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RIKEN

Successful marking of drugs exhibiting antipyretic/analgesic effects and visualization *in vivo*: Observation of *in vivo* movement of anti-inflammatory drugs by PET molecular imaging

Key Points of this Research Success

- **Labeling for use with PET of non-steroidal anti-inflammatory drugs that possess the 2-arylpropionic acid structure**
- **Successful improvement of intracerebral transfer of these drugs, and confirmation of efficacy in rats**
- **Visualization of drugs *in vivo* is expected to enable the elucidation of numerous clinical conditions and to have diagnostic applications**

In a world-first, RIKEN (Ryoji Noyori, President) has succeeded in using a radioactive carbon isotope (^{11}C) to label six commonly used (e.g., as cold remedies) non-inflammatory anti-steroidal drugs (NSAIDs), including ibuprofen, all of which possess the 2-arylpropionic structure. This successful development of a general synthesis reaction to enable NSAIDs to be studied by positron emission tomography (PET) means that a method has now been established for revealing the actions of drugs for which the *in vivo* dynamics are unknown. This result was achieved by Masaaki Suzuki, Team Leader of the Molecular Imaging Medical Chemistry Laboratory (also the CMIS Deputy Director), Misato Takashima from the Molecular Imaging Labeling Chemistry Laboratory (Hisashi Doi, Team Leader), and Miho Shukuri from the Functional Probe Research Laboratory (Hirotaka Onoe, Team Leader), at the Center for Molecular Imaging Science (Yasuyoshi Watanabe, Director).

PET is a molecular imaging technique used in areas such as cancer diagnosis, and involves introducing radioactive isotopes carbon 11 (^{11}C) or fluorine 18 (^{18}F) into substances such as drugs to reveal the location, amount, and movements of molecules within the living body. As ^{11}C and ^{18}F have short half-lives of around 20 minutes and 110 minutes, respectively, introducing these elements into drugs requires that synthesis be performed extremely quickly (ideally within 5 minutes for ^{11}C, for example). In addition to practical use for antipyretic, analgesic, and anti-inflammatory effects, NSAIDs are also known to be associated with prophylaxis against degenerative neurological disorders such as Alzheimer's and Parkinson's diseases, although the detailed mechanisms of action remain to be elucidated.

The research group succeeded in introducing ^{11}C into 2-arylpropionic acid within 2 minutes, and confirmed its poor transfer to the brain from analyzing the PET images from rats. Improvements in this process of transfer to the brain were regarded as key to elucidating the involvement of these drugs with degenerative neurological disorders, and transfer to the brain during intravenous administration in rats was improved by replacing the carboxylic acid (-COOH) group with a methyl ester (-$COOCH_3$). When the ester conjugate was administered to rats with induced inflammation of the left brain, PET image analysis was able to confirm drug accumulation at the site of inflammation.

Use of the ^{11}C-labeled 2-arylpropionic acid and the ester conjugate developed successfully in this project is expected to enable the elucidation of numerous clinical conditions, both peripheral and central, in addition to having diagnostic applications.

The results of this study is published in the German scientific journal *Chemistry – A European Journal*, **2010**,*16* 4250-4258.