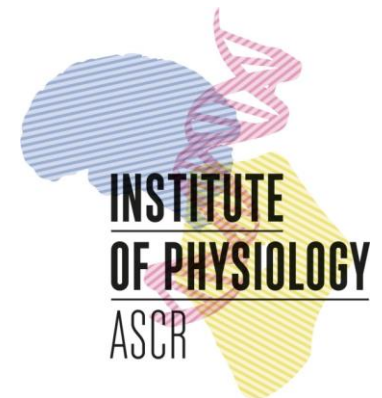


What animal tests can tell us about safety of drugs for developing brain?

Hana Kubova

Institute of Physiology CAS

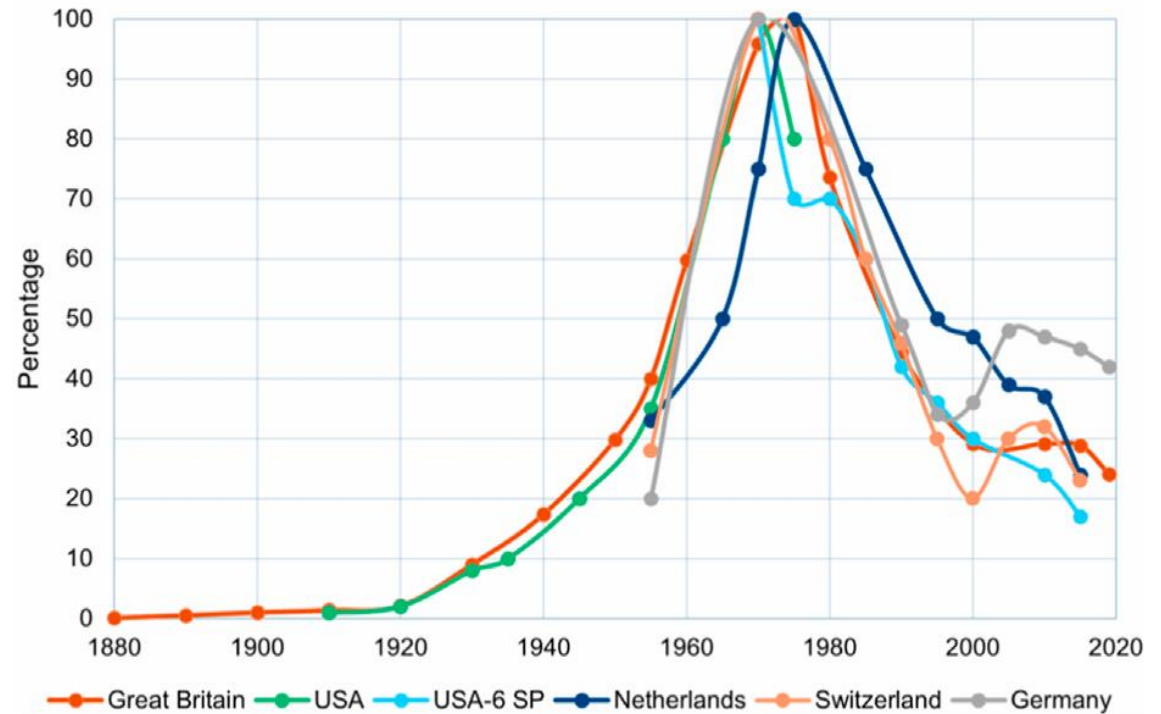
Prague, Czech Republic



Animals predominate
in new drug
development for
more than 100 years

Are animal
experiment
necessary for
new drug
development?

Relative Lab Animal Use in Different Countries
(Percentage of Peak Use for Each Country)



(Hartung, 2024)

Why so many drugs fails after being promising in preclinical studies?

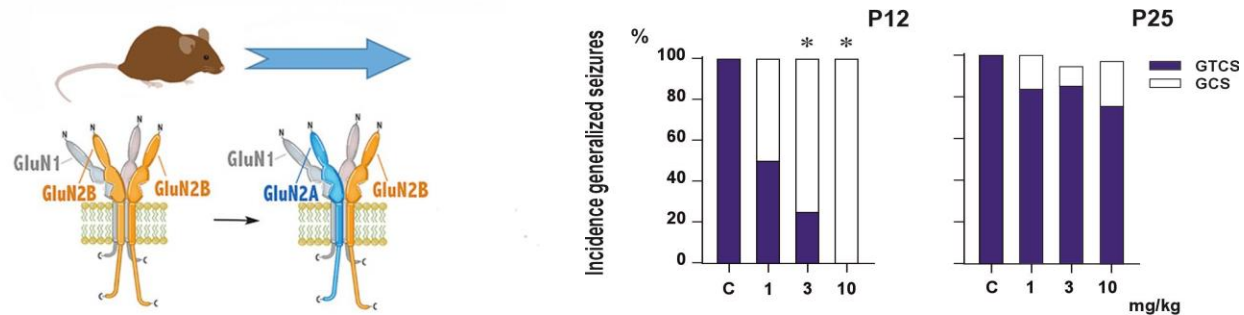
Too much reliance on animal models can also mislead drug development

Inaccurate data interpretation

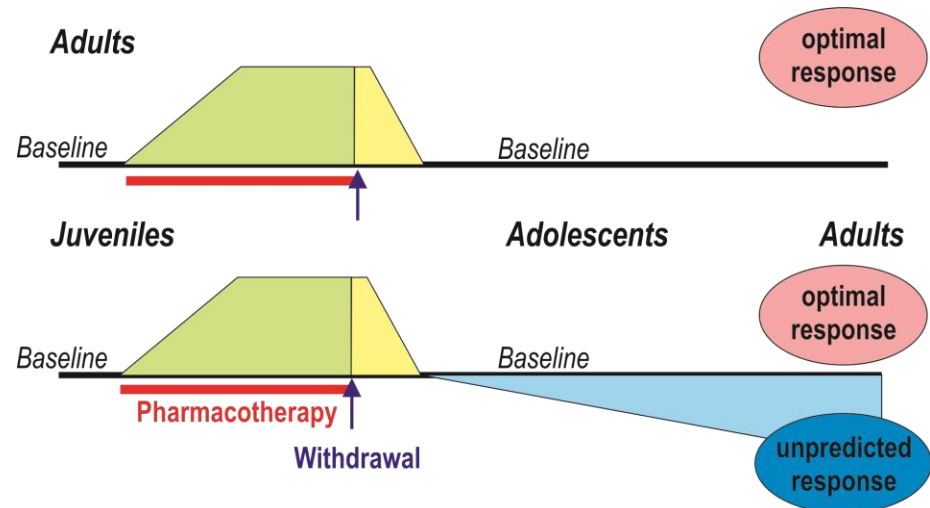
Wrong or inappropriate models we are using in preclinical studies

How can animal testing help us in search for drugs for pediatric use and for their safety?

Search for age specific drug targets



Studies on safety of drugs for developing organism



Can drug
exposure during
early
development
permanently
affect brain
functions?

Drug exposure during critical developmental periods can **permanently alter certain brain functions, increase risk of development of psychopathologies or behavioral abnormalities later in the life**

Under certain conditions, **early drug exposure can have positive long-lasting effects** – prevention of disease development or disease modifying effects, lower response to stressors, suppression of anxious behavior, etc.

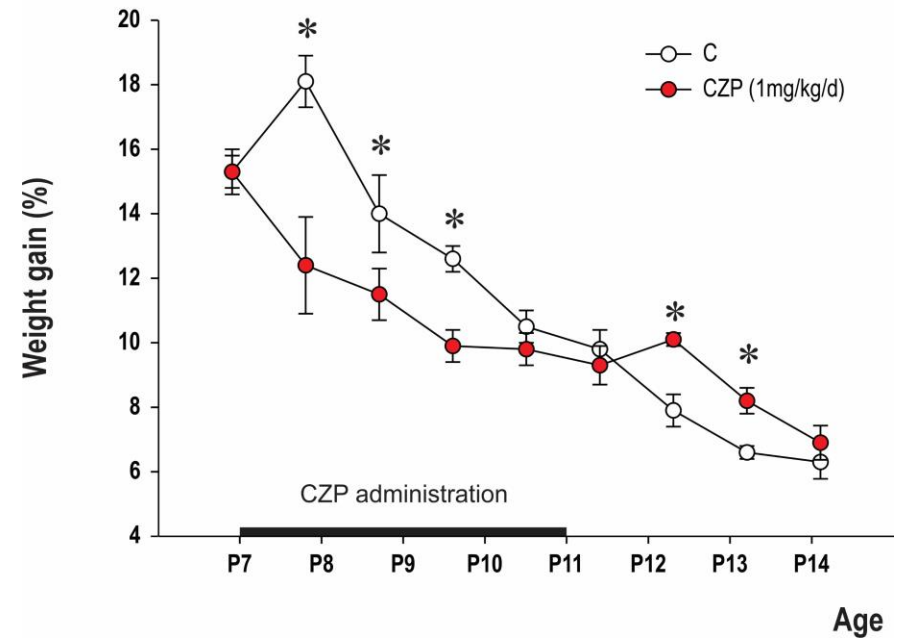
Early-life exposure to clonazepam induces long-term behavioral alterations.



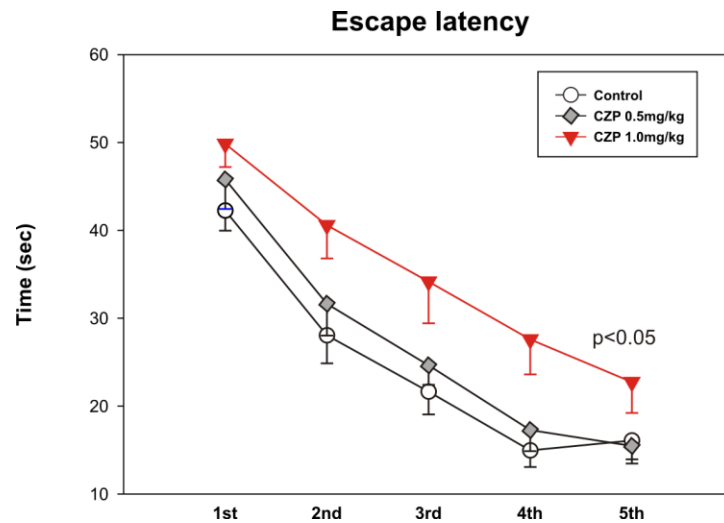
- Benzodiazepine **clonazepam** (0.5 or 1 mg/kg administered daily for 5 consecutive days P7-P11
- Behavioral testing up to adulthood
- Changes at the level of neurotransmission

Relative daily weight gain

In selected doses **CZP** exhibits anticonvulsive effects in PTZ model for 12 to 24hrs, induces mild motor impairment for about 30 min and in repeated administration has limited effects on body growth



Early-life exposure to clonazepam induces long-term cognitive impairment.



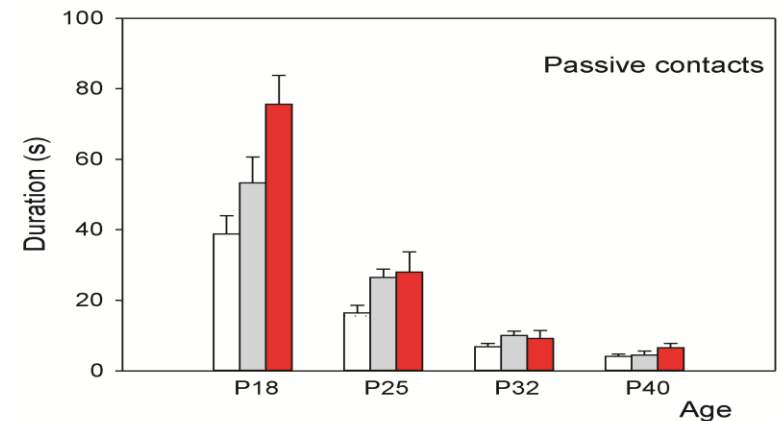
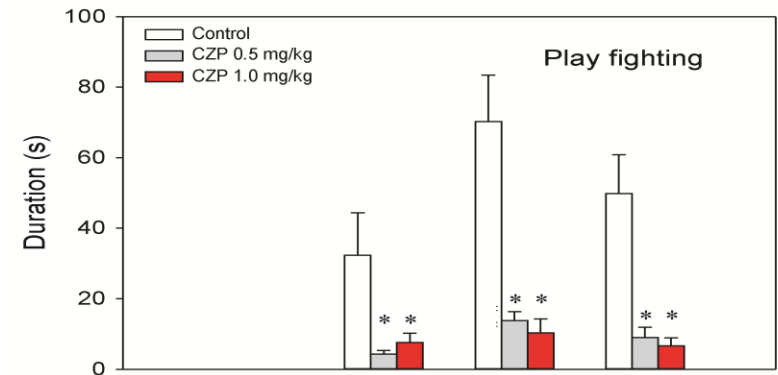
- Morris water maze
- Tested at the age of
- 3 months

Early-life exposure to clonazepam induces long-term alterations in development of play behavior.

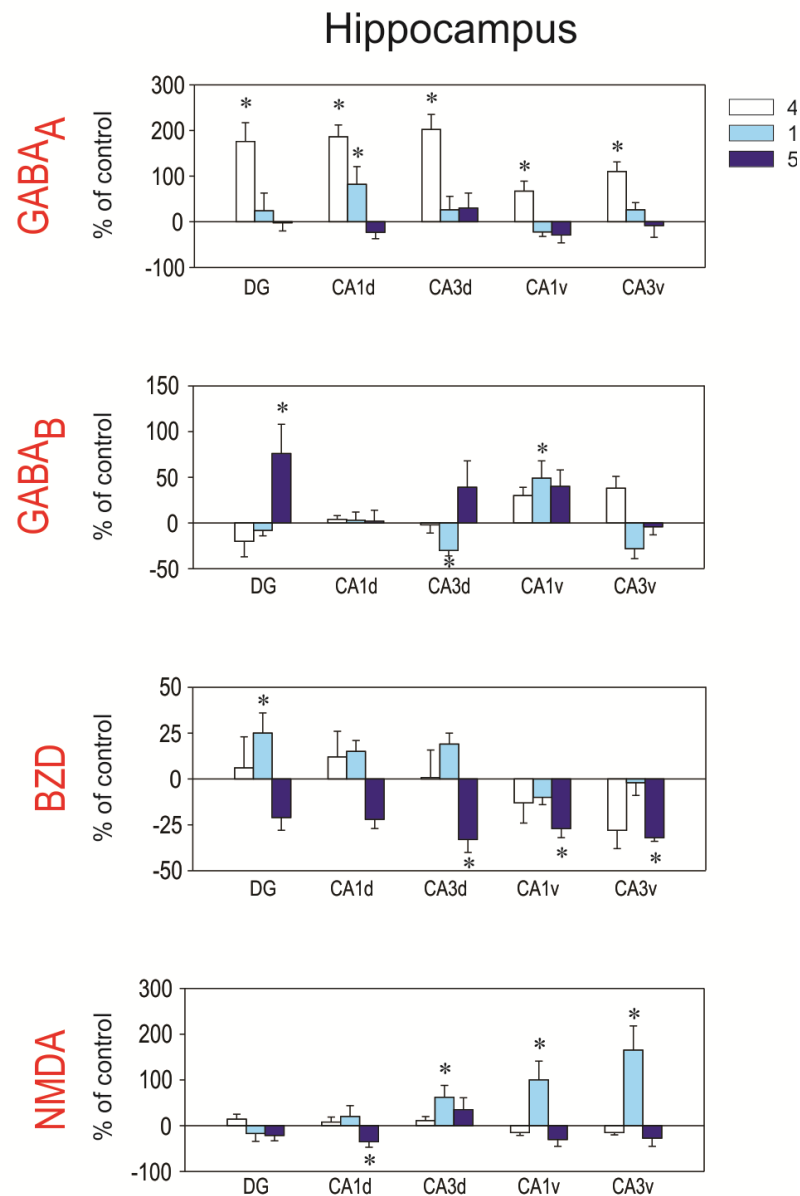
Tested in prepubescent rats (P33)



Veneema Lab



Early-life benzodiazepine exposure has long term effects on neurotransmission



Conclusions

- Clinically relevant animal models are critical in our search for new, innovative therapeutic targets including age or sex specific
- They can help us to test safety of drugs for developing organisms, delayed toxicity, etc.
- We need to develop and validate clinically relevant models and tests for juvenile animals, platform for multicentric studies as well as for training of young researchers
- Developmental studies are more expensive and time-consuming compared to regularly used screening test