Application of Animal PET in Preclinical Stage for Efficient Drug Development

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Positron emission tomography (PET) has widely been applied in the basic research with experimental animals and the clinical studies subjecting human patients. In addition, PET technology can be applicable for drug development. In the pre-clinical stage, several disease animal models are used for evaluation of pharmacological efficacy of new chemical entities. We have demonstrated with a high-resolution animal PET (Hamamatsu SHR-7700) that the general physiological parameters of cerebral blood flow (CBF) and cerebral glucose metabolism (CMRglc), were significantly lowered in aged monkeys compared to young ones. In addition, more specific neuroreceptor binding activity was evaluated to show that muscarinic acetylcholine receptor measured by [^{11}C]3-MPB was significantly reduced in the aged monkeys. We demonstrated that aged monkeys provided impaired working memory along with the lowered muscarinic acetylcholine receptor binding, and the lowered working memory performance was improved by donepezil, a cholinesterase inhibitor, in which the activity of cholinesterase inhibition was assessed noninvasively with [^{11}C]MP4A as well as with invasive microdialysis method. PET measurements with dopaminergic probes indicated that dopaminergic neuronal system in the monkey brain as well as movement performance was disrupted by chronic MPTP treatments. We applied MPTP-treated monkeys as the subjects of gene-therapy. After the injection of AAV-AADC vector into the left caudate, dopamine synthesis activity was partially restored, and the impaired movement ability in the right hand was recovered. These results indicate that the animal PET measurement with disease animal model is very useful for drug development in preclinical stage.