The Central Nervous System in Poisoning:
What can we Learn from Animal Studies?

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The Central Nervous System
Targets for toxic substances and drugs

Organophosphorus (OP) and carbamate compounds

Basic Neurochemistry, 7th ed.
The Central Nervous System
Various methodologies also in use at FFI

- **In vivo**
  - Various animal species
  - Quantitative and qualitative differences in response to toxic substances among species occur

- **Ex vivo**
  - In vitro cell cultures
  - Brain slices

A. Decreased mitochondrial activity (cell death)
B. Increased cell damage
Organophosphate (OP) intoxications
Medical management (nerve agents) – Research at FFI

- Three phase model (McDonough & Shih, 1997)
  Acetylcholine $\rightarrow$ Acetylcholine $\rightarrow$ Glutamate
  Glutamate

- Post exposure medical treatment will consist of several drugs; drugs in autoinjector(s) and follow-up drugs

- Generic drugs like oximes against all nerve agents are not available

- Presently available drugs are not sufficiently effective to prevent brain injuries

Ref: Trends in Pharmacological Sciences
Systematic screening

*In vivo* studies – a three step process - albino rat model

- Lesion studies – mapping sensitive areas
- Micro-infusions in brain to identify critical receptors
- Systemic injections (i.m.)

**Methods**

- EEG by extra- or intra-cranial electrodes
- Evaluation of neuropathology
- General performance/observation of animals
- Behavioural tests
- A number of COTS drugs and experimental drugs

Targets in the CNS
Animal models – rat

Sagittal section of the rat brain showing different brain structures and lesions where we have tested lesions and drugs against nerve agent induced seizures. Anticonvulsive effect was achieved with lesions in area tempestas (AT), mediale septum (MS), piriform cortex (PC), or perirhinal cortex (PRC) (horizontal lines). Absence of anticonvulsive effect with lesions was determined in nucleus accumbens (NA), nucleus basalis magnocellularis (NBM), hippocampus region (HCR), amygdala (AM), substantia nigra (SN) or entorhinal cortex (EC) (vertical lines). Broken lines illustrate deep structures.

Microinfusion of drugs in rat brain
Against nerve agents (OP’s)

- **Atropine**
- **Scopolamine**
- **Caramiphen**
- **Procyclidine**
- **Muscimol**
- **Ethanol**
- **Propofol**

**Area tempestas**

- **Benactyzine**
- **Biperidene**
- **Trihexyphenidyl**
- **Ketamine**
- **MK-801**
- **NBQX**
- **Diazepam**
- **Pentobarbital**

**Medial septum**

- **Atropine**
- **Scopolamine**
- **Procyclidine**

- **Ketamine**
- **Muscimol**

**Posterior piriform cortex**

- **Procyclidine**
- **Ketamine**
- **Caramiphen**
- **NBQX**

**Perirhinal cortex**

- **Procyclidine**
- **Scopolamine**
- **Ketamine**
Medical countermeasures
Neurotransmitters, receptors and sites of action – animal studies

- **Cholinergic nerves**
  - Acetylcholine
  - M and N receptors

- **GABAergic nerves**
  - GABA
  - GABA receptors

- **Glutamatergic nerves**
  - Glutamate
  - NMDA-receptors
Other drugs available?
COTS drugs

• Most countries have specific antidotes devoted to OP intoxications

• Is sufficiently amounts available in critical situations and where?

• FFI in collaboration with Oslo University Hospital, Ullevål made an inventory of all relevant COTS drugs in storage - drugs that can be used in an emergency situation

• FFI-Rapport 2009/01858 is a recommendation (www.ffi.no/publikasjoner/rapporter)
Conclusions – CNS in poisoning
What can we learn from animal studies?

- Years of animal research have provided evidence of complex interactions between chemicals and specific enzymes, molecular receptor targets, proteins and other cell constituents in the CNS
- Natural and synthetic toxins and drugs by themselves are important tools in characterization of such targets
- New effective drug regimens have been developed as a result of using various *in vitro* and *in vivo* methods
- In the development of new countermeasures against OP’s, comprehensive animal studies are of importance as research animals have brain structures similar to humans
- Using specific neuropharmacological approaches by following guidelines for research in experimental epilepsy, FFI has provided suggestions for new ways forward in the treatment of OP poisoning to prevent development of CNS injuries