

University of Medicine and Pharmacy Tîrgu Mureş
Doctoral School

PhD Thesis Summary

ANESTHESIA AND CENTRAL NERVOUS SYSTEM
MECHANISMS OF NEUROTOXICITY AND COGNITIVE DYSFUNCTION

PhD Student: Sircuța Carmen

PhD Scientific coordinator: Prof. Univ. Dr. Azamfirei Leonard

Introduction

Currently, the number of anesthetic procedures performed worldwide has reached about two hundred millions, annually. Although anesthesia has a history of more than 150 years and many anesthetic drugs have been discovered since then, the exact mechanisms of action is still not completely understood. Suspicion and fear of anesthesia persist among the patients. Since some patients develop behavioural disorders after surgical procedures performed under anesthesia, PhD thesis' efforts have been concentrated on the influence of anesthesia on the central nervous system, neurotransmission and neurocognitive functions.

1st Study: The role of Na⁺ and K⁺ channels in the effect of local anaesthetics on transmitter release

In this study, we performed the first study of the effects of two local anaesthetics (lidocaine and bupivacaine) on transmitter release during rest and in response to field (axonal) stimulation using the microvolume perfusion method and isolated prefrontal cortex and spinal cord slice preparations loaded with the radioactive transmitters [3H]dopamine ([3H]DA) and [3H]noradrenaline ([3H]NA). Because local anaesthetics are known to inhibit both sodium and potassium channels, and anaesthetic properties have been attributed to the former effect, we compared their effects with those of tetrodotoxin (TTX), a selective Na⁺ channel inhibitor with anaesthetic activity, and 4-aminopyridine (4-AP), a potassium channel blocker with convulsive activity, on transmitter release from prefrontal cortex and spinal cord slice preparations. Neurochemical evidence demonstrated that local anaesthetics administered at concentrations of 0.5-5 mM, which might have intentionally or accidentally been achieved in clinical practice (during spinal and epidural anaesthesia, peripheral nerve block, etc.), led to presynaptic failure during neurochemical transmission, in in vitro prefrontal cortex and spinal cord slice preparations, including inhibiting transmitter release associated with axonal firing and markedly enhancing extraneuronal concentrations of transmitters due to increased resting, [Ca²⁺]_o-independent release.

Tetrodotoxin, a toxin with selective Na⁺ channel blocking properties, inhibited the stimulation-evoked release, while failing to affect the resting release. In contrast, 4-AP a potassium channel inhibitor enhanced both the resting- and action potential-evoked transmitter releases. Because dopaminergic and noradrenergic mechanisms are involved in the antiallodynic action in neuropathic pain lidocaine's and bupivacaine's noradrenaline-releasing effect in spinal cord may also be involved in their pain-killing action in neuropathic pain.

2nd Study: Influence of General Anaesthesia on Impulsivity and Learning Ability- Experimental Study

The study was performed on living adult male rats, test and drug naive subjects. Animals were separated in two groups: one included the anesthetized animals and the other group was taken as control. Learning ability and impulsivity was tested 24 hours after anesthesia. During the training and testing phases of the experiment, animals learned to distinguish between a large reward and a small one. The preference for the large reward showed the learning ability, or the nonimpulsive choice. The preference for big reward progressively declined during the test phase, while the number of inadequate responses increased both in anesthetized and non-anesthetized rats. The results of this study showed that anesthesia did not influence learning ability nor impulsivity.

3rd Study: Evaluation of early postoperative cognitive dysfunction, depression and anxiety in patients who undergone a general anaesthesia

This study was a prospective observational study which included 130 patients who suffered general or cardiac with cardiopulmonary bypass surgery, under general anesthesia. Study demonstrated that postoperative neurocognitive dysfunction is present at 24 hours after stopping any medication active on central nervous system in noncardiac surgical patients as well as in cardiac surgical patients. The disorder is reversible in the majority of the cases and disappears after the first week. The study also demonstrated that surgery type does not influence the presence or absence of postoperative cognitive dysfunction, but the disorder correlates only with patient related factors as: the level of education and preoperative neuropsychiatric disorders. However, postoperative depression correlates with postoperative inotropic infusion, postoperative infectious complication and education level, while perioperative anxiety correlates with older age, only.

The PhD thesis contribute to the progress of understanding and identifies some of the neurotoxicity mechanism of anaesthetics by demonstrating the effect of locally applied anaesthetics on chemical neurotransmission in the central nervous system. As 3rd study compared pre- and postoperative neurocognitive function of each patient and postoperative neurocognitive dysfunction was identified during the first days after the surgery, with no differences between the types of surgery, it is recommended to discuss about this entity with patient, during the preanesthetic interview. The emphasis should be on predisposing factors.

Key words: anaesthesia, neurotransmitters, postoperative cognitive dysfunction.