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Institutionen för Klinisk Neurovetenskap

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

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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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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 D_2/D_3 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 [^{11}C]MNPA binding by dopamine was ~1.8 fold higher at four different doses than for the antagonist [^{11}C]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 D_2/D_3 receptors. Receptor occupancy of the exogenous agonist apomorphine was determined with [^{11}C]MNPA and [^{11}C]raclopride. Binding of [^{11}C]MNPA and [^{11}C]raclopride was inhibited monophasic and approached full saturation. ID_{50} and K_i 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 D_2/D_3 receptors are in the high affinity state *in vivo*. In study IV, the new D_1/D_5 receptors partial agonist radioligand (*S*)-[^{11}C]*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*)-[^{11}C]*N*-methyl-NNC 01-0259.

The second aim of this thesis was to evaluate the sensitivity of the new 5-HT_{1B} receptor radioligand [^{11}C]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 [^{11}C]AZ10419369 in a dose-dependent manner. In study VI the effect of fenfluramine on [^{11}C]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 [^{11}C]AZ10419369 and PET.

In conclusion, the present thesis demonstrates that the D_2/D_3 receptors agonist radioligand [^{11}C]MNPA is an improvement for measurement of dopamine release, when compared to previously used antagonist radioligands. Moreover, a novel methodology, using the 5-HT_{1B} receptor antagonist [^{11}C]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.

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