3b

Alzheimer's disease

B. Gulyás (Stockholm)

Background

In recent years the development of novel diagnostic imaging biomarkers for neuroinflammation and neurodegeneration has been in the forefront of PET radioligand research and development. The social burden of various neurodegenerative diseases, including MCI (mild cognitive impairment) and AD (Alzheimers Disease), puts a special emphasis on the problem. Molecular imaging with PET has the clinical potential to perform high through-put diagnostic screening as well as refined differential diagnosis of AD patients in early as well as advanced stages. In the seminar we survey several candidate radiotracer molecules which have recently been tested for clinical PET studies.

Current state of art

The most commonly used PET marker of beta amyloids is PIB (Pittsburgh Compound-B), labeling deposits of amyloid in the diseased human brain. Though the mechanisms of PIB-amyloid interaction is not fully understood, the ligand has proved to be an effective marker of amyloid deposition (Klunk et al., 2004). Recently, follow-up markers have been tested, with promising results. - The PBR or, as it is recently called, TSPO system is probably the "most popular" target in the search for a novel PET marker of neuroinflammation. As mentioned earlier, it is not a classical receptor system but part of the multifunctional mitochondrial membrane protein complexes (Venneti et al., 2006). The "classical" ligands of the PBR system belong to isoquinolines. Among them, PK11195 (3-isoquinolinecarboxamide) is the "golden standard" of PET ligands for the PBR system. However, its brain disposition is low. Novel PBR ligands, including Ro5-4864, DAA1106 and its analogues, PBR28, DPA-713 and vinpocetine, have been tested with varying success (Cagning et al., 2002; Maeda et al., 2004; Gulyás et al., 2005) . Of them the most promising ligand is DAA1106 with favourable brain disposition and relatively high affinity. - Of the "classical neuroreceptor systems, predominantly the monoamine systems has been in the focus of recent research. Both the 5HT1A receptor system and the serotonin transporter system (SERT), as well as the norepinephrine transporter (NET) have been investigated in relation to their alterations in neurodegeneration (Kepe et al., 2006). - More recently, dedicated the use of PET tracers for labelling neurotransmitter metabolic pathways has come to the fore. Recent research has indicated that some metabolic pathways responsible for the metabolism of monoamine neurotransmitters may be early affected in the disease. The MAO-A and MAO-B systems show early on alterations and, consequently, these systems can be specifically targeted with PET radioligands, including e.g. 11C-deprenyl (Fowler et al., 2005). A search for more specific enzyme tracers usable in molecular neuroimaging of neuroinflammation are underway.

Conclusion

The search for dedicated PET biomarkers of neuroinflammation and neurodegeneration has a major emphasis in now-a-days' PET tracer development. Both neurodegeneration and neuroinflammation can be targeted by various ways, including the classical neuroreceptor systems, the PBR or TSPO system, metabolic enzymes or amyloid plaques. It can be expected that in the near future other targets may come into the focus of biomarker research, including tau proteins, inappropriate apoptosis-related targets or other metabolic compounds specific for the pathophysiology of the disease.

References

1. Cagnin A, Gerhard A, Banati RB. The concept of in vivo imaging of neuroinflammation with [11C] (R)-PK11195 PET. Ernst Schering Res Found Workshop. 2002 (39):179-91.
2. Fowler JS, Logan J, Volkow ND, Wang GJ. Translational neuroimaging: positron emission tomography studies of monoamine oxidase. Mol Imaging Biol. 7(2005):377-387.
3. Gulyás B, Halldin C, Vas A, Banati RB, Shchukin E, Finnema S, Tarkainen J, Tihanyi K, Szilágyi G, Farde L. [11C]vinpocetine: a prospective peripheral benzodiazepine receptor ligand for primate PET studies. J Neurol Sci. 229-230(2005):219-223.

4. Kepe V, Barrio JR, Huang SC, Ercoli L, Siddarth P, Shoghi-Jadid K, Cole GM, Satyamurthy N, Cummings JL, Small GW, Phelps ME. Serotonin 1A receptors in the living brain of Alzheimer's disease patients. Proc Natl Acad Sci U S A. 103(2006):702-707.
5. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergström M, Savitcheva I, Huang GF, Estrada S, Ausen B, Debnath ML, Barletta J, Price JC, Sandell J, Lopresti BJ, Wall A, Koivisto P, Antoni G, Mathis CA, Langström B. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 55(2004):306-319.
6. Maeda J, Suhara T, Zhang MR, Okauchi T, Yasuno F, Ikoma Y, Inaji M, Nagai Y, Takano A, Obayashi S, Suzuki K. Novel peripheral benzodiazepine receptor ligand [11C]DAA1106 for PET: an imaging tool for glial cells in the brain. Synapse. 52(2004):283-291.
7. Venneti S, Lopresti BJ, Wiley CA. The peripheral benzodiazepine receptor (Translocator protein 18kDa) in microglia: from pathology to imaging. Prog Neurobiol. 80(2006):308-322.