Press release

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Basic information

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Department of: Clinical Medicine

Main supervisor: Associate Professor Anne M. Landau

Title of dissertation: Imaging synaptic dysfunction in naïve animals and in models of Parkinsin's disease

Date for defence: September 3rd at (time of day): 15:00 Place: online at Zoom (https://aarhusuniversity.zoom.us/j/68748915728)

Press release (Danish)

PhD forsvar: Billeddannelse af synaptisk dysfunktion i naïve dyr og i dyremodeller af Parkinsons sygdom

Et nyt ph.d.-projekt fra Aarhus Universitet, Health. Projektet er gennemført af Majken B. Thomsen, der forsvarer det d. 3/9

Parkinsons sygdom (PD) er en neurodegenerativ sygdom, der er karakteriseret ved et progressiv tab af dopaminerge neuroner i substantia nigra (SN) og af dopaminerg innervation i striatum. Tab eller dysfunktion af de præsynaptiske terminaler spiller en stor rolle i en lang række af neurologiske sygdomme, heriblandt PD. Positron emission tomography (PET) er et vigtigt in vivo værktøj til undersøgelse af mennesker og dyremodeller for sygdomme. Det nyudviklede PET sporstof, [11C]UCB-J, binder til det synaptiske vesikelprotein 2A (SV2A) og giver derved mulighed for at studere synaptisk densitet i levende mennesker og dyr. Vi validerede [11C]UCB-J PET billeddannelse i hjernen af henholdsvis Göttingen minigrise og rotter. Vi fandt at [11C]UCB-J kom ind i hjernen hurtigt, bandt specifikt til SV2A, metaboliserede hurtigt og kunne modelleres med 1 tissue compartment modellen i begge arter. [11C]UCB-J PET bindingsværdier af Göttingen minigrisen kunne korreleres til post mortem [3H]UCB-J autoradiografiværdier og til SV2A proteinniveauer målt ved Western blotting. Vi beviste at [11C]UCB-J er i stand til at påvise unilateralt fald i [11C]UCB-J optag i rottemodeler for Parkinsonisme, induceret ved unilateral striatal injektion af 6-hydroxydopamin (6-OHDA), og alfa-synuclein præformede fibriller (PFF). I PFF modellen fandt vi desuden progressive fald i [11C]DTBZ PET bindingen i den ipsilaterale striatum, hvilket blev bekræftet ved post mortem histologi. Vi fandt også patologisk aggregering af alfa-synuclein bilateralt i hjerneområder forbundet med striatum og ipsilateralt i SN. Dette var ledsaget af tab af nigrale dopaminerge neuroner og aktivering af imunsystemet i den ipsilaterale SN. I konklusion har vi valideret [11C]UCB-J som en lovende in vivo markør af synaptisk densitet i hjernen af Göttingen minigrise og rotter, der er i stand til at detektere in vivo ændringer i dyremodeller af PD. Vi har vist at striatale injektioner af alfa-synuclein PFF inducerer alfa-synuclein patologi og ændringer i dopaminerg innervation og synaptisk densitet, hvilket kan monitoreres ved in vivo PET billeddannelse.
Forsvaret af ph.d.-projektet er offentligt og finder sted den 3/9 kl. 15.00 online på Zoom (https://aarhusuniversity.zoom.us/j/68748915728). Titlen på projektet er ”Billeddannelse af synaptisk dysfunktion i naïve dyr og i dyremodeller af Parkinsons sygdom”. Yderligere oplysninger: Ph.d.-studerende Majken B. Thomsen, e-mail: majken.thomsen@biomed.au.dk.

Vejledere: Anne M. Landau, Associate professor, Marina Romero-Ramos, Associate professor og David J. Brooks, Professor, Aarhus Universitet
Bedømmelsesudvalg: Pedro Rosa-Neto, Associate Professor, McGill Universitet og Douglas Research Centre, Benjamin Dehay, INSERM principal investigator, Bordeaux Neurocampus
Komite formand: Mai Marie Holm, Associate Professor, Aarhus University

Press release (English)

PhD defense: Imaging synaptic dysfunction in naïve animals and in models of Parkinsin's disease

The project was carried out by Majken B. Thomsen, who is defending her dissertation on September 3rd.

Parkinson's disease (PD) is a debilitating neurodegenerative disorder, characterized by progressive loss of dopaminergic neurons in the substantia nigra (SN) and dopaminergic innervation in the striatum. Loss or dysfunction of presynaptic terminals play a major role in a wide variety of neurological diseases, including PD. Positron emission tomography (PET) is an important in vivo tool for studying humans and animal models of disease. The newly developed PET tracer, [11C]UCB-J binds to synaptic vesicle protein 2A (SV2A) and provides the opportunity to study synaptic density in living humans and animals. We validated [11C]UCB-J PET imaging in the Göttingen minipig and rat brain. We found [11C]UCB-J to enter the brain rapidly, bind specifically to SV2A, metabolize fast and be modeled appropriately using the 1-tissue compartment model in both species. [11C]UCB-J PET imaging binding values of the Göttingen minipig could be correlated to post mortem [3H]UCB-J autoradiography and SV2A protein levels measured by Western blotting. [11C]UCB-J was proven able to detect unilateral decreases in [11C]UCB-J uptake in rat models of Parkinsonism, induced by unilateral striatal injections of 6-hydroxydopamine (6-OHDA), or alpha-synuclein preformed fibrils (PFF). Furthermore, in our PFF rat model, we found progressive reductions in [11C]DTBZ PET binding in ipsilateral striatum, confirmed by post mortem histology. We also found pathological aggregation of alpha-synuclein bilaterally in brain areas connected to striatum and ipsilaterally in SN. This was accompanied by loss of nigral dopaminergic neurons and immune activation in the ipsilateral SN. In conclusion, we have validated [11C]UCB-J PET as a promising in vivo marker of synaptic density in the Göttingen minipig and rat brain, able to detect in vivo changes in animal models of PD. We have found injections of alpha-synuclein PFFs into rat striatum to induce alpha-synuclein pathology and changes in dopaminergic innervation and synaptic density, which can be monitored by in vivo PET imaging.
The defence is public and takes place on September 3rd at 3pm online at Zoom (https://aarhusuniversity.zoom.us/j/68748915728). The title of the project is Imaging synaptic dysfunction in naïve animals and in models of Parkinsin's disease. For more information, please contact PhD student Majken B. Thomsen, email: majken.thomsen@biomed.au.dk.

Supervisors: Anne M. Landau, Associate professor, Marina Romero-Ramos, Associate professor and David J. Brooks, Professor, Aarhus University
Assessment committee: Pedro Rosa-Neto, Associate Professor, McGill University and Douglas Research Centre, Benjamin Dehay, INSERM principal investigator, Bordeaux Neurocampus
Chair of the committee: Mai Marie Holm, Associate Professor, Aarhus University

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