Tissue plasminogen activator (tPA)

tPA is a key component of the fibrinolytic system

- tPA activates plasminogen to plasmin
- plasmin degrades fibrin

tPA is expressed and active in the nervous system

- acts as plasminogen activator (PA)
- other substrates, e.g. extracellular matrix
- non proteolytic mechanisms of action

- cell migration, axon growth, synapse selection
- induction by neural activity, involvement in LTP
- induced by motor learning
- mediator of cell death (stroke, epilepsy)

Antiproteases in the nervous system

Serpins inhibit serine-proteases by formation of stable complexes

Protease nexin-1 *(PN-1)*

- expressed by glia and neurons
- promotes neurite outgrowth
- LTP augmented in Thy/PN-1 mice, reduced in KO
- inhibits **thrombin** > tPA, uPA, plasmin, trypsin

Neuroserpin *(Ns)*

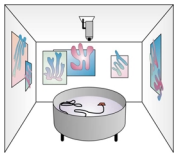
- released from growing DRG axons
- expressed in adult and developing nervous system
- inhibits **tPA** > plasmin = uPA >>> thrombin

Genetic models with disturbed protease-antiprotease balance

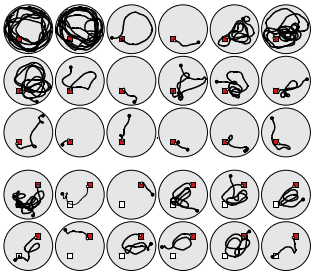
Mouse models	tPA KO	Thy/cNs ✕ Thy/tPA		Ns KO
tPA activity	0%	45%	400%	100%
CA1 LTP	red		incr	
active avoidance	def	def		norm
spatial reference memory	norm	norm	incr	norm
episodic-like memory		red?		
anxiety-like behaviors	norm	(incr)	norm	incr

Spatial reference memory task in the watermaze

"Morris watermaze"

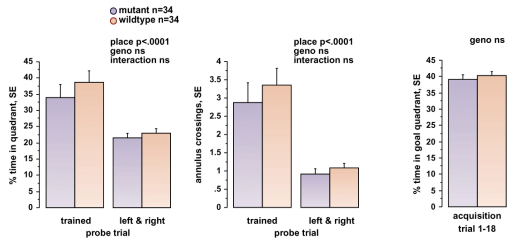


- 5 days x 6 trials
- trial max 120s
- ITI 30-60min
- pool 150cm
- water 24-26°C
- probe: trial 19 (60s)



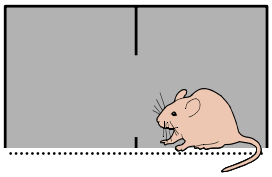
Normal spatial reference memory in tPA KO mice

Huang et al. PNAS 93:8699-8704, 1996



2-way active avoidance task

(shuttle box)



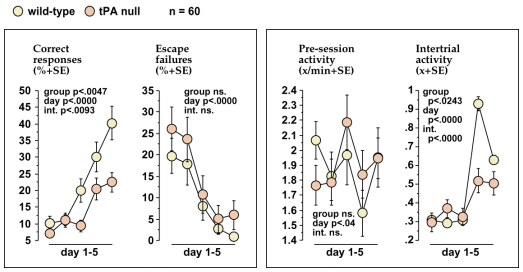
- 15s CS
- CS + US max 5s
- 5-15s ITI

- **escape**:
  current off by animal
- **correct** response:
  current avoided
- **failure**:
  current off automatically

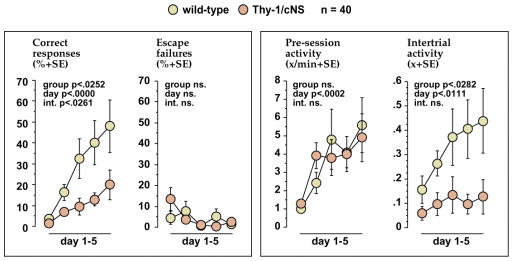
- 5 days x 80 trials
- presession activity
- intertrial activity

Poor active avoidance learning in tPA KO mice

Huang et al. PNAS 93:8699-8704, 1996

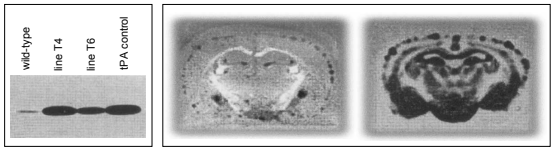


Impaired active avoidance learning in Thy/cNs transgenic mice



tPA activity is increased in Thy/tPA transgenic mice

Madani et al. EMBO J. 18:3007-3012, 1999

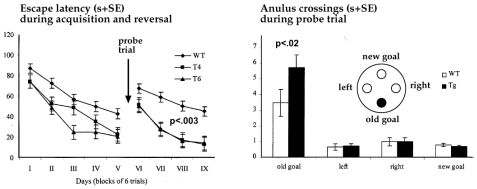


zymography

wild-type Line T4

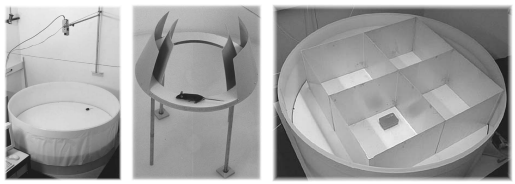
Enhanced watermaze learning in Thy/tPA transgenic mice

Madani et al. EMBO J. 18:3007-3012, 1999



Tests of exploratory activity

Open field **Zero maze** **Emergence & Novelty**



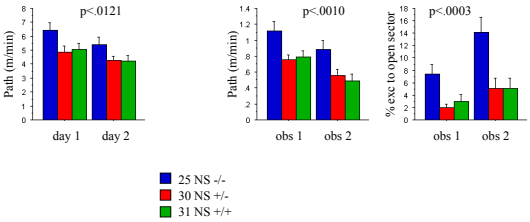
2x 10 min
activity
center time

2x 5 min
activity
open sector exploration

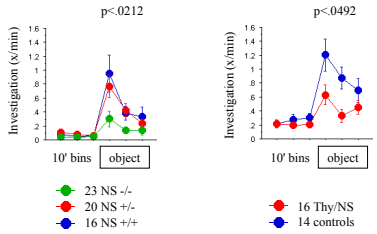
3x 30 min
activity
time in box - reaction to novelty

Increased anxiety and reduced activity in Ns null mice

Open field **Zero maze**



"Neophobia" in mice with altered expression of Ns



Extracellular serine proteases in brain tissue

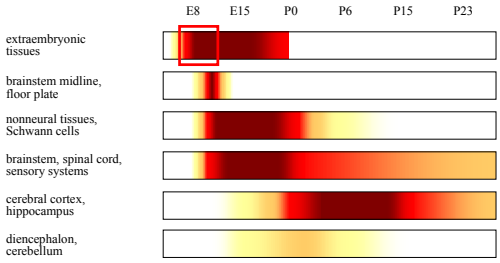
- tissue plasminogen activator (tPA)
- neuropsin *(Chen et al. JNS 15:5088, 1995)*
- neurosin *(Yamashiro BBA 1350:11, 1997)*
- neurotrypsin *(Gschwend et al. MCN 9:207, 1997)*
- BSP1/2 *(Davies et al. JBC 273:23004, 1998)*

Neurotrypsin

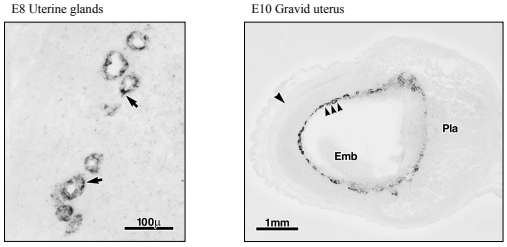
(Gschwend et al. MCN 9:207-219, 1997)

- amplified from P10 mouse brain RNA
- mosaic protein of 761 amino acids
- trypsin-like serine protease
- in situ hybridization in adult mouse: expression restricted to nervous system
- substrates ?
- regulators ?

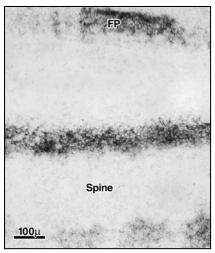
Time course of neurotrypsin mRNA expression



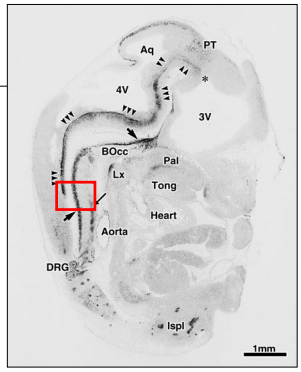
Neurotrypsin mRNA in trophoblast and maternal tissues



Neurotrypsin mRNA in midline structures

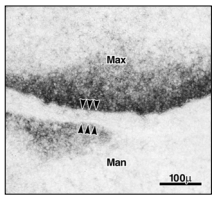


E12 floor plate

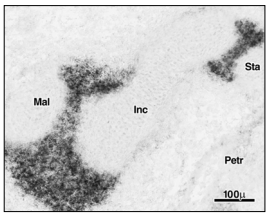


E12 embryo sagittal

Neurotrypsin mRNA at embryonic tissue boundaries

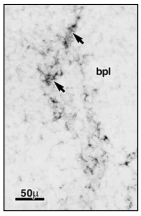


E12 gingival mesenchyme

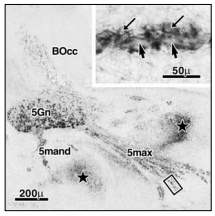


E17 auditory ossicles

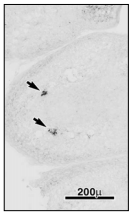
Neurotrypsin mRNA in Schwann cells / precursors



E11 brachial plexus

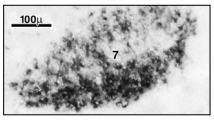


E12 trigeminal nerve & ganglion

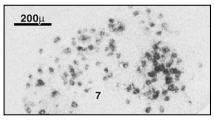


E17 dig. nerves

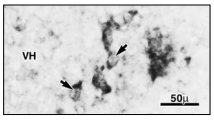
Neurotrypsin mRNA in embryonic and adult motor neurons



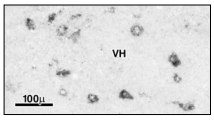
E15 facial motor nucleus



Adult facial motor nucleus

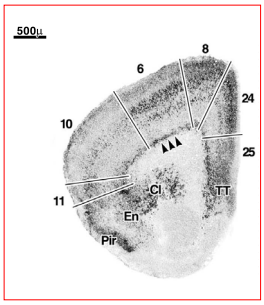


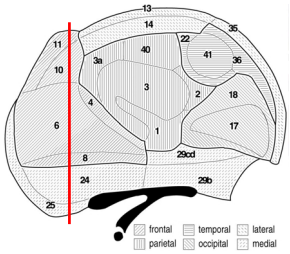
E17 ventral horn



Adult ventral horn

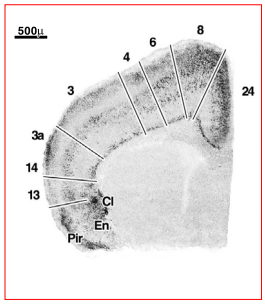
Neurotrypsin mRNA in postnatal cerebral cortex

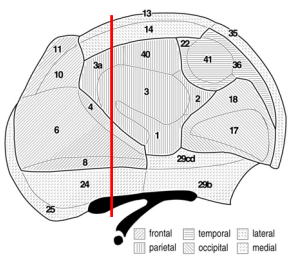




Caviness, Jr. JCN 164:247, 1975

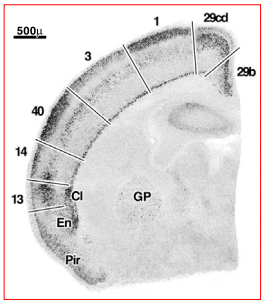
Neurotrypsin mRNA in postnatal cerebral cortex

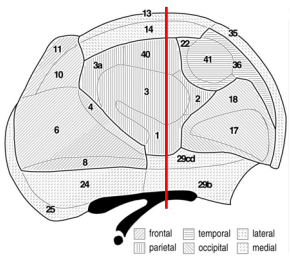




Caviness, Jr. JCN 164:247, 1975

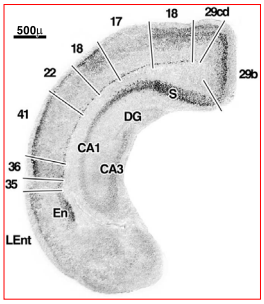
Neurotrypsin mRNA in postnatal cerebral cortex

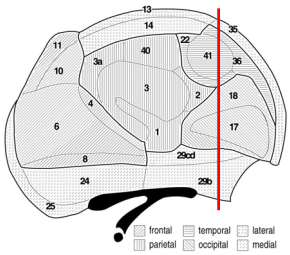




Caviness, Jr. JCN 164:247, 1975

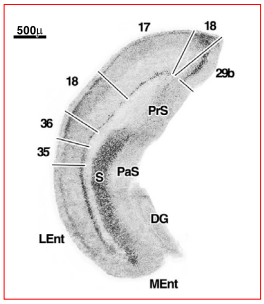
Neurotrypsin mRNA in postnatal cerebral cortex

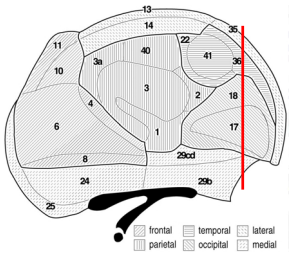




Caviness, Jr. JCN 164:247, 1975

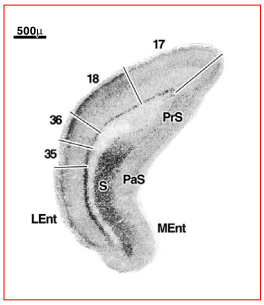
Neurotrypsin mRNA in postnatal cerebral cortex

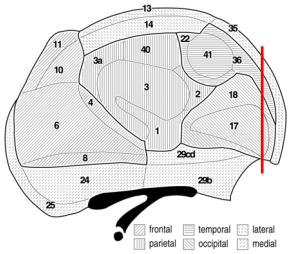




Caviness, Jr. JCN 164:247, 1975

Neurotrypsin mRNA in postnatal cerebral cortex





Caviness, Jr. JCN 164:247, 1975

Synopsis of neurotrypsin mRNA in postnatal cerebral cortex