Medical Xpress

Alzheimer's disease diagnostics could become more accessible

February 9 2021

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A team of researchers from the Laboratory of Biophysics at NUST MISIS, Lomonosov Moscow State University and D. Mendeleev University of Chemical Technology of Russia has summarized metal-

containing diagnostic agents for positron emission tomography (PET), magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT) imaging of Alzheimer's disease (AD). According to the researchers, metal-containing radiopharmaceuticals are not only highly effective for detecting early markers of Alzheimer's disease, but also synchrotron-independent and long-lived. Thus, their use could improve access to diagnostic imaging of AD among the risk groups. The review was published in the *International Journal of Molecular Sciences*.

Alzheimer's disease is the most common form of dementia. It is a progressive neurological disease that leads to a decline in memory and other cognitive abilities. AD is associated with the deposition of so-called amyloid protein plaques in the brain that disrupt communication among neurons, resulting in loss of function and cell death. Amyloid plaques are a hallmark of AD, occurring 7-15 years before the onset of cognitive symptoms of the pathology. They allow doctors to diagnose Alzheimer's earlier—even before any symptoms appear.

Timely diagnostic imaging plays an important role in managing AD. Identifying it at an early stage and initiating therapy can delay the progression of the disease. Amyloid deposits in the brain can be PET-traced using special radioactive markers that bind to different amyloids. However, using these drugs requires an expensive laborious synthesis with confirmation of radio purity at each stage. The short half-lives of the currently used radionuclides carbon-11 (11C) and fluorodeoxyglucose (18F)—20 and 109 minutes respectively—may also limit the widespread use of these imaging agents, since they can only be transported a short distance before use and have to be used immediately upon arrival.

The solution could lie in metal-containing diagnostical agents. Copper, zinc and iron cations have been proven to bind to amyloids, highlighting

amyloid plaques, which raises the possibility of designing copper-, zinc and iron-based metal complexes for the diagnosis and theranostics of AD. AD diagnostic agents radiolabeled with the copper isotope 64Cu are attractive not only due to the simple and fast introduction of radionuclide at the last stage of non-radioactive synthesis, but also due to its 12-hour half-life, perfect for PET imaging.

Another promising PET radionuclide is gallium-68 (68Ga). Its parent nuclide, 68Ge, has a half-life of 271 days, and the existing generators can provide sufficient quantities of 68Ga for up to one year, resulting in a relatively inexpensive and reliable source of a positron-emitting radionuclide. In addition to PET imaging of amyloids, metal-containing agents could be used for AD visualization by the means of single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI).

However, the development of AD imaging agents is restricted by the presence of the blood-brain barrier (BBB) which limits the substance from reaching the cerebral target. The BBB is a highly selective mechanism that controls the passage of substances from the blood into the cerebrospinal fluid and thus into the brain, and serves as the clearance path for waste metabolites of the brain. Thus, the BBB makes it difficult to develop new treatments of brain diseases, or new radiopharmaceuticals for neuroimaging of the brain.

A few metal-based agents have demonstrated the ability to cross the BBB and bind with amyloid in the brain: 64Cu, 68Ga and 99mTc (technetium-99 m). These isotopes are significantly easier to produce than 11C and 11F, with a longer life-span. Among the variety of compounds considered in the review, the most promising results were shown by copper-based coordination compounds for PET imaging, gallium-based coordination compounds for MRI, and technetium -based coordination compounds for SPECT imaging.

More information: Olga Krasnovskaya et al, Metals in Imaging of Alzheimer's Disease, *International Journal of Molecular Sciences* (2020). DOI: 10.3390/ijms21239190