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REVIEW ARTICLE

Neuroanesthesia: from bench to bed

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Abstract It has been over 40 years since the term "neuroanesthesia" emerged. The anesthesiologists specializing in neuroanesthesia have actively conducted basic research on cerebral ischemia as well as on cerebral blood flow and metabolism. However, translating the results of basic research using experimental animals into clinical applications has been often unsuccessful, especially in the area of cerebral ischemia. The negative results produced by a series of hugely costly and time-consuming collaborative multicenter trials have disappointed many researchers. It could be argued that discrepancies in the efficacy of an agent ought to be viewed in the context of the differences between experimental animals and humans since they have considerably different higher-order functions, and consequently the relevance of using experimental animals is brought into question. Nevertheless, the accuracy of basic research can be improved by taking measures to reduce bias. Taking such measures may enable more careful judgments to be made at the basic research stage and prevent unnecessary clinical studies. Although it could be seen as taking a slight detour, it is advisable to create a system that facilitates confirmation of the original findings by a multicenter basic research project before starting a collaborative multicenter clinical trial.

Keywords Neuroanesthesia · Cerebral ischemia · Neuroprotection

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Introduction

A group of anesthesiologists specializing in neurosurgical anesthesia was formed at the Mayo Clinic in the early 1960s. Members of this group also actively conducted basic research on cerebral ischemia as well as on cerebral blood flow and metabolism. The term 'neuroanesthesia' subsequently emerged and became known worldwide following publication of Michenfelder's review article entitled "Neuroanesthesia" in *Anesthesiology* in 1969 [1].

When looking back at over 40 years of its history, it is noticeable that some but not all areas of neuroanesthesia research have been well translated into clinical applications. For example, cerebral blood flow and metabolism, studied using the Kety–Schmidt method in the early days, is now examined in humans by means of positron emission tomography (PET) and local changes can be depicted in detail. Thrombolytic therapy with tissue plasminogen activator (tPA), which accelerates the early re-establishment of cerebral blood flow, was regarded as groundbreaking in the treatment of stroke. On the other hand, despite making full use of molecular biology and genetic engineering approaches to understand the mechanisms of central nervous system (CNS) ischemia, the findings of basic research have not yet been well translated into clinical applications to protect the CNS. In this paper, issues in translating basic research outcomes into clinical applications are discussed, with an emphasis on CNS ischemia.

Lessons from research on the cerebroprotective properties of thiopental

It is not an exaggeration to say that the research examining drug-induced cerebral protection started with anesthetic

agents. In the early 1960s, a group in Philadelphia, the focal point of research using the Kety–Schmidt method at that time, reported the strong inhibitory effect of thiopental on cerebral metabolism in a study examining the influence of hyperventilation during anesthesia on cerebral blood flow and metabolism [2]. Around the same time, it was reported that general anesthesia during carotid endarterectomy might improve neurological prognosis [3]. These reports were the first to suggest a possible link between cerebral metabolic suppression by anesthetic agents and cerebral protection.

In the 1970s, Michenfelder [4], mentioned above, established the basic concept behind thiopental-induced suppression of cerebral metabolism. Examining the patterns of cerebral metabolism in a dog that continuously received thiopental, he found that the electroencephalogram (EEG) became isoelectric following the administration of thiopental, but that further dosages of thiopental thereafter did not result in further suppression of cerebral metabolism. On the basis of these findings, he proposed the concept of two-component neuronal metabolism, comprising a component related to electrical activity (approximately 60%) and a component necessary for cell survival (approximately 40%), concluding that thiopental suppresses only the former.

Around the time when the potential of anesthetic agents for cerebral protection via cerebral metabolism suppression and the effects of thiopental on cerebral metabolism had become clear, a study using a rhesus monkey model of global cerebral ischemia demonstrated that a large dose of thiopental after ischemia reperfusion protected the brain [5]. The influence of this study was immense, and raised hopes for the treatment of postresuscitation encephalopathy. However, the study was also controversial, mainly due to the lack of rationale: as mentioned earlier, thiopental selectively suppresses metabolism associated with cerebral electrical activity, and therefore the cerebral protection afforded by thiopental cannot be expected in the case of global ischemia where EEG is isoelectric [6]. Moreover, the study design had some problems. For example, postoperative management differed between the control group and the group receiving thiopental, and many animals were excluded before data analysis. Incidentally, other research groups replicating the experiment using a dog model of global cerebral ischemia [7] or a cat model of ventricular fibrillation [8] found no cerebral protection by thiopental. Furthermore, the group that had demonstrated the efficacy of thiopental in rhesus monkeys addressed the problems in their original experiment by setting up a new experiment using pigtailed monkeys, but failed to reproduce their original findings [9]. Meanwhile, a collaborative multicenter study had started before consensus on the protective effect of thiopental in post-resuscitation encephalopathy was reached from animal model results [10]. But again, this multicenter study in which 1-year prognosis was examined in patients who had received 30 mg/kg of thiopental between 10 and 50 min after resuscitation found no protective effect of thiopental [10].

When the repeat study by the group that had initially demonstrated cerebral protection of thiopental was published, it was preceded by an editorial entitled "Brain Resuscitation: The Chicken Should Come before the Egg" [11]. Briefly, this editorial stated that without solid results (the chicken), experiments seeking a theoretical explanation (the egg) wasted time and money, implying that the studies performed at many institutes following the initial publication of thiopental-induced cerebral protection were in fact fruitless [11]. The main lesson to be learned from the research into the protective effect of thiopental in postresuscitation encephalopathy is that when the results from animal models appear to be groundbreaking and promising, we should temper our enthusiasm and rigorously test the credibility of the results in accurate follow-up studies involving multiple groups. A clinical trial should be started only in keeping with the findings of the follow-up studies, not prematurely.

Reasons for the failure to translate basic research results into clinical applications

The cerebroprotective effect of thiopental in postresuscitation encephalopathy was a topic of active discussion in the 1970s and 1980s. However, no neuroprotective drug has been authorized worldwide. It has been very difficult for the promising findings of cerebral protection shown in the animal model studies to be found in clinical studies. More than 15 potential cerebral protectants were proven ineffective in clinical studies, despite their significant protective effects in animal models [12]. A series of failed trials has continuously disappointed researchers and pharmaceutical companies around the world.

There are several possible reasons why the efficacy of cerebral protectants seen in animal models has not been demonstrated in clinical studies. The first is that brain structure differs between humans and experimental animals. The rodent brain has a high percentage of gray matter, while the human brain has a high percentage of white matter. The infarct volume is a common index used in evaluating the effects of cerebral protectants in rats, but it mainly represents gray matter infarcts. Thus, one could argue that the effects seen in rats are irrelevant as white matter lesions constitute the main changes in cerebral infarction in humans.

The ideal situation would be for basic research results to ultimately be confirmed in primates. However, experiments

using large primates are costly. For this reason, the common marmoset, a small primate species weighing 300–450 g, has become an increasingly attractive model animal in recent years. The common marmoset is slightly larger than the rat and is highly fertile. As the species lives in family units and there is paternal as well as maternal rearing of offspring, the marmoset is also considered to be a good model for studies of higher function. Furthermore, a group from Keio University has succeeded in transgenic intervention in this species [13], and with improvements in transgenic technology, the common marmoset will no doubt serve as a good experimental model of various diseases, advancing research still further.

The second reason for the discrepancies between the animal and clinical studies concerns the issue of timing in cerebral protectant administration. The glutamate level in the extracellular fluid increases within a few minutes of cerebral ischemia, triggering the activation of various enzymes. Inflammatory responses are then exacerbated over hours, leading to necrosis and apoptosis that occur over hours and days. In experimental animal models, it is possible to administer cerebral protectants when the glutamate level in the extracellular fluid is high or when various enzymes are active; in clinical cases on the other hand, patients are likely to arrive at the hospital after these early reactions have completed. Therefore, when cerebral protectants inhibit the reactions in the early stage of ischemia, it is difficult to reproduce their effects in clinical cases.

The third reason, which is becoming increasingly relevant, concerns the accuracy of animal experiments. Multicenter trials involving research groups in Europe, North America, and Oceania were carried out between 2003 and 2006 to test the efficacy of the free radical scavenger NXY-059 as a cerebral protectant [14, 15]. Although these large-scale trials with a total enrollment of 5,000, which were led by the Stroke Academic Industry Roundtable (STAIR), were started after careful examination of basic research results, they failed to confirm the efficacy of NXY-059. This failure was a considerable shock to all interested parties. Of course, the trials themselves had several weaknesses, in that the rate of tPA use increased as the trials proceeded, consequently making the protective effect of NXY-059 alone unclear, and NXY-059 was administered for only 3 days after cerebral ischemia. However, when re-examining the pre-clinical animal experiments, some problems were found [16]. For example, the literature contains 9 peer-reviewed studies that measured infarct volume using a focal cerebral ischemia model. Among them, only 3 clearly stated the protocol involved random allocation, blinded induction of ischemia, and blinded assessment of outcome [16]. In addition, the efficacy of NXY-059 was clearly less impressive in the studies with random allocation and blinded induction of ischemia than in those without them [16]. This suggests that the studies without random allocation and/or blinded induction of ischemia contained bias, albeit unintentionally.

Measures to translate basic research outcome into clinical applications

As mentioned above, although unintentional, bias can occur in research studies. Here, bias at the experimental stage and bias at the publication stage are discussed separately from the viewpoint of reducing study bias as a whole.

We would like to propose that creating a system that facilitates collaborative multicenter basic research projects will reduce bias at the experimental stage. For example, let's say that an agent showed possible cerebroprotective effects in several basic studies. In the proposed system, a committee would be promptly formed to rigorously examine the existing data from animal experiments. Once potential clinical applications were indicated, the findings would be first tested in a collaborative multicenter basic research project, rather than in a collaborative multicenter clinical trial. Using a range of different animal models would be preferable. Every participating research group would be required to disclose all data (including the number of animals excluded). The results obtained by each group would be examined collectively to decide whether a collaborative multicenter clinical trial was justified. Following such a process would reduce the risk of deciding to conduct a clinical trial prematurely based only on the basic research findings obtained by a limited number of groups.

As for bias at the publication stage, journals tend to accept studies with positive data more than those with negative data, and this bias should somehow be addressed. One possible system is a research society-lead system in which the society would look for research groups to test promising candidates for cerebral protection and guarantee publishing both negative and positive results in the society's official journal. In this system, it would be necessary to assess the past achievements of the participating groups and judge whether they meet certain technical standards. This system would create an environment in which researchers would not hesitate to carry out repeat experiments, even if likely to produce negative results, and would work purely to obtain evidence. It should be welcomed that some journals have recently begun efforts to publish negative data [17, 18].

Summary

Translating the results of basic research using experimental animals into clinical applications is often unsuccessful. The

negative results produced by a series of hugely costly and time-consuming collaborative multicenter trials have disappointed many researchers. In addition, the negative results are not rewarding for the participating patients. It could be argued that discrepancies in the efficacy of an agent ought to be viewed in the context of the differences between experimental animals and humans since they have considerably different higher-order functions, and consequently the relevance of using experimental animals is brought into question. Nevertheless, the accuracy of basic research can be improved by taking measures to reduce bias. Taking such measures may enable more careful judgments to be made at the basic research stage and prevent unnecessary clinical studies. Although it could be seen as taking a slight detour, it is advisable to create a system that facilitates confirmation of the original findings by a multicenter basic research project before starting a collaborative multicenter clinical trial.

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