Use of reference tissue models for quantification of histamine receptor functions in human brain by using positron emission tomography and [^{11}C] doxepin tracers

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Abstract

The histamine neuronal system in the brain is involved in important roles in various physiological functions such as awareness, cognition and memory. These functions of brain histamine are mediated mainly by histamine H_1 receptors (H1Rs) of the four types of histamine receptors (H_1, H_2, H_3, and H_4) known. For mapping the distribution of H1Rs in human brain, positron emission tomography (PET) has been used with [^{11}C]doxepin, a potent H1R antagonist labeled with ^{11}C. [^{11}C]doxepin has been a tracer of choice because of its high affinity to the H1Rs and of its favorable penetration across the blood-brain barrier. PET with [^{11}C]doxepin has been applied to the investigation of human brain in various pathological states such as Alzheimer's disease and epilepsy as well as in a state of sedation induced in neurologically healthy people by H1R antagonists (antihistamines) for treatment of allergic diseases. For quantitative PET measurement of receptor density, an appropriate model to describe the underlying kinetics of the individual radioligand should be developed because the different models are used among the ligands, even though the target receptor is identical. Most of receptor imaging studies to evaluate receptor density was carried out by compartment model analysis. Basically, a compartment model for receptor analysis should describe the kinetic behavior of tracers in the target organs. Usually the behavior is described by a three-compartment model (3CM), three-compartment model with fixed distribution volume in the reference tissue (3CM') or a two-compartment model (2CM). So far, in most of these H1R mapping studies, the binding potential (BP) of [^{11}C]doxepin to H1Rs was calculated using the graphical method introduced by Logan et al, which makes no assumption on the number of compartments in advance. However, the rationale of these models for [^{11}C]doxepin has not been comprehensively verified yet. Thus, in order to determine the best model which describes the kinetics of ^{11}C-doxepin, we investigated the applicability of some model-based analyses to the quantitative evaluation of H1Rs in the human brain by using [^{11}C]doxepin and PET. In principle, compartment

model analysis requires blood sampling as input function, however, blood sampling is invasive for patients. Thus some reference tissue models allowing to omit blood sampling were developed. As for the reference tissue models, two major methods are available: Simplified reference tissue model (SRTM) and Logan graphical method with reference tissue (LGAR). In the present study, we propose a new model-based method without blood sampling. In this method, a standard input function is introduced instead of the individual plasma time activity curve (pTAC) and parameter estimation is based on Logan Graphical Analysis. Therefore, this method is called Logan Graphical Analysis with Standard input function (LGAS). The standard input function is averaged pTAC over five subjects. We examined the possibility of applying 3CM, 3CM', 2CM, SRTM, LGA, LGAR and LGAS to [^{11}C]doxepin data.

The comparison of binding potential (*BP*) values estimated by LGAR and the one tissue model showed good agreement; on the other hand, SRTM turned out to be unstable concerning parameter estimation in several regions of the brain. By including the results of noise analysis, LGAS became a reliable method for parameter estimation of [^{11}C]doxepin data in the cortical regions.

Acknowledgments

The authors thank Ph.D Yuichi Kimura, Ph.D Hideki Mochizuki, Ph.D Kenji Ishii, Ph.D Hiroshi Watabe, and Ph.D Kiichi Ishiwa for their valuable comments and advices.