

MICE TIMES

From cerebral pacemaker to cell replacement therapy

Primate studies open up new avenues in the treatment of Parkinson's disease

Hans-Peter Ludin, 77, formerly Head of Neurology at St. Gallen Cantonal Hospital, witnessed them all during his medical career: the little steps forward and the major advances that have been made in the treatment of Parkinson's disease over the last 50 years. In the 1950s and 1960s there were the initially rather clumsy attempts of doctors to overcome the disease using stereotactic surgery. Here, tissue in certain areas of the brain was coagulated (destroyed) with electric currents or with heat or cold, so that the contralateral tremor could be suppressed. The start of the 1970s then saw a major breakthrough when the launch of the dopamine replacement substance L-dopa laid the foundations for effective pharmacological treatment of Parkinson's. In the 1980s and 1990s came the gradual establishment of deep-brain stimulation, i.e. the stimulation of targeted areas of the brain, which is a standard therapy today especially for patients with advanced disease. The fight against Parkinson's, then, has seen significant advances over the decades. This success has particular importance for a society whose population is steadily aging, as Prof. Ludin points out: "Parkinson's will increase further because people are getting older. Society faces a huge challenge here, especially since we know that people with Parkinson's have a five times higher risk of developing dementia."

Treatment success right on target

In present clinical practice, Parkinson's is treated mainly with drugs in the first few years. If the disease is advanced, then deep-brain stimulation is used; experts estimate that this is the case in around 15 to 20 percent of patients. Dr. Thomas Funk is principal consultant at the Klinikum Frankfurt/Oder GmbH and one of the pioneers of this treatment method. The cerebral pacemakers used by Funk consist of a four-pole electrode with a diameter of 1 mm.



Fig. 1 Introduction of the electrode

The electrode is surgically placed in the subthalamic nucleus. Here, with a voltage of around 2 V and a frequency of 180 Hz, it stimulates a group of cells that no longer work properly and thus give rise to the tremor seen in Parkinson's patients. The electrical stimulation regulates the overactive cells, bringing them down to a normal level of activity and thus restoring the 'healthy' balance between the build-up and release of tension. The electrode receives electrical impulses from a pacemaker that is usually implanted in the pectoral muscle or abdominal fat.

The cerebral pacemaker produces an improvement



Fig. 2 Inter-operative control of the electrode with image converter, conductor, transducer



Fig. 3 Inter-operative test of the effect and side-effect

in more than 90 percent of patients. “The procedure gives patients an extra ten years. We return them to the condition characterized by the disease ten years ago”, says Funk. Full therapeutic success with a minimum of side effects is only achieved, however, if the

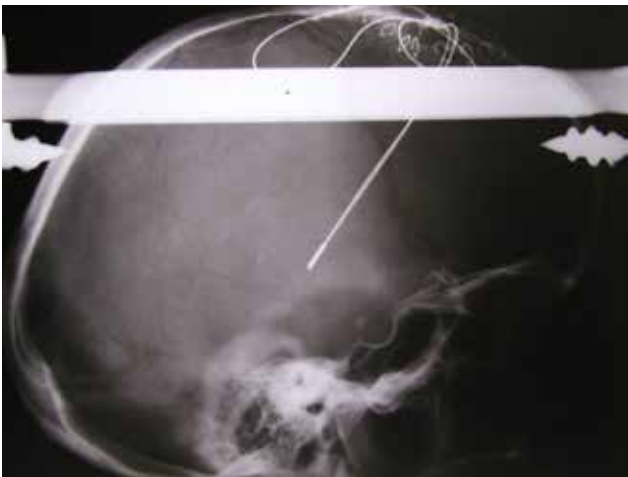


Fig. 4 Inter-operative final control of the position of the electrode (side view)

surgeon places the electrode with millimeter accuracy. Otherwise, there is a risk of speech or movement disorders. A lot of research was needed in the last few decades to determine the suitable sites for the electrode. This included individual therapeutic studies in patients. “Most problems can be clarified in studies with rodents (rats and mice). But in such complicated disorders as Parkinson’s there are certain questions that can only be answered with studies in monkeys”, says Prof. Andreas Kupsch, neurologist at the University Clinic of Magdeburg, who played a defining role in helping to develop the treatment method from 1990 to 2010.

Kupsch refers to studies in the early 1990s with which the behavior of the subthalamic nucleus was investigated and which made possible the triumph

of the cerebral pacemaker in the years that followed. He believes primate studies are also indispensable in Parkinson’s research: “The similarity of the network circuits in the brain is much closer between monkey and human than it is between rodent and human. In some cases, therefore, it is necessary to fall back on non-human primates, i.e. monkeys, for research studies. Anyone who wants to investigate how dystonia (a movement disorder) occurs in the hand cannot do this in the paw of a rat. You need monkeys for this, because the function of the hand is more similar between monkey and human”, says Kupsch. Meanwhile, the success of deep-brain stimulation extends far beyond Parkinson’s. The method is being used in more and more diseases, such as dystonia and also depression, obsessive-compulsive disorder and alcohol addiction. Work is also under way on Alzheimer’s.

Connective tissue cell becomes nerve cell

For some years, scientists have now opened up a new chapter in Parkinson’s research. The magic phrase is cell replacement therapy. Once again, researchers are stepping out into uncharted territory with a new form of treatment. Once again it involves complex procedures in the human brain that are inevitably accompanied by risks. Before cell replacement therapy becomes available for patients, extensive studies in the animal model are called for. “I would consider experiments in humans very critical and unethical at the present time, because we don’t yet know whether the treatment really offers a great opportunity for relief or even a cure”, says Prof. Rüdiger Behr, stem cell biologist at the German Primate Center (DPZ) in Göttingen. Parkinson’s is not a disease that runs an acute, life-threatening course, so higher ethical hurdles apply before a new therapy can be tested in humans than is the case with fatal diseases, says Behr.

Many researchers around the world are working on the development of cell replacement therapy. The basic idea is simple in principle: The aim is to cure the brain tissue that is damaged in Parkinson’s patients – the dopamine-producing nerve cells in the substantia nigra of the midbrain – by transplanting healthy replacement cells. Feverish research is under way today in an attempt to cultivate suitable replacement cells. The basis for this research is a method that enables such replacement cells to be

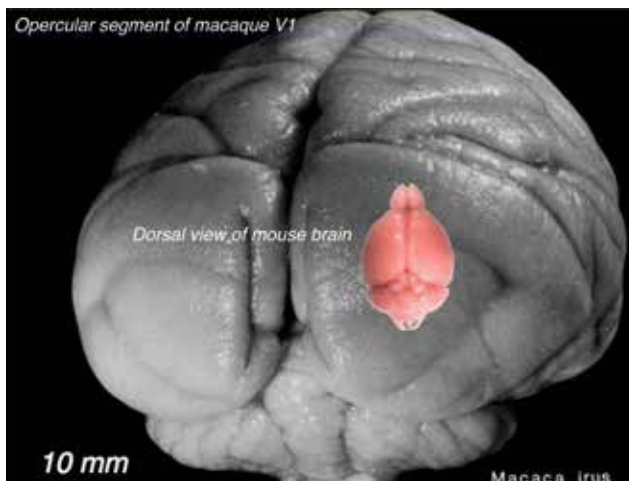


Fig. 5 Comparison of the size of a macaque monkey and a mouse brain

produced and was awarded the Nobel Prize for Medicine in 2012. In this method, connective tissue cells (fibroblasts) are isolated from the skin of the patient. The fibroblasts can be returned to a quasi-embryonic state by inserting so-called transcription factors. The resulting ‘pluripotent stem cells’ possess the fascinating ability to develop into any given cell of the body. Researchers hope that these all-rounder stem cells can now differentiate into nerve cells that will then replace the brain tissue damaged in Parkinson’s patients.

Reliable animal model for Parkinson’s

So far, cell replacement therapy is a promise for the future. Researchers reckon it will take years, if not decades, until a safe and effective treatment of this kind will be available to Parkinson’s patients. Extensive efforts are needed, with research in cell cultures, in animals and finally in humans. With a view to achieving this long-term objective, scientists are working on the development of a reliable animal model, i.e. a method with which the efficacy and safety of the novel Parkinson’s therapy can be studied in primates. A research project of this kind is being carried out in the following steps: In the first step, a suitable substance is used to induce Parkinson’s disease in monkeys; the animals are then monitored for symptoms of Parkinson’s such as motor deficits or sleep disturbances for three to four months. Grip tests are carried out to assess fine motor skills and the animals’ sleep-wake behavior is studied.

The second step consists in the cultivation of replacement cells of primates. These are produced from the connective tissue of the monkeys using the

method described above and can then be transplanted in the suitable regions of the primate brain. The success of treatment is then studied in various behavioral tests with the inclusion of a control group (that is not treated with replacement cells). Neurologists today assume that the use of cell replacement therapy will only make sense in the early phase of Parkinson’s disease. With appropriate experiments, therefore, it would be important to induce only very mild symptoms of Parkinson’s in the laboratory animals that would correspond to the early phase of the disease in humans.

Three studies with replacement cells in primates

Numerous studies on cell replacement therapy have already been carried out in mice and rats. To date, however, only isolated research has been carried out in primates. DPZ researcher Behr knows of three published studies in this context from the years 2005, 2007 and 2012. In two studies the replacement cells transplanted into monkeys came from humans, and in the third study embryonic monkey stem cells were used. “None of the studies were optimal, but all authors say there were symptomatic improvements in the animals”, says Behr, offering a very cautious summary of the primate studies to date. The scientist warns against exaggerated optimism. A longer-term improvement in the condition as a result of transplanting replacement cells has not yet been demonstrated, according to Behr. “But this is precisely what needs to be demonstrated in animal studies before Parkinson’s patients can be expected to submit to a relatively difficult procedure.”

Even before cell replacement therapy was on the research agenda, primates were being used for the study of Parkinson’s disease. To date, the substance usually used for this is MTBT, which has long been known to induce Parkinson’s symptoms in humans and animals. MTBT is not administered locally in the brain, but can be easily administered into the blood stream. However, the substance has the disadvantage that the occurrence of disease symptoms is not stable and the animals can spontaneously return to health, which compromises the reliability of the animal model. Researchers like Rüdiger Behr are convinced that these deficiencies can be overcome with the 6-OHDA model, which is based on 6-hydroxy dopamine. The substance 6-OHDA is adminis-

tered locally and exerts its effect with pinpoint accuracy. Moreover, the induced symptoms are more stable, which is an important aspect when studying the efficacy of a therapy. The three studies mentioned above used the MTBT model.

Besides the pharmacological animal models (MTBT model and 6-OHDA model) researchers are also working on genetic models. Here Parkinson's disease is induced in laboratory animals not with chemical substances, but by administering genes that induce Parkinson's. So far, rats and mice have been used for these studies. Researchers would also like to go down this path in future with primates as well. At present, no genetic primate models are available.

Risks of tumor and rejection reactions

It may seem surprising at first glance that Parkinson's researchers work with primates, although Parkinson's does not occur as a disease in primate (unless it is induced by external chemical or genetic factors). Nevertheless, researchers stress the need for such animal studies. The risks of new treatment methods first need to be studied in laboratory animals before tests are ethically acceptable in humans, they say. The risks of cell replacement therapy include, for example, tumors that could occur with uncontrolled growth of the implanted cells. Moreover, when replacement cells are implanted – as with any other transplantation – rejection reactions by the immune system have to be expected. “We need primates, which live longer than rodents, so that we can test the long-term safety and efficacy of new treatments, i.e. over the course of several years”, says DPZ researcher Behr. Professor Hansjörg Scherberger, like Behr a researcher at the German Primate Center, considers primate studies to be indispensable in Parkinson's research. “We still don't know today exactly why deep-brain stimulation actually works with cerebral pacemaker. Primate experiments serve as a way of researching this in precise detail.”

It would be ideal if we could understand the complicated mechanisms of a body without stressful animal experiment. Unfortunately that is not yet possible today. But the dilemma will remain for a long time to come: basic research without experiments in animals would mean abandoning any medical progress. «Mice Times» aims to explain why and therefore reports on medical success stories that were only possible thanks to animal experiments.

IMPRESSUM

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Figs. 1-4: Dr. Thomas Funk

Fig. 5: Photomontage from the following publications:

Macaque brain: Valverde, F. (1985) The organizing principles of the primary visual cortex in the monkey. In *Cerebral Cortex*, Vol 3, ed. A. Peters and E. Jones. Plenum Press: New York, Fig. 2A

Mouse brain: Airey DC, Lu L, Williams RW (2001) Genetic control of the mouse cerebellum: identification of quantitative trait loci modulating size and architecture. *J Neurosci*. 21:5099-5109, fig 1