EFFECTS OF THE GENERAL ANESTHETICS ON THE CENTRAL NERVOUS SYSTEM

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[Effetti a carico del S. N. C. degli anestetici generali. Potenzialità e limiti]

SUMMARY

Currently the potentialities and the limits of the general anesthetics on the CNS (Central Nervous System) are still matter of study. Concerning this, recent scientific achievements raise perplexity against the neuroprotective effects of general anesthetics.

In this study the authors want to focus both the neuroprotective and neurotoxic effects scientifically tested on animal samples. Aware that today wide clinical experiments have failed the purpose to individualize the relationship between exposure to general anesthetics and neurotoxicity, they conclude affirming that a cautious use of the various anaesthetic agents used today can avoid the onset of side- effects, sometimes even irreversible.

Key words: General anesthetics, ischemic injury, apoptosis, neurodegenerative disorders, irreversible cognitive impairment

RIASSUNTO

Le potenzialità ed i limiti degli anestetici generali sul S.N.C. sono attualmente tuttora oggetto di studio. Recenti acquisizioni scientifiche sollevano a tal proposito perplessità riguardo a effetti neuroprotettivi degli stessi. In questo studio gli autori si propongono di metterre a fuoco sia gli effetti neuroprotettivi che quelli neurotossici scientificamente provati su modelli animali.

Consapevoli che oggi estesi trial clinici hanno fallito nell'obiettivo di individuare il rapporto tra esposizione agli anestetici generali e neurotossicità, concludono affermando che un uso giudizioso dei vari agenti anestetici oggi adoperati può evitare l'insorgenza di effetti indesiderati, a volte anche irreversibili.

Parole chiave: *Anestetici generali, insulto ischemico, apoptosi; disordini neurovegetativi, compromissione cognitiva irreversibile*

Introduction

Hypnotic agents and sedatives have a remarkable effect on the vital functions of the human organism and particularly on the CNS (Central Nervous System), modulating and influencing its various processes. The general anesthetics, both intravenous and inhalatory, are liposoluble compounds and therefore are able to spread through the cellular plasmatic membranes, to penetrate in the cytoplasm and to interact with numerous cellular compounds. Their pharmacological effects have been for long time considered rapid and completely reversing.

Recent scientific achievements have however raised some perplexities and consequently denied such considerations, stimulating a motivated interest to the explanation of the real effects and modifications induced against the CNS (Central Nervous System) from such pharmacological category. Currently it's a largely approved opinion that the general anesthetics are able to influence the gene expression, the protein transcription and synthesis and various other cellular functions in ways not yet fully elucidated and producing short-and long-term effects in many tissues, throughout the Central Nervous System.

Anesthetic agents exposure: neuroprotection and neurotoxicity

While in the most greater part of the patients submitted to general anesthesia for surgical procedures it has been observed a rapid and complete functional recovery against the Central nervous

System, in animal models, the various anesthetics have caused numerous long-term unexpected effects, especially during the period of the CNS (Central Nervous System) development and specific pathophysiological contexts. The degree of reversible changes induced by the temporary exposure to general anesthetics is significantly wide, going from rapid recovery of the nervous functions to the cessation of the hypnotic effect to states of deep coma with long-term disappearance of nociceptive reflexes. The possibility that the anaesthetic preconditioning minimizes and protects from ischemic injury against the Central Nervous System is more and more an evident datum in literature, but it's very probable that these types of neuroprotective effects hide wider and not necessarily long-term benefits effects.

The ischemic injury against the Central Nervous System is characterized by precocious death of the neurons for an essential mechanism of glutamatergic excito-toxicity, leading to repeated and uncontrolled release of glutamate at the synaptic level and subsequent post-synaptic depolarization-mediated by NMDA (N-methyl-D-aspartate) and AMPA (alpha-amino-3-hydroxy-5-4 propionic metilisoxazolil) receptors. In addition to affect the neuronal survival, a component of delayed death intervenes in causing the damage from nervous ischemic insult due to essentially apoptosis factors.

This would seem to arise from the fact that under ischemia conditions the mechanisms of control of ion flow become altered against the plasma membrane, resulting in accumulation of Ca and Na ions at intracellular level, cellular balance disruption and release of proteolytic and lipolytic enzymes that trigger the extrinsic and intrinsic system of activation of the apoptotic process.

More and more adjourned data indicate that general anesthetics provide a protective effect during nervous ischemic injury and are renowned for their inhibitory effect against glutamatergic nerve transmission system (mediated by AMPA and NMDA receptors) and promoters of the GABAergic tone (GABA A) with a consequent reduction in the basal cerebral metabolism, cerebral blood flow and increased inhibitory synaptic transmission at cortico-basal level.

As a result, several studies in this matter have shown, mainly in animal models, that the main general anesthetics are able to reduce the consequences of the nervous ischemic insult but in short term contexts (post-ischemic period of not more than 3-5 days) and moderate to mild ischemic injury. It hasn't been demonstrated long- term neuroprotective effects (post-ischemic period of more than 7 days) by the above mentioned pharmacological agents since not able to counteract the processes of apoptosis induced by the ischemic insult, although experimental data indicate that there is a possible inhibitory influence of general anesthetics on the system of extrinsic activation of the apoptosis. But it refers to data not yet confirmed and validated in the clinical field. In this sense, the adoption of the protocols of administration of antagonists of capsasi (key enzymes in the apoptotic program execution) in combination with general anesthetics, has aroused considerable interest, specifically inhaled agents, showing a greater reduction and long-lasting of nervous ischemic injury, with a mean range of survival over 14 days.

This allows us to state that a considerable proportion of neuronal loss, as a result of an ischemic insult, can be attributed to the apoptosis process. Therefore it can be seen how the various general anesthetics, from the barbiturates to the propofol and to the inhalator agents, are potentially characterized by undeniable useful effects for the protection of the neurons submitted to surgical and post-traumatic ischemic risk, but that still today the aforesaid effects are only able to delay an evolution of the ischemic damage but not to prevent it or avoid it. At the same time further experimental and clinical close examinations are required in the definition of the actual role of the general anesthetics in neuroprotection field. Today, we shouldn't be involved in a superficial optimism because of the clamor generated by the results regarding the possible use of anesthetic agents in neuroprotective field and in other particular contexts.

Although it is difficult to attribute certain effects to the unexpected and sometimes tragic general anesthetic drugs themselves or to the conditions that occur during general surgery, data from multiple experimental studies indicate the possible event of prolonged effects and harm against the CNS (Central Nervous System) after general anesthesia.

The international study of postoperative cognitive dysfunction published in 1998 showed convincingly the existence and prevalence of a clinical entity well-defined of post-operative cognitive dysfunction in elderly patients (mean age 69 years). The main risk factor identified in this study was the old age and, without specifying the pathophysiolog-

ical mechanism, the possibility of summation of chronic-degenerative diseases, deficit function of different organs and / or altered response to general anesthetics.

Exposure to different types of surgery, performed with general anesthesia techniques, has also led to hypothesize a promoting role for the early manifestation of neuro-degenerative disorders still latent in the CNS, such as dementia of Alzheimer type (AD). This hypothesis can occur in the post-operative event as a form of post-operative cognitive dysfunction which develops in Mild Cognitive Impairment (MCI) that is often the prelude to latent forms of AD.

Although these results are not yet supported by clinical data, the possibility that general anesthetics, alone or in combination with surgical stress, may alter the neuronal homeostasis or even encourage, through specific mechanisms, the development of neuro-degenerative disorders, has substantially modified the approach of the research in neurotoxicity field by anesthetic drugs.

In contrast, pediatric age and neuro-cognitive development, highlight that the early exposure to general anesthesia procedures may cause abnormalities of neuro development, has radically changed the approach of neuro-pharmacological research. The CNS of rodents in the neonatal period and infantile is still immature and the possibility that it is susceptible to damage induced by general anesthetic drugs is already tested. The involved mechanisms are altered formation and maturation of synaptic connections, changes in the neuronal plasticity processes, delayed neurogenesis and early apoptosis of multiple neuronal populations.

Recent data have failed to determine and clarify the actual neurotoxic effects in experimental models of primates. The incidence of learning disorders in children with multiple exposures to general anesthesia during the first four years of age was twice diagnosed with similar forms in older age without exposure to multiple anesthetics. In this sense, however, the authors' non-specific approach in this field was questioned, in relation to the role effectively played by general anesthetics and / or surgical stress or other conditions relating to the outcome of pediatric patients. Currently laboratory and clinical work is nearly to be completed that might clarify and define the implications that have been already experimentally demonstrated.

Considerations and conclusions

Today, extensive clinical trials have failed the objective to define or exclude a well defined causal relationship between exposure to general anesthetics and neuro toxicity. It is also not perfectly clear the role played by the same agents on an evolution towards an early irreversible cognitive impairment. In addition, the demonstration of potential neuroprotective effect and/or that general anesthetics are able to counteract and delay the damage from ischemic injury during anesthesia and major surgical procedures, has raised the need to deepen and widen our knowledge on the matter, for a more appropriate use of these drugs. Once defined the limits imposed by various clinical processes in human field, linked to logistic problems and long-term control of the various experimental models, the research still needs to establish its bases on animal models to better understand the mechanisms underlying the changes induced by general anesthetics and identify new clinical targets.

In view of the fact that in the clinical field there are no real alternatives to the different anesthetics used in the surgical field, it has become essential for many anesthesiologists and intensivists a cautious use of the various agents used today, meanwhile, possible strategies are searched to counteract the possible deleterious long-term effects.

This reminds us that even if today there aren't drugs without deleterious side-effects , their use and knowledge, derived from clinical practice, allow us to reassure patients undertaking general anesthesia procedures regarding their safety.

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