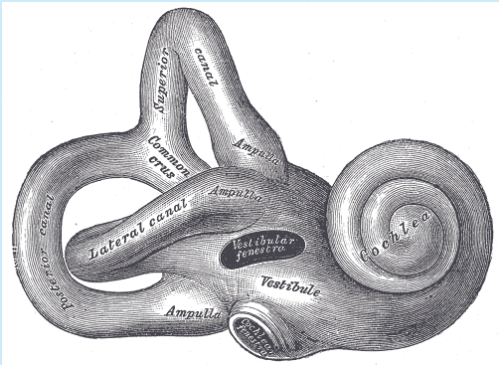
Gentofte Hospital



REGION

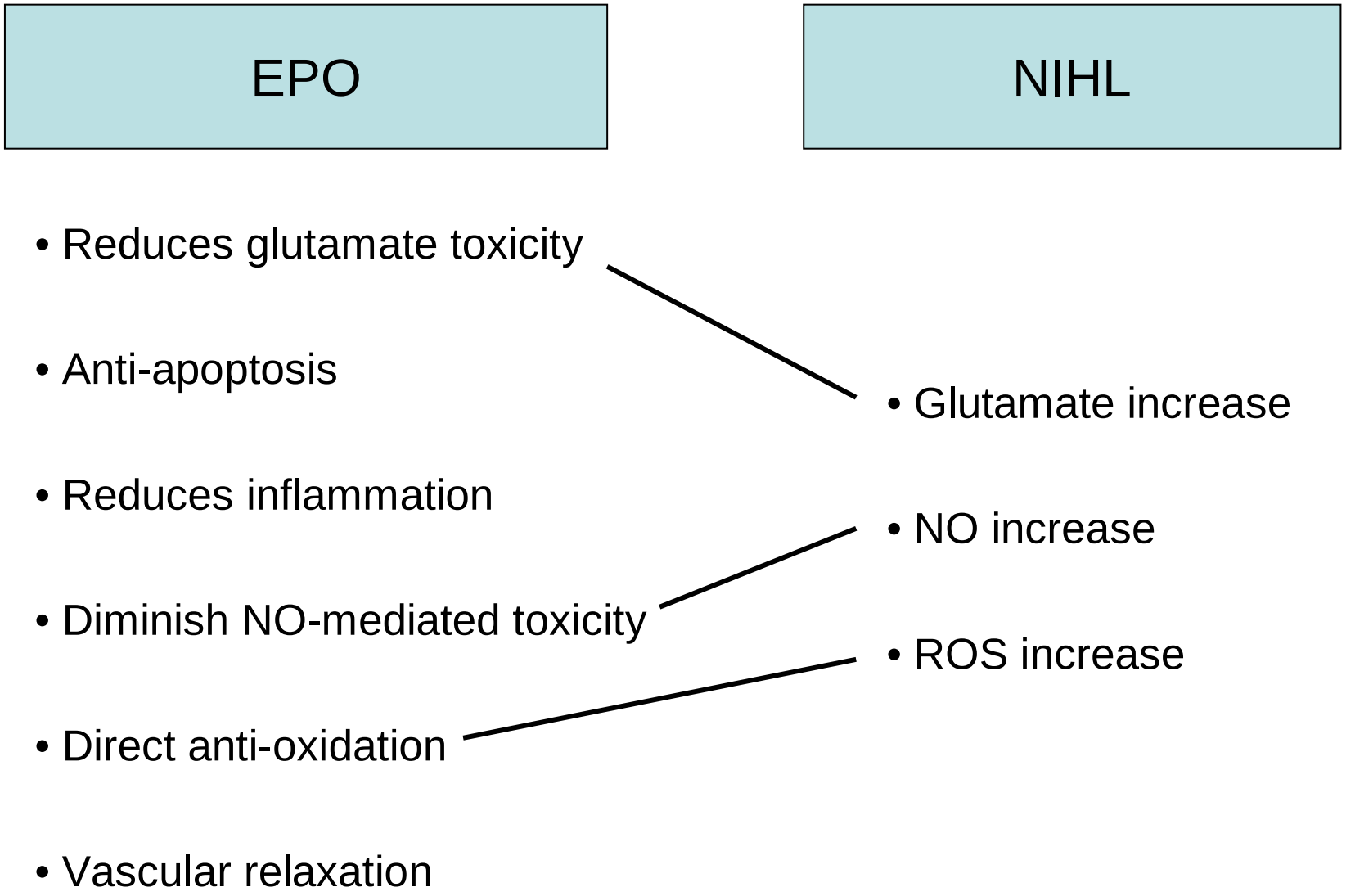
Intratympanic EPO for prevention of noise-induced hearing loss

- BL Frederiksen, N Wagner, SP Lund, K Asal, J Thomsen,
- NV Olsen and P Cayé-Thomasen

BACKGROUND

- Erythropoietin (EPO) has neurotrophic and neuroprotective effects in the CNS and in the retina

- These are results of several effects of EPO receptor binding :
    - decrease of glutamate toxicity
    - generation of neuronal anti-apoptotic factors
    - decrease of nitric oxide mediated injury
    - direct anti-oxidation
    - reduction of inflammation

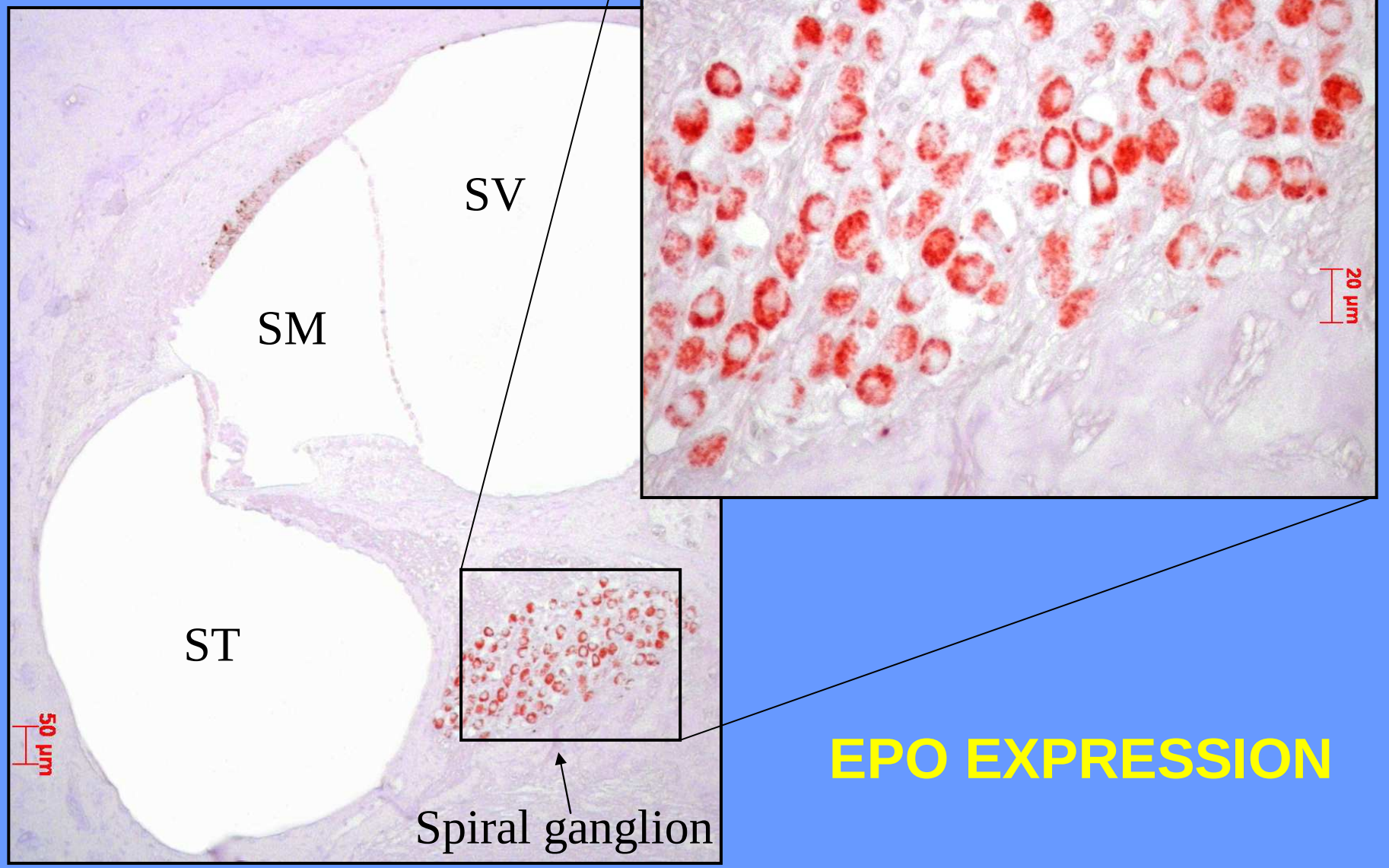


STUDY AIM

- To investigate the expression of EPO and the EPO receptor in the guinea pig inner ear

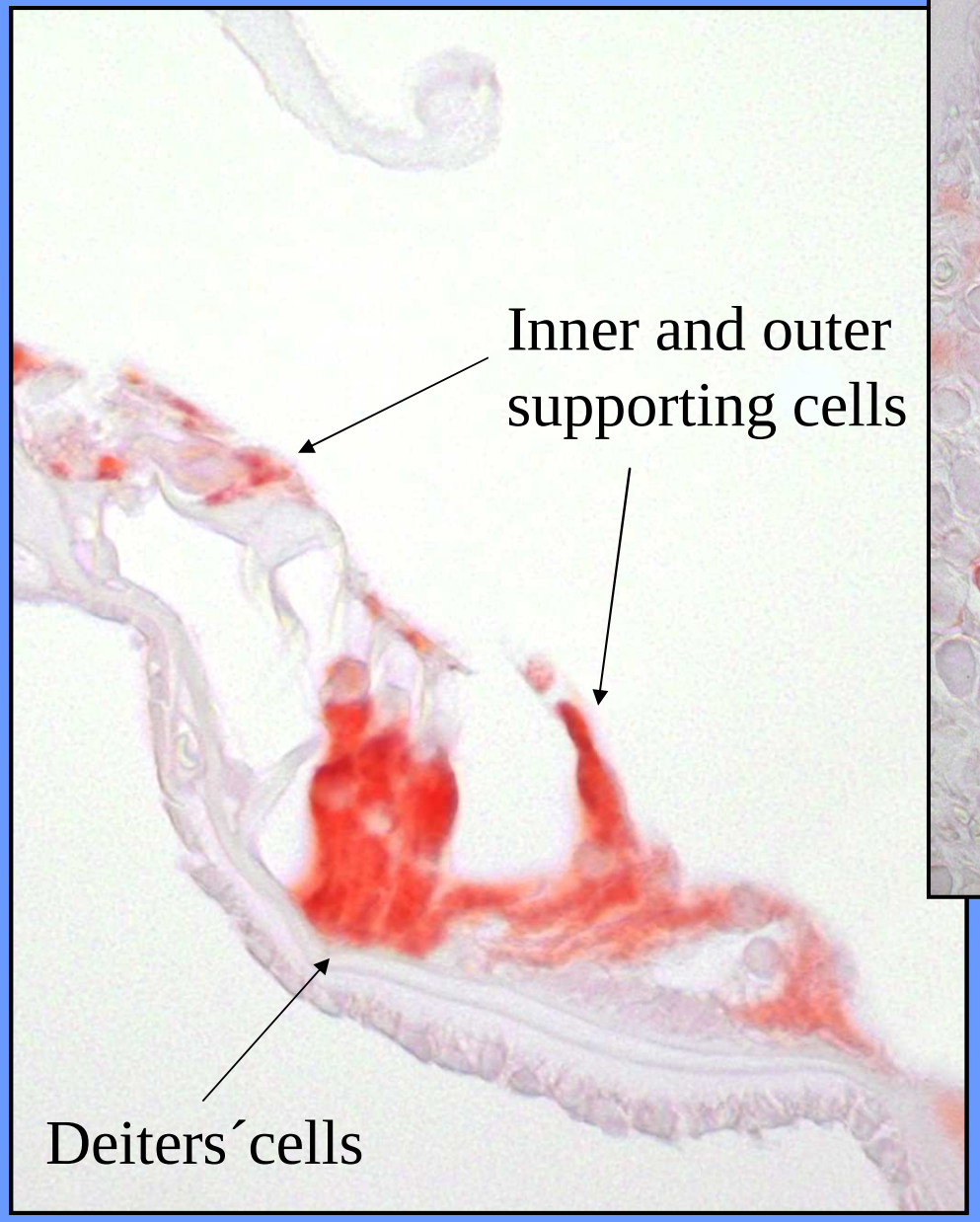
- To investigate the effect of EPO treatment on noise induced hearing loss (NIHL) in rodents

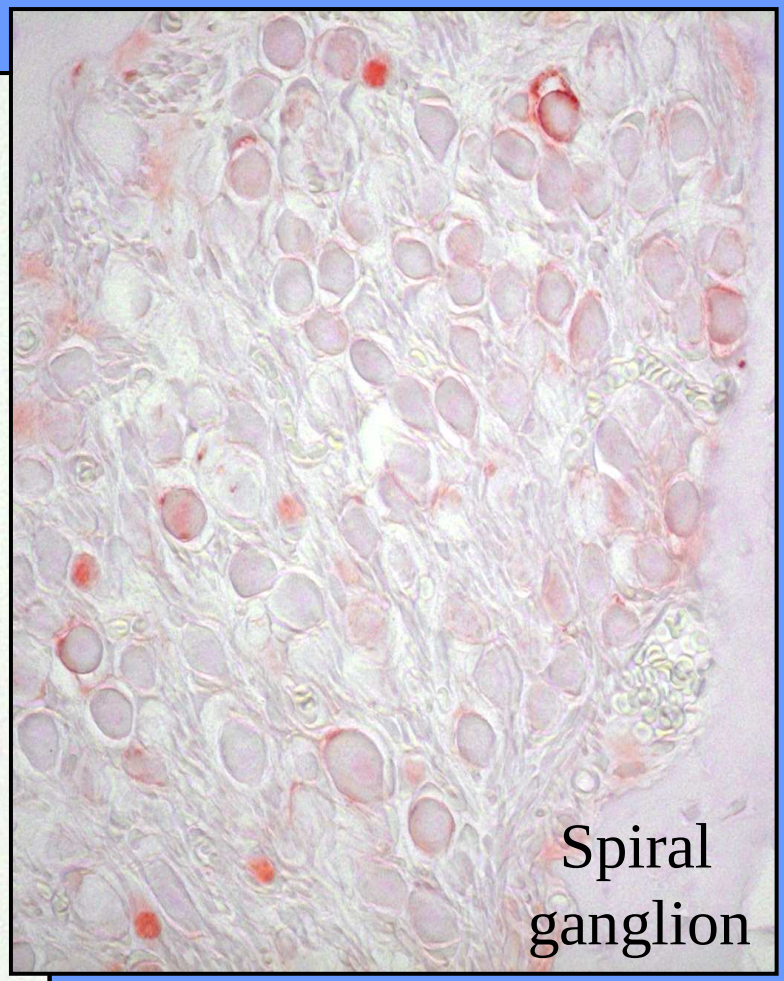
Guinea pig cochlea



EPO EXPRESSION

Guinea pig cochlea





EPO RECEPTOR EXPRESSION

CONCLUSION

EPO is expressed in spiral ganglion neurons

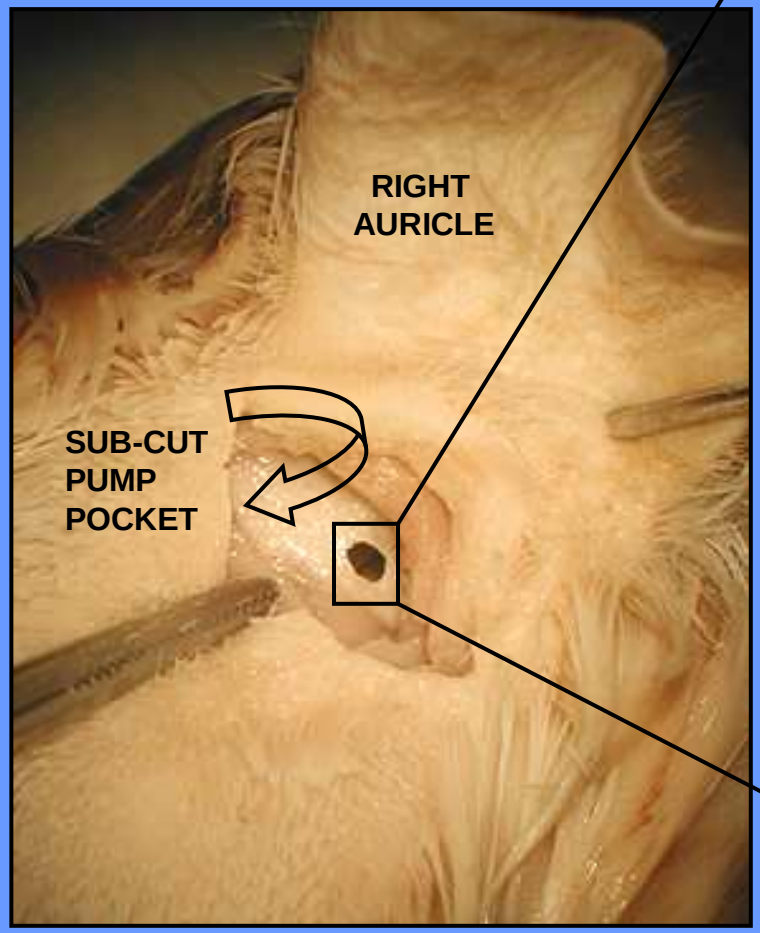
The EPO receptor is expressed
in a number of inner ear cells

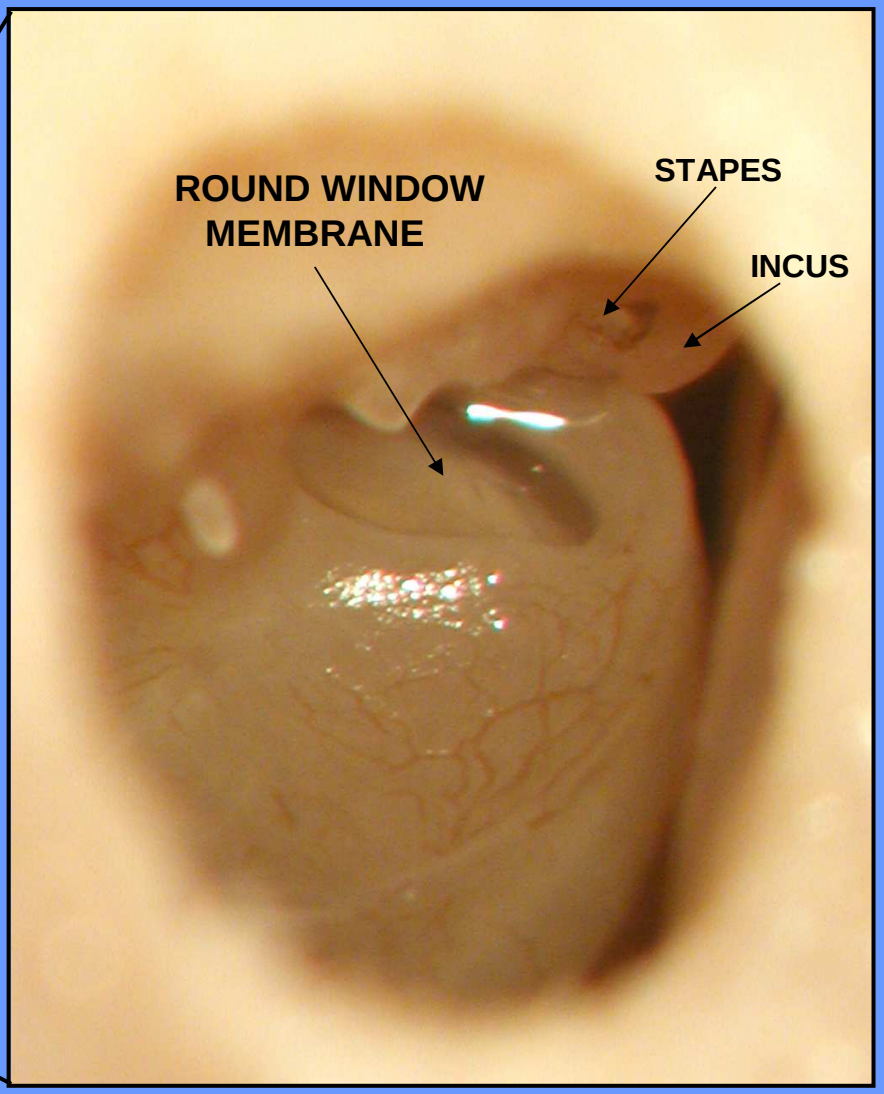
STUDY AIM

- To investigate the expression of EPO and the EPO receptor in the guinea pig inner ear

- To investigate the effect of EPO treatment on noise induced hearing loss (NIHL) in rodents

THE ANIMAL MODEL





THE MODEL

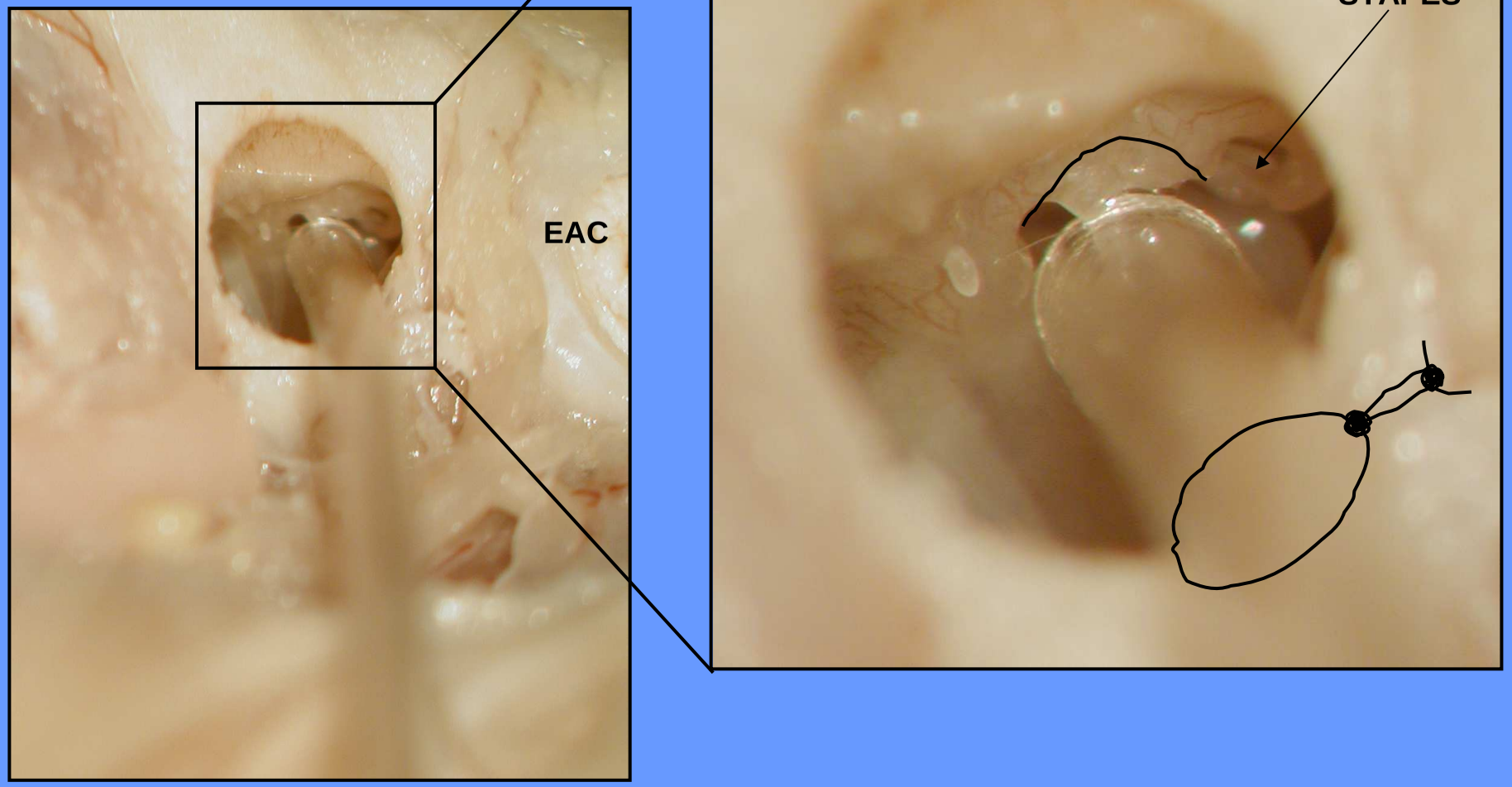


Table 1
Intratympanic EPO

Guinea pigs	Pre-noise measurements Day -1 (dB)		Post-noise measurements Day 8 (dB)		Loss (dB)	
Treatment (Intratympanic)	CDP	ABR	CDP	ABR	CDP	ABR
Sustained EPO (n=10)	15.6 ± 4.6	32.5 ± 3.4	-6.9 ± 0.8	85.0 ± 11.2	22.5 ± 4.9	52.5 ± 10.6
Sustained H_2O (n=8)	14.3 ± 4.9	30.7 ± 1.4	-6.9 ± 0.4	89.3 ± 8.0	21.2 ± 5.1	58.6 ± 8.9
Instilled EPO (n=8)	14.2 ± 6.5	30.6 ± 2.3	-5.6 ± 1.9	79.4 ± 13.6	19.8 ± 5.8	48.8 ± 12.5

Trial 1. Results (means) of pre- and post-noise measurements of the cubic distortion product (CDP) and auditory brainstem response (ABR) in guinea pigs treated intratympanically with erythropoietin (EPO) or saline (H_2O). The mean loss of hearing is shown to the right. There was no significant effect of EPO treatment. The ± values are the 95% confidence intervals.

Table 2 Intratympanic EPO

Rats Treatment (Intratympanic instillation)	Pre-noise measurements Day -1 (dB)		Post-noise measurements Day 8 (dB)		Loss (dB)	
	CDP	ABR	CDP	ABR	CDP	ABR
EPO 1 h post-noise (n=10)	27.5 ± 1.5	27.5 ± 1.9	0.1 ± 4.3	68.8 ± 13.7	27.4* ± 4.8	41.3 ± 14.0
H_2O 1 h post-noise (n=8)	27.5 ± 2.1	25.0 ± 3.2	12.6 ± 9.4	57.0 ± 19.4	14.9* ± 9.1	32.0 ± 21.6
EPO 14 h post-noise (n=10)	26.4 ± 2.4	28.3 ± 1.8	0.4 ± 2.8	64.4 ± 14.5	26.0§ ± 4.2	36.1 ± 14.0
H_2O 14 h post-noise (n=8)	27.5 ± 8.5	29.2 ± 1.7	7.3 ± 5.0	54.2 ± 16.2	20.3§ ± 7.0	25.0 ± 16.9
All EPO (n=20)	26.9 ± 1.4	27.9 ± 1.2	0.2 ± 2.4	66.5 ± 9.5	26.7# ± 3.1	38.5¤ ± 9.4
All H_2O (n=16)	27.5 ± 1.0	27.3 ± 2.8	9.7 ± 5.6	55.5 ± 16.1	17.8# ± 5.6	28.2¤ ± 17.5

Trial 2. Results (means) of pre- and post-noise measurements of the cubic distortion product (CDP) and auditory brainstem response (ABR) in rats treated by intratympanic instillation of erythropoietin (EPO) or saline (H_2O). The mean loss of hearing is shown to the right. EPO treatment augmented the hearing loss in the early treatment group (p= 0.025, Students t-test, degrees of freedom: 16)(*) and overall (p= 0.006, Students t-test, degrees of freedom: 32)(#). § symbolizes a p-value of 0.09 (Students t-test, degrees of freedom:16) and ¤ symbolizes a p-value of 0.1 (Students t-test, degrees of freedom: 32) .
The ± values are the 95% confidence intervals.

Table 3
Intraperitoneal EPO

Rats Treatment (Intraperitoneal, day -1)	Pre-noise measurements Day -1 (dB)		Post-noise measurements Day 14 (dB)		Loss (dB)	
	CDP	ABR	CDP	ABR	CDP	ABR
8 h noise + EPO (n=12)	26.3 ± 1.2	30.4 ± 1.9	4.7 ± 4.9	65.4 ± 10.3	21.7 ± 5.3	35.0 ± 10.4
8 h noise + H_2O (n=11)	26.2 ± 1.0	31.4 ± 1.4	5.0 ± 5.2	66.4 ± 9.4	21.2 ± 5.8	35.0 ± 9.0
3 x 8 h noise + EPO (n=12)	24.8 ± 4.1	31.7 ± 1.5	2.1 ± 2.8	71.7 ± 4.9	22.7 ± 2.7	40.0 * ± 5.1
3 x 8 h noise + H_2O (n=11)	27.0 ± 0.7	31.4 ± 2.4	6.0 ± 4.3	62.3 ± 8.8	21.0 ± 4.1	30.9 * ± 9.0

Trial 3. Results (means) of pre- and post-noise measurements of the cubic distortion product (CDP) and auditory brainstem response (ABR) in rats treated by intraperitoneal injection of erythropoietin (EPO) or saline (H_2O). The mean loss of hearing is shown to the right. EPO treatment in combination with noise for 3 x 8 hours produced a significant increase of the ABR threshold shift (asterisks) (p= 0.048, Students t-test, degrees of freedom: 21). The ± values are the 95% confidence intervals.

CONCLUSION

EPO augments NIHL
in rodents

Synergy of decreased blodflow?