Technology Offer

Radiopharmaceutical for low-cost, high-sensitivity diagnosis of early-stage dementia and tissue viability in acute stroke

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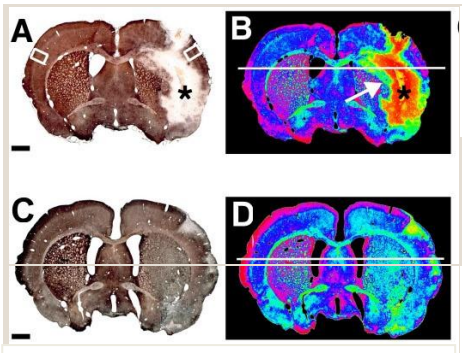
ascenion

A Company of the Life-Science Foundation for the Promotion of Science and Research

Challenge

Neuronal activity critically depends on transmembrane potassium (K^+) fluxes and on the maintenance of intra- to extracelluar K^+-gradients. K^+-fluxes increase with increasing activity. K^+-equilibrium potentials – and intracellular K^+-contents - change with changes in membrane potential that can occur upon long-term up- or down-regulations of electrical activity. Breakdown of K^+-gradients indicates failure of energy supply. Conversely, maintenance of K^+-gradients is a viability marker. In addition, clearance of K^+ out of the brain is related to the integrity of the blood-brain barrier (BBB).



Distribution of Thallium after injection in rat brain at 15 min (A,B) and 7 days (C,D) after introduction in cerebral ischemia. The asterisk in B indicates the center of the ischemia.

Brain K^+-metabolism thus is of fundamental clinical relevance. In particular, imaging the spatial patterns of chronically up- or down-regulated neuronal activity and of transport rates across the BBB in early stages of dementia as well as tissue viability in acute stroke are of substantial interest in neurology. Attempts have been made to image cerebral K^+-content using magnetic resonance imaging of 42K, but the technique is insensitive and not able to image the dynamics of K^+-uptake and -excretion. In principle, K^+-turnover can be imaged using the well-established K^+-probe ^{201}Thallium ($^{201}Tl^+$, or simply ^{201}Tl), a radionuclide suitable for detection with single-photon emission computed tomography (SPECT). SPECT is a relatively inexpensive widely available clinical imaging modality that, with newest generation scanners, can provide the same spatial resolution as positron emission tomography (PET). ^{201}Tl-SPECT is in use since many decades for imaging myocardial ischemia and infarction. The transport of ^{201}Tl through the BBB, however, is slow and only minute amounts of ^{201}Tl can be found in the brain in the first hours after intravenous injection of ^{201}Tl chloride. Without catalyzing the transport of ^{201}Tl through the BBB, the radionuclide cannot be used for imaging brain K^+-metabolism.

Technology

The lipophilic diethyldithiocarbamate anion (termed DDC^- or $DEDTC^-$) catalyzes the transport of $^{201}Tl^+$ through the BBB. $^{201}Tl^+$ and DDC^- reversibly form the electroneutral lipophilic chelate complex ^{201}TlDDC that passes the BBB. ^{201}Tl-content in the brain shortly after intravenous ^{201}TlDDC injection is about 100 times higher than after ^{201}Tl chloride injection.

After passage through the BBB, ^{201}Tl is released from the compound. Neurons and astrocytes take up the Tl^+-ion and the kinetics of Tl^+-efflux from the brain mimic the kinetics of the slow K^+-efflux. The relatively long half-life of ^{201}Tl of 72 hours makes it possible to monitor uptake, redistribution and clearance from the brain over at least 24h.

We have shown, in mouse models of dementia, that after intravenous ^{201}TlDDC injection both initial brain uptake patterns of ^{201}Tl and the kinetics of ^{201}Tl-loss differ from those in wild-type mice, and that monitoring the ^{201}Tl-loss kinetics provides additional information not contained in the early images. Both, ^{201}Tl-uptake and –loss, were also severely altered in rodent stroke models, and our data show that ^{201}Tl-retention after ^{201}TlDDC injection can serve as a viability-marker.

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Synthesis of ^{201}TlDDC is a quick one-step procedure that works by just mixing $^{201}Tl^{+}$ with sodium diethyldithiocarbamate (NaDDC). DDC^{-} is an inexpensive compound. It is well-known in medicine as it is generated in vivo from Disulfiram (Antabus©), which is prescribed in doses far exceeding those needed for SPECT-imaging.
^{201}TlDDC is a radiopharmaceutical for SPECT-imaging of brain K^{+}-metabolism easily synthesized from two well-characterized components. Compared to SPECT-imaging of cerebral blood flow and PET-imaging of glucose metabolism it offers an additional dimension by imaging not only the uptake but also the kinetics of redistribution and clearance from the brain.

Commercial Opportunity

In-licensing (exclusive or non-exclusive) is possible.

Developmental Status

Pre-clinical studies completed (see Reference Literature), ready to submit for clinical trial.

Patent situation

Patents have been granted in Europe, US and Korea with priority of 2005.

Reference Literature

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Wanger T et al. (2012) The use of thallium diethyldithiocarbamate for mapping CNS potassium metabolism and neuronal activity: Tl+ -redistribution, Tl+ -kinetics and Tl+ -equilibrium distribution. J Neurochem 122:106-14.

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Goldschmidt J et al. (2017) BMBF-Vorhaben „Validierung des Innovationspotenzials wissenschaftlicher Forschung – VIP" – ^{201}TlDDC-SPECT zur Frühdiagnostik dementieller Erkrankungen, Abschlussbericht. Technische Informationsbibliothek 2017
(BMBF funded project, validation of the innovative potential of scientific research – ^{201}TlDDC-SPECT for early diagnosis of dementias, final report).

Stöber et al. in preparation: SPECT-imaging of K^{+}-metabolism in acute cerebral ischemia using ^{201}TlDDC, a lipophilic chelate complex of the K^{+}-probe $^{201}Tl^{+}$.

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