htt were transiently transfected with NMDA receptor heterodimers (NR1/NR2A or NR1/NR2B) and then exposed to polyamines or polyamine biosynthesis inhibitors. Intracellular polyamine levels were determined by HPLC, cell viability was measured by MTT assay and the changes in protein expressions of huntingtin, inhibitor protein kappa B and ornithine decarboxylase were performed by western blotting.
Results It was found that exogenously applied Spd, Spm, -difluoromethyl ornithine and cyclohexylamine, but not putrescine, cause an increase in the mutant huntingtin aggregates. On the other hand, polyamines and -difluoromethyl ornithine increased the cell viability in mutant huntingtin expressing cells. Similar results were found for NR1/NR2A and NR1/NR2B expressing cells.
Conclusions The results showed that polyamines may contribute to HD pathology. However, future experiments are required to determine their contribution in detail.

A27 TARGETING GLUTAMINE DEHYDROGENASE ACTIVITY TO INDUCE AUTOPHAGY AND AMELIORATE NEURONAL DEGENERATION; STUDIES USING A DROSOPHILA MODEL FOR HUNTINGTON' DISEASE

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Background Pathological evidences showed that glutamate might play a role in HD. In the brain glutamate is maintained at physiological level by a non-autonomous cycle between glia and neurons called glutamate-glutamine cycle (GGC).
Aims In order to understand the function of this cycle in neuronal survival and HD, we decide to use the flexibility of the genetic model Drosophila melanogaster to manipulate in neurons the expression of key enzyme of the GGC, such as