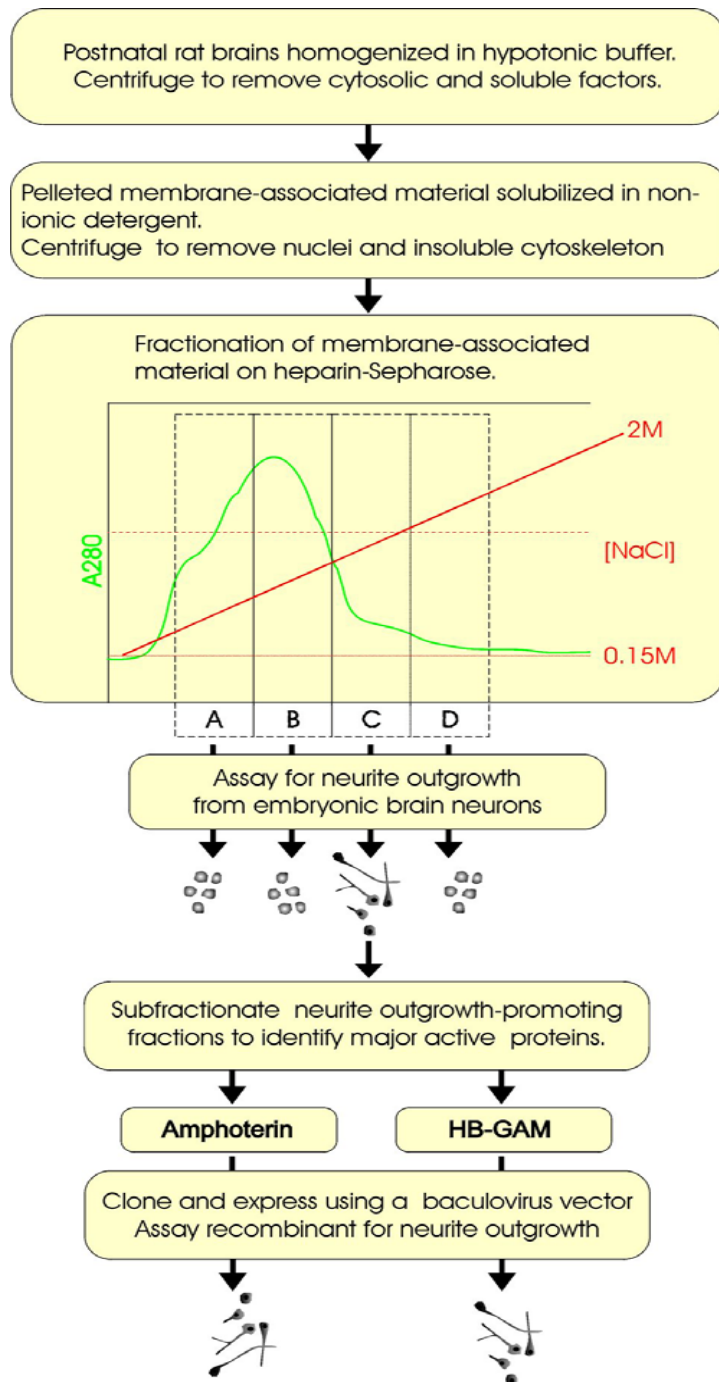


A General Theme

**Environmental Stimuli Regulate Expression of Cell Surface
and Matrix Molecules in Brain**

Changes in Expression Levels Regulate Behavior

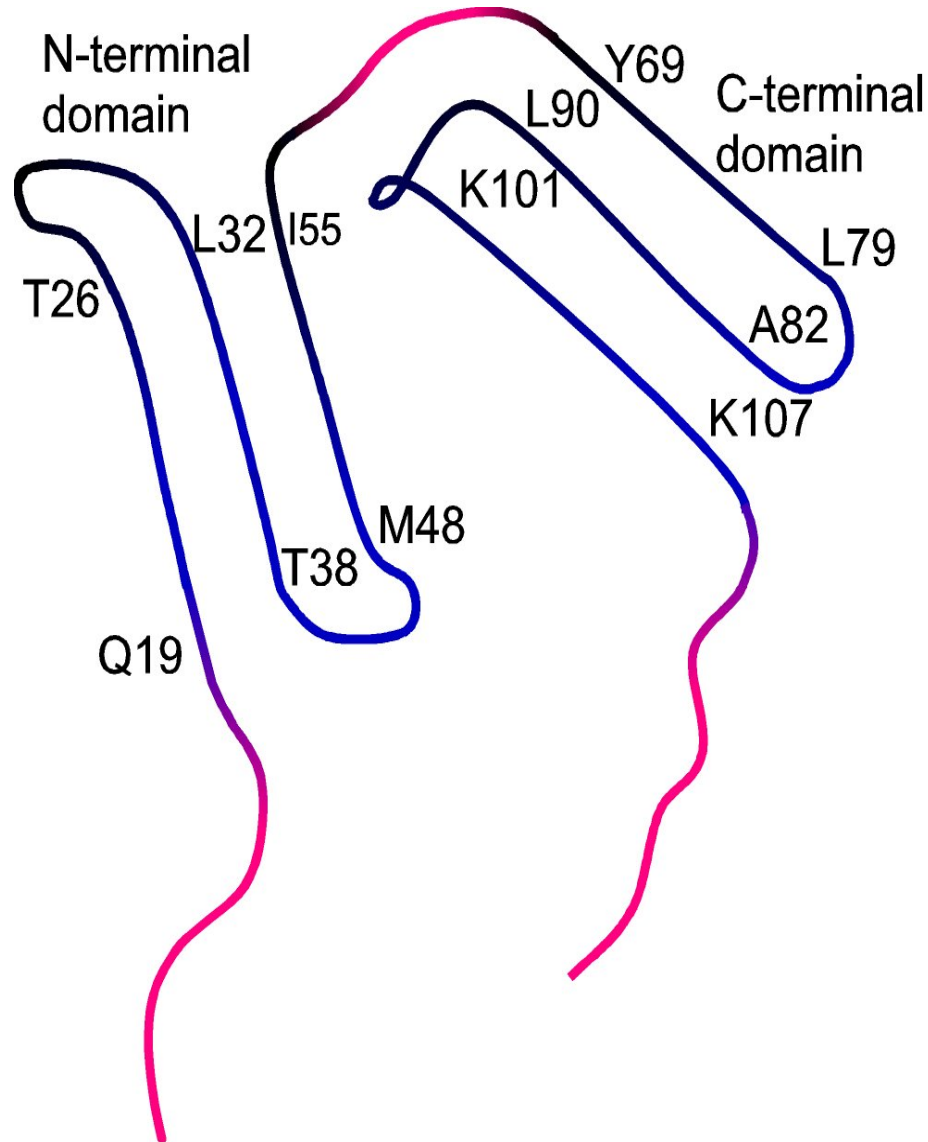


Research Strategy

Amphoterin and HB-GAM (Heparin-binding Growth-associated Molecule) were defined as major neurite outgrowth-promoting proteins of perinatal rat brain.

HB-GAM Contains Two β -sheet Domains Connected by a Flexible Linker

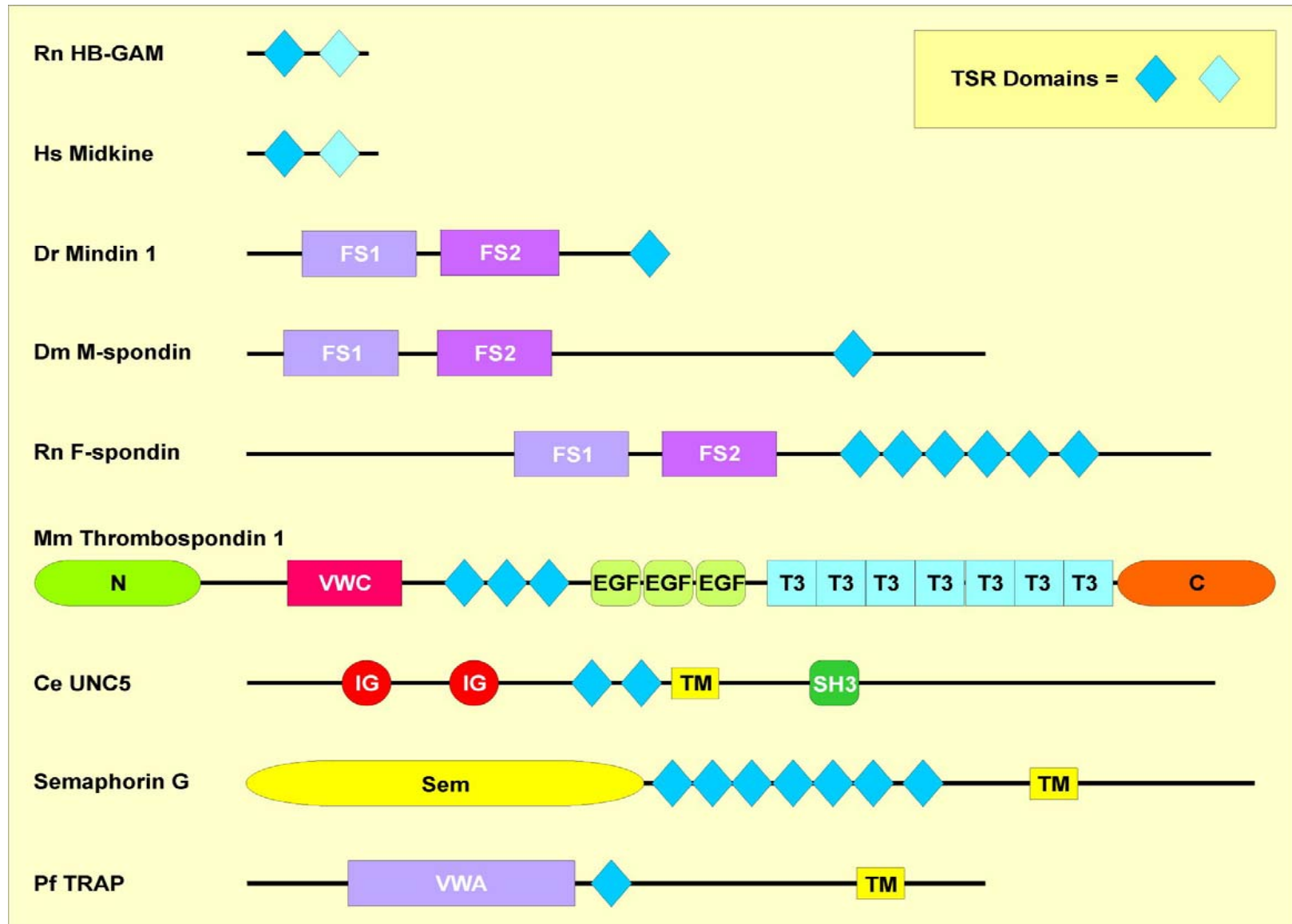
The N-terminal and C-terminal Polylysine Tails Form Random Coils



Kilpeläinen, I., Kaksonen, M., Kinnunen, T., Avikainen, H., Fath, M., Linhardt, R.J., Raulo, E., and Rauvala, H. (2000). **J. Biol. Chem.** 275: 13564-13570.

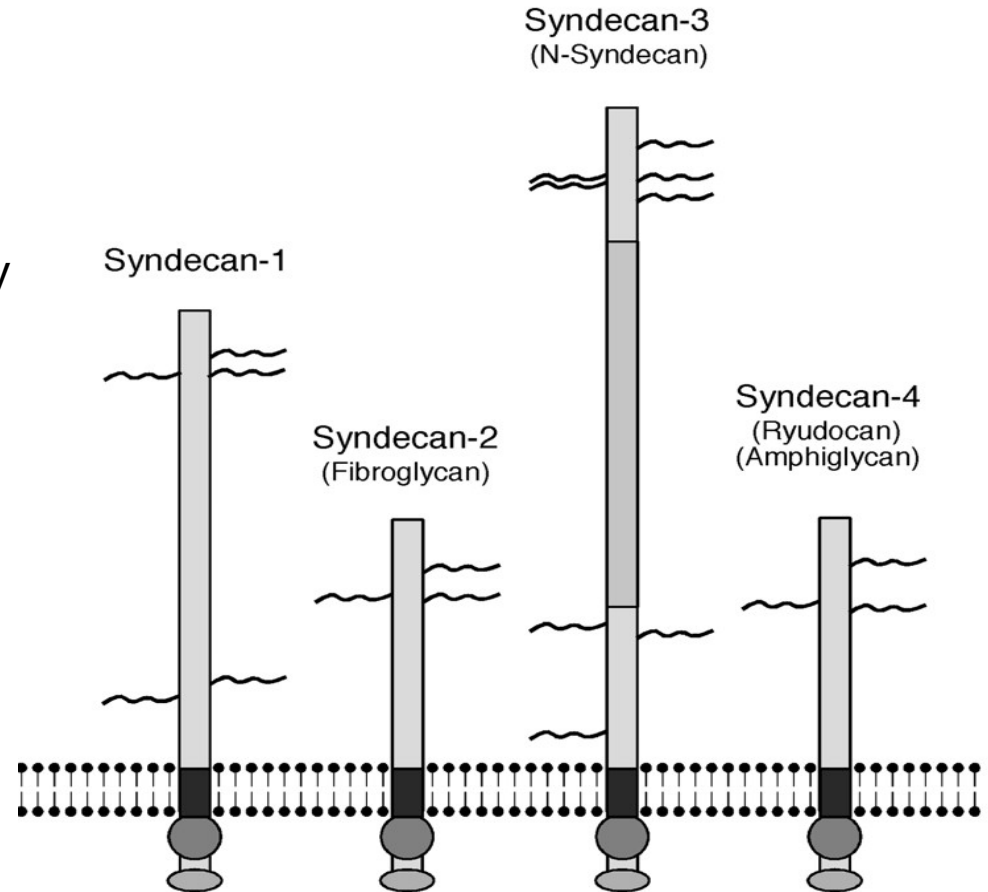
The β -sheet domains are responsible for binding to heparin/HS (syndecan-3)

The β -sheet Domains of HB-GAM Correspond to the Thrombospondin Type I (TSR) Repeat Found in Many Proteins that Bind to Cell Surface or Extracellular Matrix



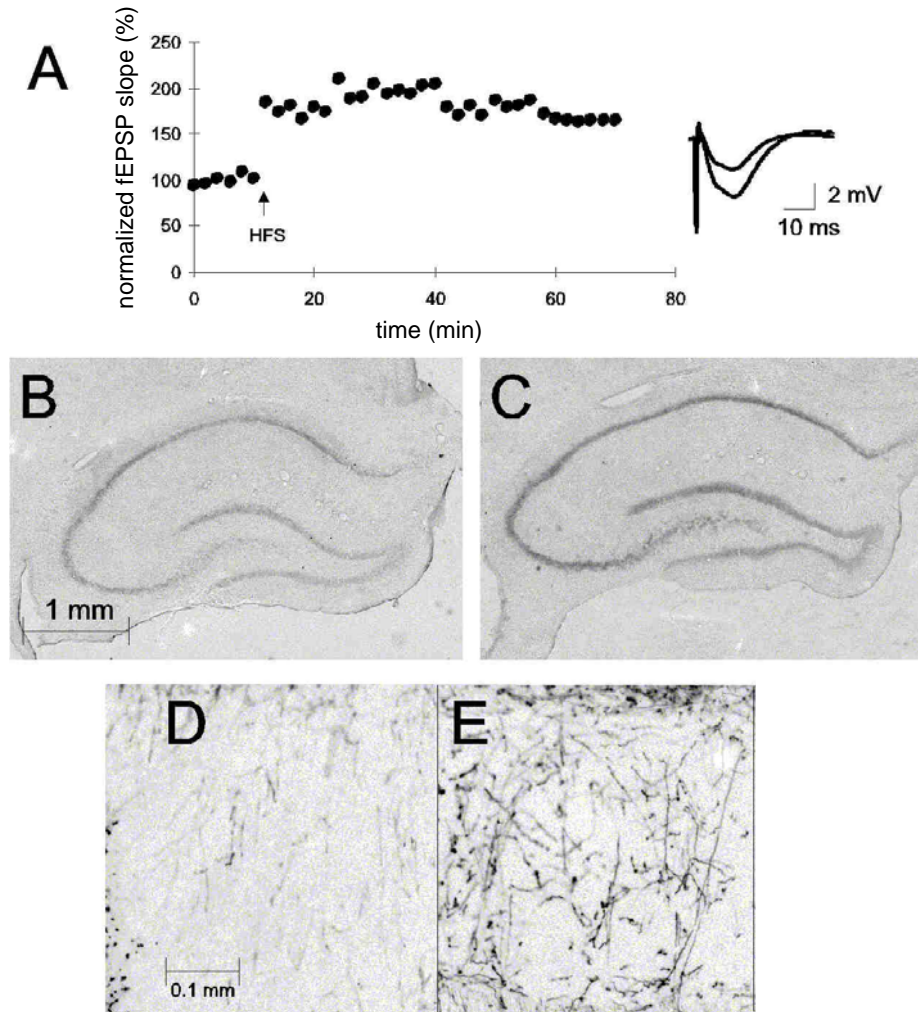
Syndecan-3

- **Syndecans** together with **glypicans** form the two major families of cell surface **HSPGs**
- Syndecan-3 (N-syndecan) is mainly expressed in the *nervous system* especially during the *development*
- Syndecan-3 is involved in cell adhesion, neurite guidance and cell migration
- Syndecan-3 is expressed in activity-dependent manner
- Application of soluble syndecan-3 inhibits LTP



Syndecan-3 Expression is Regulated by Neuronal Activity

(Lauri, S.E., Kaukinen, S., Kinnunen, T., Ylinen, A., Imai, S., Kaila, K., Taira, T., and Rauvala, H., 1999. *J. Neurosci.* 19: 1226-1235)



Syndecan-3 Knockout Mice

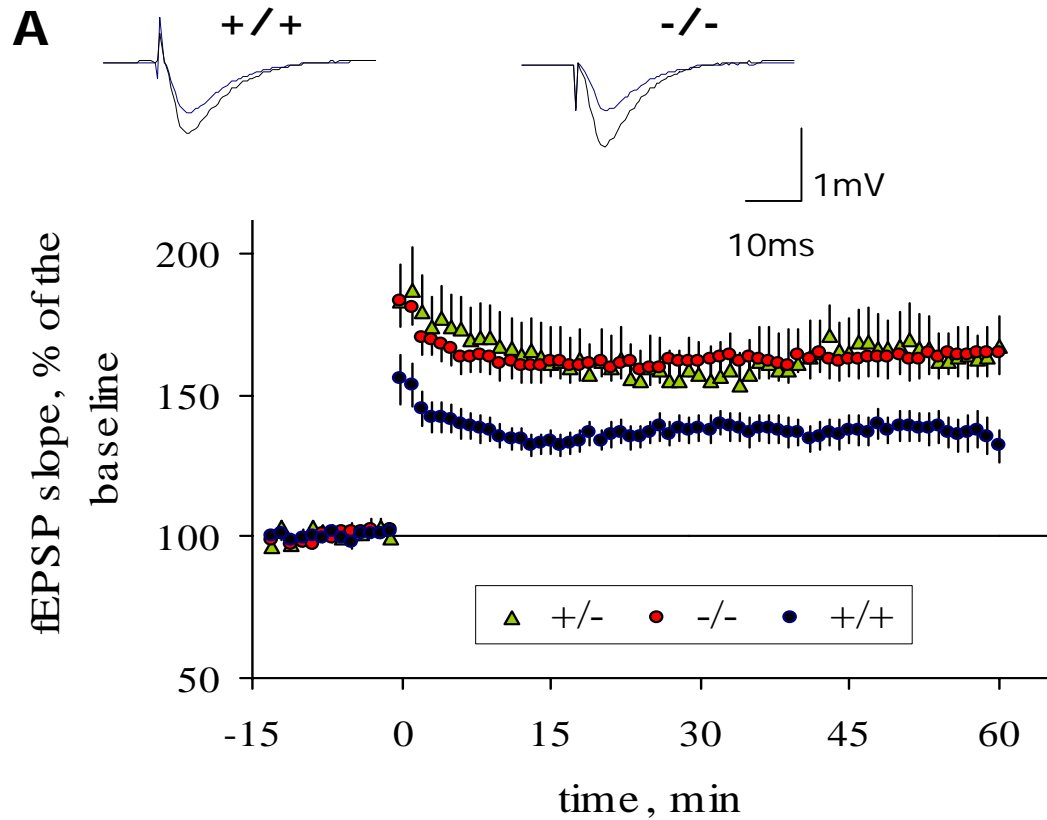
-/- +/- +/+



Northern blot

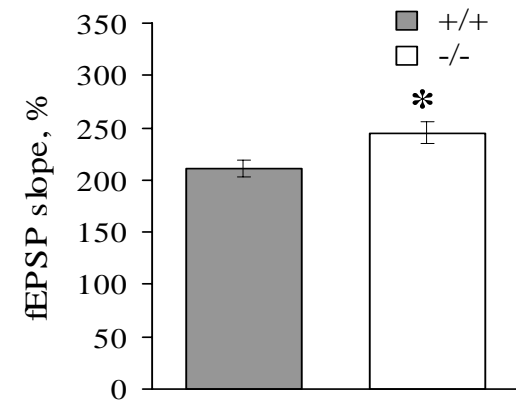
No signal is detected in the -/- samples, and in the +/- samples the signal is about half of that in the +/+ samples.

LTP is enhanced in syndecan-3-deficient mice



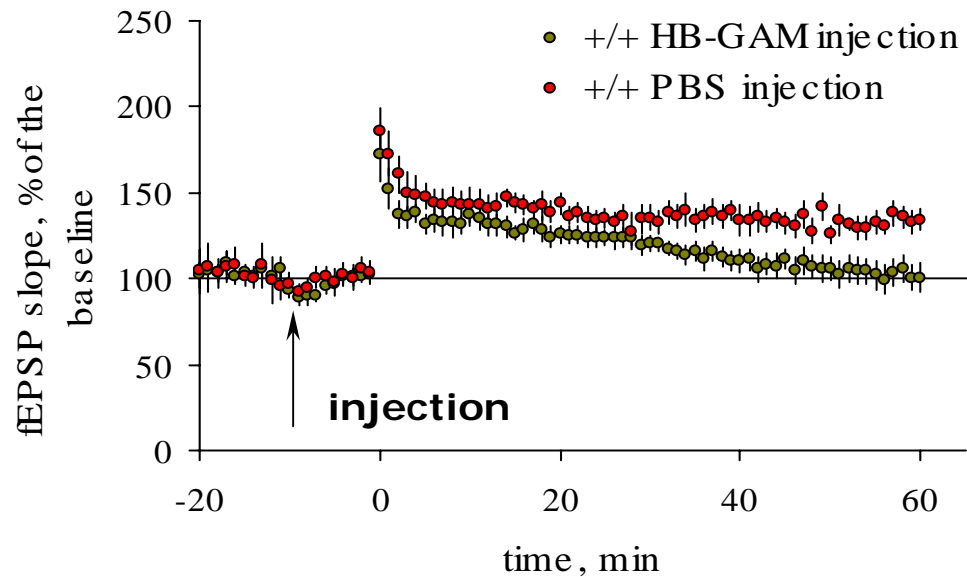
B

LTP saturation level is higher in the syndecan-3 knockout mice

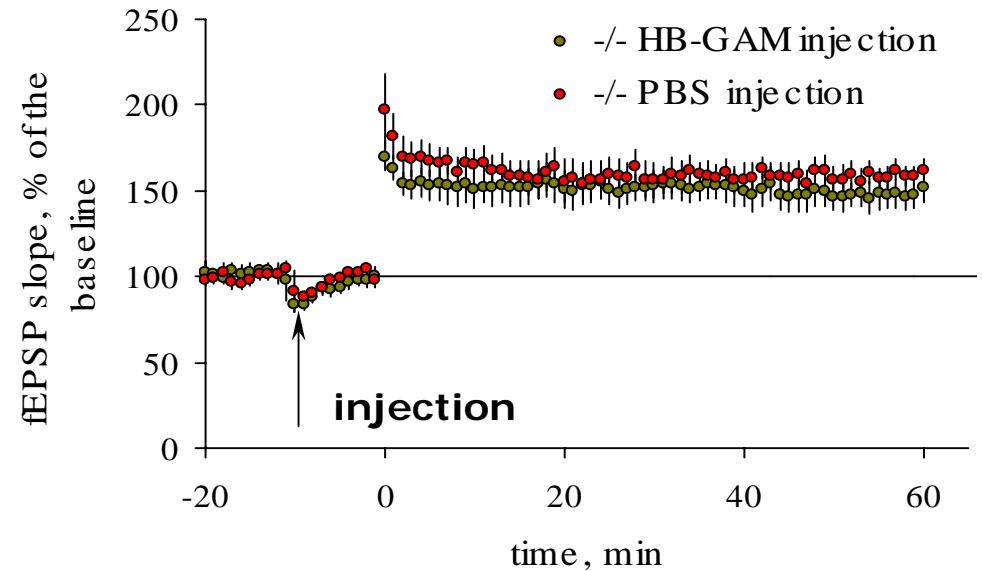


Syndecan-3 is involved in modulation of LTP by HB-GAM

Wild-type mice

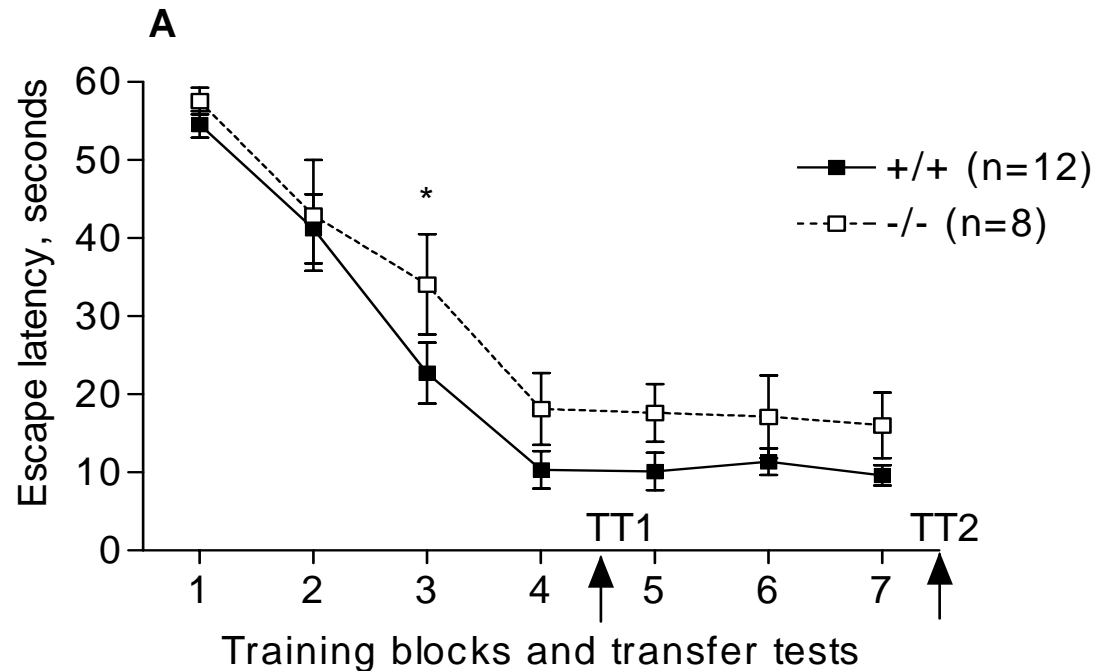


Knockout mice



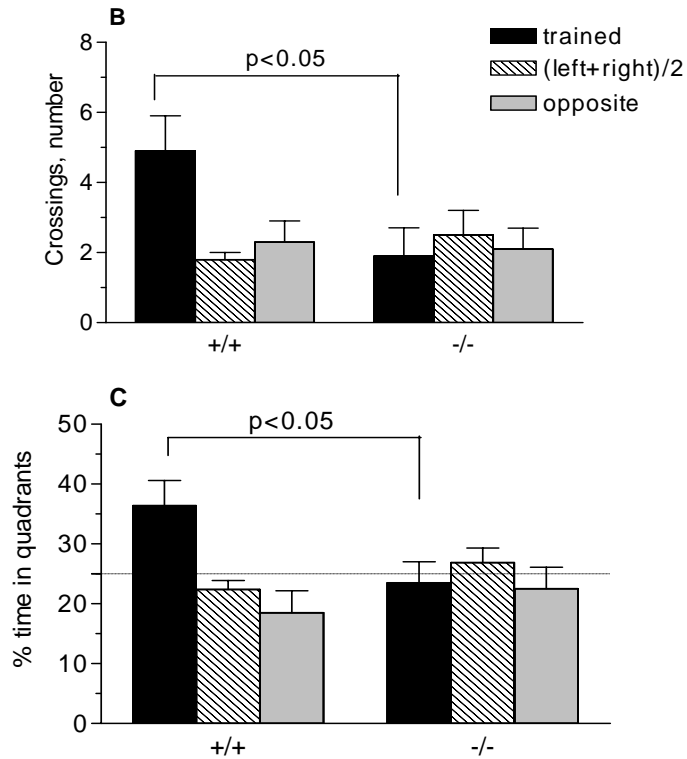
Impaired memory of the syndecan-3-deficient mice in water maze

Escape latency to the hidden platform

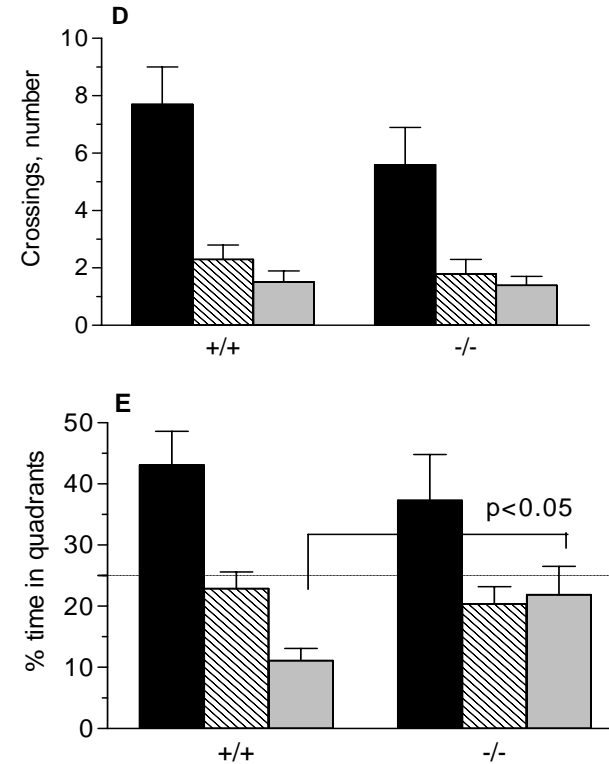


Impaired memory of the syndecan-3-deficient mice in water maze

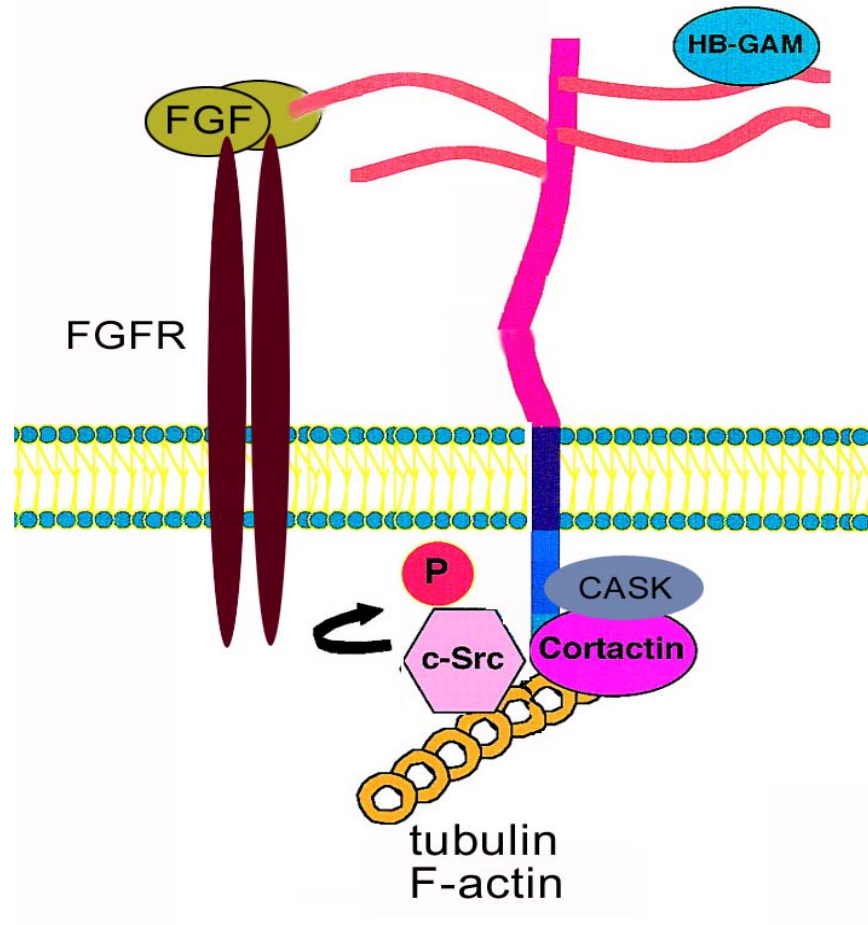
Transfer Test 1



Transfer Test 2



Schematic model of putative syndecan-3 signaling mechanisms



Phenotype of the mutant mice lacking or overexpressing HB-GAM

Genotype	LTP	Learning & memory
HB-GAM KO	Enhanced	Decreased
HB-GAM overexpressing	Decreased	Enhanced
Syndecan-3 KO	Enhanced	Decreased

CONCLUSIONS

- Syndecan-3 in mouse is not essential for basic processes of development
- Syndecan-3 is involved in the activity-dependent regulation of synaptic strength in hippocampus.
- Syndecan-3 deficiency also impairs hippocampus-dependent memory.

AUTHORS

- Marko Kaksonen
- Ivan Pavlov
- Vootele Võikar
- Sari Lauri
- Anni Hienola
- Ruusu Riekki
- Tomi Taira
- Heikki Rauvala