**Introduction**

The use of minute particles as drug carriers for targeted therapy has been studied and discussed for more than 20 years. A selective accumulation of active substances in target tissues has been demonstrated for certain so-called nanocarrier systems that are administered bound to pharmaceutical drugs. Great expectations are placed on nanocarrier systems that can overcome natural barriers such as the blood-brain barrier (BBB) and transport the medication directly to the desired tissue and thus heal neurological diseases that were formerly incurable. The BBB represents the border between the circulating blood and the fluid in the central nervous system. It functions to protect the sensitive nerve cells from foreign substances and infections from the blood. Whether nanoparticles enter the brain unintentionally and induce health problems is also being debated. This dossier illustrates how the BBB functions and the positive effects of the new therapy possibilities, but also discusses the negative impacts of nanoparticles that enter the brain unintentionally.

**The blood-brain barrier**

The brain is permeated with a network of fine blood vessels. These so-called capillaries supply the brain with nutrients and oxygen. Combined, the walls of these blood vessels form the so-called blood-brain barrier. In all mammals, as well as in humans, it serves as a physiological barrier between the blood circulation system and the brain. Its task is to protect the brain from disease-causing agents, toxins and messenger substances circulating in the blood. The BBB therefore represents a highly selective filter through which the nutrients needed by the brain pass in one direction and the resulting metabolic wastes in the other. This supply and removal involves a series of special transport processes.

Within the central nervous system, the spaces between the neurons (nerve cells) are almost entirely filled by glia or endothelial cells and their processes (Figure 1).

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* Corresponding author
The metabolism of the nerve cells is via these endothelial cells. These cells serve to insert, isolate and supply the nerve cells and their neurons. One type of glia cells are the astrocytes (Figure 2). They bear numerous processes with which they attach themselves to the walls of the capillaries and form a nearly uninterrupted coating surrounding the capillaries. One feature distinguishes the vessel walls of the capillaries that form the blood-brain barrier from other blood vessels in the body: there is a solid connection between the adjoining vessel wall cells (so-called capillary endothelial cells). They are formed by special protein complexes known as tight junctions. Tight junctions (Figure 3) are slender bands consisting of membrane proteins that entirely wound around the epithelial cells and are in close contact with the bands of the neighboring cells. This enables the tight junctions to seal the cell interspaces and form a so-called diffusion barrier that controls the flow of molecules across the epithelium.

Tight junctions therefore have three key functions: i) a barrier function by closing up the intercellular spaces, ii) the mechanical stabilization of the epithelial cell aggregates and iii) maintaining the polarity of the epithelial cells by preventing the free floating of membrane components along the cell membranes. Substances that need to enter the brain from the blood or move from the brain into the blood cannot circumvent these cells, but must be channeled directly through the vessel wall cells by special transport systems (Figure 4). This controlled process enables a selective exchange of substances between nerve cells and blood, and protects the nerve cells from penetration by harmful substances. Those substances that are necessary for supplying the brain can pass unhindered, namely oxygen and carbon dioxide. At the same time, specific transport systems transfer D-glucose, D-hexose, several L-amino acids and certain lipid-soluble substances through the BBB. This is accompanied by a release of degradation products into the blood. The terminal processes of the astrocytes represent a barrier for numerous substances such as certain hormones, non-lipid-soluble, water-soluble and chemical substances, along with proteins, which helps maintain a constant milieu for the neurons of the nervous system.

The permeability of the blood-brain barrier is also affected by fluctuations of physiological conditions. Thus, normal life processes can trigger temporary fluctuations in permeability. Chronically altering the permeability of the BBB or of the capillary walls can enable the passage of substances and damage the surrounding nerve cells. For example, strong temperature increases promote BBB permeability. Medical therapies can take advantage of this phenomenon. At the same time, this barrier hinders or prevents many potential treatments of neurological diseases because many active substances cannot pass the BBB. Overcoming the BBB is therefore an important field of current research that seeks better treatments for diseases of the central nervous system.

As noted above, the BBB – despite its function as a protective barrier – must also enable the transport of nutrients to the brain and the corresponding removal of metabolite products. Accordingly, water-soluble substances and peptides overcome this barrier via specific transporters or special canals in the cell membrane (diffusion, paracellular transport, specific transporter proteins, receptor-mediated transport, adsorptive transport, see Figure 4), while the other soluble compounds pass this barrier via passive diffusion.
Nanoparticles and the blood-brain barrier: An opportunity for the treatment of diseases – Are there associated risks?

Nanoparticles can be used as carrier systems to overcome the BBB and deliver specific medications to regions of the brain that would normally be inaccessible. Their surfaces can be coated with certain materials or manufactured such that they can pass the BBB and transport the pharmaceuticals to the sites where they are needed. Thus, nanoparticle carrier systems can distribute medications spatially and temporally in the brain and help cure diseases that were previously untreatable. This enables a tissue-specific accumulation of drugs, special depot effects and overcomes the body’s own barriers such as the blood-brain barrier. This would allow stronger concentrations of medications to be applied with improved effects. This is a booming research and development field and shows ever greater promise in treating diseases such as Alzheimer’s, Parkinson’s or certain brain tumors. Currently, most applications of nanoparticle carrier systems involve drugs that are already in clinical use. Research is being conducted on various scenarios for the application of nanoparticle carrier systems. For example, experiments are being performed on rats to determine whether the direct transport of genes (gene therapy) is possible into specific regions of the brain via nanocarriers in order to replace damaged hereditary substances and therefore treat Parkinson’s disease, for example.

One currently used form of therapy, although it does not overcome the BBB, is the so-called hyperthermia therapy, which uses nano iron particles to treat brain tumors such as glioblastoma. Here, magnetized, iron-containing nanoparticles are injected directly into the brain tumor. These nanoparticles, also known as “Trojan horses”, are actively taken up by the tumor cells because they are coated with a layer of sugar molecules. This approach packs the cancer cells full of iron-containing particles, which can then be pinpointed and heated by electromagnetic fields. This overheating kills the tumor cells. What remains unclear is the fate of the nanoparticles remaining in the brain, what effect they have there or whether they are eliminated.

An in-vitro study showed that TiO₂-nanoparticles can trigger oxidative stress, especially in certain brain cells, namely in the so-called microglia cells (phagocytizing immune cells of the central nervous system). This effect is only possible if the BBB is crossed. In vivo studies have been unable to definitively confirm this. In experiments on rats, injecting TiO₂-nanoparticles directly into the bloodstream did not lead to accumulation of the particles in the brain. A recent more study, however, shows that relatively high concentrations of TiO₂-nanoparticles injected into pregnant mice were detectable in the brain of the offspring. A further study by the same group revealed changes in the DNA (gene expression) in the brain tissue of the fetuses. In this case, the BBB as well as the barrier between the mother and placenta may have been breached. Another mechanism beyond crossing physiological barriers might be at play here because, during the embryonic phase, the BBB is not yet fully developed. The researchers point out, however, that the determined effects are not directly transferable to humans. In particular, the biological relevance of the described gene alterations is unclear. Unfortunately, there are still too few results to draw definitive conclusions on the permeability of TiO₂-nanoparticles through the blood-brain barrier.

Another route by which nanoparticles can enter the brain is via the olfactory nerve, circumventing the blood-brain barrier. The olfactory nerve (nervus olfactorius) has a direct connection to the brain by way of its long processes (axons). It is therefore conceivable that inhaled nanoparticles enter the olfactory nerve and are transported to the brain along the axons. This phenomenon has been observed in rats. After inhalation, individual carbon-containing nanoparticles entered the olfactory bulbs in the nose and were then transported along the olfactory nerve to the brain. The extent to which this result is transferable to humans remains unclear because the brain anatomy of rats and humans differs considerably. In this case as well, no final conclusions can be drawn as to whether the concentrations of nanoparticles transported in this manner – which are probably minimal – is biologically relevant and therefore relevant from a health perspective. Health effects would be expected only under continuous exposure and exposure to high concentrations of nanoparticles.

Notes and References


9 Shimizu, M., Tainaka, H., Oba, T., Mizuo, K., Umezawa, M. and Takeda, K., 2009, Maternal exposure to nanoparticulate titanium dioxide during the prenatal period alters gene expression related to brain development in the mouse, Part Fibre Toxicol 6, 20


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