Imaging inflammation in the living brain

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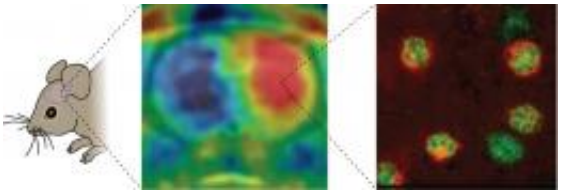

Figure 1: A PET imaging probe can be used to visualize COX-1 expression in living animals (red, middle image). Activated microglia and macrophages (red, right) in the mouse brain express the protein COX-1 (green, right) after injury. Credit: 2011 Society of Nuclear Medicine

Inflammation occurs in the human brain during illnesses such as Alzheimer's disease, Parkinson’s disease, stroke and traumatic brain injury. Now, a research team in Japan has developed a probe that can bind to the pro-inflammatory enzyme cyclooxygenase (COX). The probe, 11C-ketoprofen methyl ester, enables researchers to observe when and where the enzyme is acting in the brains of living animals using positron emission tomography (PET) imaging.

In PET imaging, a radioactive tracer that binds specifically to a specific molecule in the body is injected into a living organism. Images are then taken with a PET scanner, indicating where in the body that tracer is found.

Led by Hirotaka Onoe at the RIKEN Center for Molecular Imaging Science in Kobe, the researchers had previously discovered that 11C-

ketoprofen methyl ester could recognize COX, but not which of its two forms. To determine which isoform is responsible for binding their molecular probe, Miho Shukuri, a young member of Onoe's team, utilized a series of mice lacking the genes for either COX-1 or COX-2. She found that the PET probe could bind to the brains of COX-2-deficient mice, but not to those lacking COX-1. According to the researchers, 11C-ketoprofen methyl ester is therefore the first PET probe that is specific to COX-1 in living animals.

When Shukuri injected bacterial antigens into the brain of rats to induce inflammation, she saw the PET probe build up in the brain within six hours to one day after antigen injection. The levels dropped a week later. Because COX-1 is rapidly activated by brain injury, this may mean that administration of drugs that block COX-1 soon after injury could prevent the progression of brain damage. "COX-1 could therefore be a promising target for the neurodegenerative diseases that exhibit neuro-inflammation," explains Onoe.

Microglia are immune cells in the brain that proliferate in response to injury, while macrophages are immune cells normally found within the blood that invade the brain after injury. The researchers observed that the injury-induced increase in brain COX-1 seemed to occur within microglia and macrophages (Fig. 1), which also became more numerous in the brain after exposure to bacterial antigens. Other research groups have found COX-1-expressing microglia in diseases such as Alzheimer's disease, Parkinson's disease and multiple sclerosis. This suggests to Onoe and colleagues that 11C-ketoprofen methyl ester could be used to track the time course and localization of increased COX-1 expression in living organisms, including humans, suffering from diseases linked to neuro-inflammation.

More information: Shukuri, M., et al. In vivo expression of cyclooxygenase-1 in activated microglia and macrophages during

neuroinflammation visualized by PET with 11C-ketoprofen methyl ester. The Journal of Nuclear Medicine published online 1 July, 2011 (doi: 10.2967/jnumed.110.084046).

Takashima-Hirano, M., et al. General method for the 11C-labeling of 2-arylpropionic acids and their esters: construction of a PET tracer library for a study of biological events involved in COXs expression. Chemistry 16, 4250–4258 (2010).

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