Institutionen för Klinisk Neurovetenskap

Assessment of Dopamine and Serotonin Release in the Non-Human Primate Brain using PET

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i stora föreläsningssalen, hus Z8:00, Karolinska Universitetssjukhuset i Solna, Stockholm.

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av
Sjoerd J. Finnema

Huvudhandledare:
Professor Christer Halldin
Karolinska Institutet
Institutionen för Klinisk Neurovetenskap
Sektionen för Psykiatri

Bihandledare:
Professor Lars Farde
Karolinska Institutet
Institutionen för Klinisk Neurovetenskap
Sektionen för Psykiatri

Professor Håkan V. Wikström
University of Groningen
Department of Medicinal Chemistry
Groningen, The Netherlands

Dr. Benny Bang-Andersen
H. Lundbeck A/S
Lundbeck Research Denmark
Valby, Denmark

Fakultetsopponent:
Dr. Hideo Tsukada
Hamamatsu Photonics K.K.
Central Research Laboratory
Hamamatsu, Japan

Betygsämnd:
Professor Sven Ove Ögren
Karolinska Institutet
Institutionen för Neurovetenskap
Enheten för Beteendeneurovetenskap

Docent Paul Cumming
Ludwig-Maximilians-University
Department of Nuclear Medicine
Munich, Germany

Professor Jan Booij
University of Amsterdam
Department of Nuclear Medicine
Amsterdam, The Netherlands

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ABSTRACT

The molecular imaging technique positron emission tomography (PET) allows for non-invasive examination of biochemical markers in the living brain. For over three decades PET studies have provided important insight into the relationship of monoaminergic neurotransmitter systems to brain functioning and psychiatric disorders. A more recent application of PET is the study of endogenous neurotransmitter release in vivo. Clinical relevance of such methods is found in studies demonstrating enhanced amphetamine-induced dopamine release in schizophrenia patients, whereas PET studies in non-human primates provide a translational model for evaluation of the pharmacological mechanisms before initiation of studies in man.

The first aim of this thesis was to develop improved methods for measurement of endogenous dopamine levels. In study I the potent D2/D3 receptors agonist (R)-(−)-2-methoxy-N-n-propyl-norapomorphine (MNPA) was radiolabeled with carbon-11 and found suitable for in vivo characterization of the high affinity state. In study II, amphetamine-induced displacement of [11C]MNPA binding by dopamine was ~1.8 fold higher at four different doses than for the antagonist [11C]raclopride and demonstrated that an agonist radioligand has improved sensitivity to endogenous neurotransmitter level. Study III aimed to further obtain in vivo support for the existence of two affinity states for the D2/D3 receptors. Receptor occupancy of the exogenous agonist apomorphine was determined with [11C]MNPA and [11C]raclopride. Binding of [11C]MNPA and [11C]raclopride was inhibited monophasic and approached full saturation. ID50 and Ki values of apomorphine were indistinguishable when measured with the agonist or antagonist radioligand. Study III did not support the existence of two affinity states and a possible explanation could be that all D2/D3 receptors are in the high affinity state in vivo. In study IV, the new D1/D5 receptors partial agonist radioligand (S)-[11C]N-methyl-NNC 01-0259 was found insensitive to dopamine levels, and receptor binding was inferior to previously developed antagonist radioligands. Moreover, a COMT formed radiometabolite was found to enter the brain but the formation could be prevented with the use of a COMT inhibitor. COMT inhibition provides a methodology enabling quantitative PET measurements with (S)-[11C]N-methyl-NNC 01-0259.

The second aim of this thesis was to evaluate the sensitivity of the new 5-HT1B receptor radioligand [11C]AZ10419369 to alterations in endogenous serotonin concentration. Previous serotonergic PET radioligands have ambiguously shown sensitivity to serotonin level. In study V the effective serotonin releaser fenfluramine decreased the binding of [11C]AZ10419369 in a dose-dependent manner. In study VI the effect of fenfluramine on [11C]AZ10419369 binding was confirmed using an equilibrium approach with a bolus infusion protocol. The further developed methodology is suitable for exploring the sensitivity limit to serotonin levels as measured using [11C]AZ10419369 and PET.

In conclusion, the present thesis demonstrates that the D2/D3 receptors agonist radioligand [11C]MNPA is an improvement for measurement of dopamine release, when compared to previously used antagonist radioligands. Moreover, a novel methodology, using the 5-HT1B receptor antagonist [11C]AZ10419369 and PET, was developed for measurement of serotonin release in the living brain. These newly developed methodologies may help to further understand the treatment and pathophysiology of several major neurological and psychiatric disorders.