PET imaging of adenosine A2A receptors
Zhou, Xiaoyun

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
References


96. Jarvis MF, Schulz R, Hutchison AJ, Do UH, Sills MA, Williams M. [3H]CGS 21680, a selective A2 adenosine receptor agonist directly labels A2 receptors in rat


164. Ferré S, Fuxe K. Dopamine denervation leads to an increase in the interaction between adenosine A2 and dopamine D2 receptors in the neostriatum. *Brain Res*. 1992;594:124-130.

References


212. Ciruela F. Presynaptic Control of Striatal Glutamatergic Neurotransmission by


224. Latini S, Pedata F. Adenosine in the central nervous system: Release mechanisms


Acknowledgements

After one and a half years of painstaking experiments on my first project — PET imaging of alpha-synuclein, I was sitting in Rudi’s office, feeling sad about the termination of my first project, and worried about the plan B — imaging of adenosine A\textsubscript{2A} receptors. I had no clue about the A2A project, so I asked a good deal of questions based on the limited literature that I had read, hoping to get some support and comfort from Rudi and my daily supervisors — Philip and Erik. But rather disappointingly, Rudi seemed unsatisfied at my reaction to my new project, he responded that I should not only post questions but find the way to solve them. ‘What! I am just a beginner. It’s already a great encouragement to ask these questions’, I went out of the office, unhappy. Rudi is right. Finally, I truly understood his attitude one year after the appointment. Now I am at the end of my PhD career and I know how a responsible researcher should be: asking interesting questions and dealing with them to the best of your ability. Thanks Rudi, your criticism pushes me moving forward in science.

Philip and Erik, my daily supervisors, thank you for your tolerance. I think I am a rather tough student, but don’t be annoyed with me. I challenged you as I challenge myself. When I disagreed, it usually means that I want more elaboration. Philip and Erik, thank you for your guidance and support during the past 5 years. I can still recall the moment when I had the telephone interview with Erik. I found it very stressful. I wrote down tips and taped them everywhere in the room: on the walls, tables, chairs, wardrobe doors…I was struggling to memorize and pronounce the names of isotopes correctly. At that time, I had no confidence about my level of English and no idea of radiochemistry. Through your education of me, I become a qualified radiochemist, an independent researcher, and am capable of completing my thesis, writing articles, and presenting my work in international conferences. I would like to thank Philip for providing me with opportunities and freedom to try my ideas. Without your help, I would not be able to test my compounds with alpha-synuclein in my first project and have successful cooperation with researchers from Japan in my second project. Erik, thank you for your constructive criticisms of my research and my writings. Your criticisms were difficult to handle and sometimes
made me feel awkward, but they were extremely helpful in improving my thinking and the quality of my manuscripts. Furthermore, thank you for saving many C-11 syntheses by fixing problems of RESY on time!

I would also like to thank my reading committee — Adriaan Lammertsema, Guy Bormans, and Teus van Laar — for spending the time critically reading and approving my thesis.

Many thanks are also addressed to Johan de Jong, my supervisor of the dosimetry study. Thank you for being my friend and for all the interesting discussions on wide variety of topics. I want to express my deep gratitude to Ronald Boellaard, thank you for teaching me everything interesting in kinetic modeling and your efforts in improving the quality of research in our department. I was impressed by your open and positive attitude on learning new things. Aren, I felt very happy and relaxed during our discussions. You are a very knowledgeable and kind person. Especially thank you for your patience and cooperation in our AcertaPharma project. Janine, because of your help with the Inveon camera, we have succeeded in the application of preclinical PET imaging in dosimetry studies. Thank you! Also many thanks for your involvement in the PD rat study. Chantal and Jürgen, thank you for being my paranymphs. Jürgen, I really appreciate all the work you have done for me. Thank you for providing the surgical training. Thank you for arranging PET scans, transporting and preparing animals. You were the unsung hero of my research. A special ‘thanks’ goes to Chantal. Your suggestions on [\(^{11}\)C]preladenant synthesis was a great help on optimization of tracer production. Also thank you for your friendship and help with my study. Bram and Rolf, you were always there when I needed your support. Your enormous help made my research much easier and more enjoyable. I will always remember the time we worked together in the PET lab. I would also like to thank Hilde, Michèl, Janet, and Petra, for your efforts to keep our lab clean and well organized. I want to thank Gert and Marianne for your help with metabolite analysis and LC-MS analysis. I am particularly grateful to Antoon and Michel Koole for the informative discussions on the basics of pharmacokinetic modeling, which sparked my interest in this field. Thanks to Klaas Willem for solving ICT-related problems. Sarita and Annegrit, thank you very much for your help with all arrangements and dealing with the many financial problems during my PhD.

Thanks to the Chinese Scholarship Council for providing financial support during my PhD study. Many thanks to Riekje, Mathilde and Maaike from GUIDE office
for your help with administrative issues. Thanks to CDP officers Miriam and Catherine, for reviewing my DEC applications and providing helpful advice on animal studies. Special thanks to Annemieke and Michel Weij for the training and help with animal experiments.

My thanks also go to the collaborators of my research outside the NGMB. Cindy, you initiated the PET study in PD rats. You are an excellent researcher and cooperator. The work could not be done without your help. I appreciate your knowledge in animal models and data analysis and your encouragement in dealing with difficulties and trying new things. I would like to thank Kiichi, Hideo, and other collaborators from Japan. Thank you for your active involvement from the very beginning in the monkey study — experimental design — up to the acceptance of the research article. Special thanks to Kiichi, thank you for your enthusiasm in the A2AR project and your many inputs to the study protocol. I would like to thank Vinod Subramaniam, Ine Segers-Nolten, and Christian Blum from the University of Twente, for providing alpha-synuclein and allowing me to perform experiments in your lab. I want to thank Henny van der Mei and Prashant K. Sharma from the Department of Biomedical Engineering, UMCG. Thank you for your help with in vitro monitoring of ligand-protein interaction. I want to thank Hetty Timmer-Bosscha and Linda Pot from the Department of Medical Oncology, UMCG for cell culture training. I am grateful for the help, supports, discussions and suggestions from the AcertaPharma team. Thanks to Tjeerd Barf, Allard Kaptein, Diana Mittag, Bart Van Lith, Tim Ingallinera, and Saskia Verkaik for your cooperation in my last project.

I am very lucky to be a member of NGMB. Not only have I received the best education and support in all aspects, but also I have been inspired, and helped by my brilliant fellow colleagues. First, I would like to thank Shiva. Shiva, you guided me through the first experiment on C-11 radiolabeling and you were involved in several of my projects. Thank you for your hands-on experience on radiosynthesis and making tracers for me! Thank you for your kindness and cooperation. I would like to thank Anja Huizing, my master student who worked with me for 5 months. To be a supervisor of an outstanding student like you is challenging. I appreciate your genuine enthusiasm in organic chemistry and your help with my first animal experiment! I wish you good luck in your career. Thanks to Marcel Segbers, Noortje, Nathalie, Siddesh, Paula, Anniek, Heli and Mingzan, for being my officemates and for many pleasant conversations. Inês, thank you for your great help at the beginning of my PhD. Many thanks to Ewelina, David, Luis, Isadora,
Andrea Monroy, Andrea Parente, Verena, Anna, Gaurav, Vineet, Ate, Marcel Benediba, Jason, Alex, Daniele, Zilin, Soumen Paul, Willem-Jan, Vladimir, Khayum, Merhsima, Chao, Leila, Nisha, Giuseppe, Valentina, for your willingness to provide help, and for the precious time we spent in the office and labs. Especially thanks to David for the time and effort you took in setting up standards for preclinical data analysis and solving practical issues of PhDs.

My sincere gratitude goes to my Chinese friends in Groningen: Lei Zhu, Nana Yu, Yanan Wang, Guowei Li, Yanping Geng, Qiuyan Yang, Hui Ai, He Sun and Jiawei Rong, Youtao Liu, Honghao Ren, Yanping Zhao, Deli Zhang, Ming Li, Yinan Zhu, Ranran Li, Rui Wu, Ye Yuan, Yingfen Wei, Si Chen, and many others. Thank you for your company and the memorable moments we spent together during the past years. Special thanks to my roommates: Lei Zhu, Nana Yu, Yanan Wang, and Guowei Li. You are my family in Groningen. You made my life more interesting and colourful. Thanks for sharing your space, food, and thoughts, thanks for traveling together and having fun together! I will miss you.

Thanks to my parents. Mama, Baba, no words can express how much I love you. You always show me your concern as I am still your little girl, but at the same time, you give me freedom to take risks, make mistakes, and pursue whatever future that I chose. Thank you for your understanding and great support!

Finally, my love goes to Guohui Huang. My achievement is partly yours. Thank you for all your affection, even though it is coming from thousands of miles away, I can still feel the warmth of your love. You are the person I believe and trust the most, and the reason why I strive to achieve my best. Because of you, I have managed to keep healthy and overcome all obstacles, because I believe in the future, our future.

Xiaoyun Zhou
26 November 2016

‘In a thousand different forms you may hide yourself, but all the same, my best-beloved, I will recognize you’

— Johann Wolfgang von Goethe
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ</td>
<td>Amyloid-β peptide</td>
</tr>
<tr>
<td>A_nR</td>
<td>Adenosine A_n receptor</td>
</tr>
<tr>
<td>AC</td>
<td>Adenylyl cyclase</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>AIC</td>
<td>Akaike information criterion</td>
</tr>
<tr>
<td>AIM</td>
<td>Abnormal involuntary movement</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ARG</td>
<td>Autoradiography</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood brain-barrier</td>
</tr>
<tr>
<td>BD</td>
<td>Biodistribution</td>
</tr>
<tr>
<td>B_{max}</td>
<td>Total density of target molecules</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood oxygenation-level dependent</td>
</tr>
<tr>
<td>BP_{ND}</td>
<td>Non-displaceable binding potential</td>
</tr>
<tr>
<td>Bq</td>
<td>Becquerel</td>
</tr>
<tr>
<td>BRET</td>
<td>Bioluminescence resonance energy transfer</td>
</tr>
<tr>
<td>cm</td>
<td>Centimeter</td>
</tr>
<tr>
<td>CBV</td>
<td>Cerebral blood volume</td>
</tr>
<tr>
<td>Ci</td>
<td>Curie</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COV</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>C_P</td>
<td>Radioactivity concentration in plasma</td>
</tr>
<tr>
<td>C_R</td>
<td>Radioactivity concentration in a reference region</td>
</tr>
<tr>
<td>C_T</td>
<td>Radioactivity concentration in tissue</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>Da</td>
<td>Atomic mass unit / dalton</td>
</tr>
<tr>
<td>D_nR</td>
<td>Dopamine D_n receptor</td>
</tr>
<tr>
<td>DMAA</td>
<td>N,N-Dimethylacetamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>2D-OSEM</td>
<td>2-Dimensional ordered-subset expectation maximization algorithm</td>
</tr>
<tr>
<td>DVR</td>
<td>Distribution volume ratio</td>
</tr>
</tbody>
</table>
ED  Effective dose
$ED_{50}$ Drug dose corresponds to 50% occupancy
ERK Extracellular signal–regulated kinase
ESI-HRMS Electro-spray ionization high-resolution mass spectrometry
fmol Femtomole
fMRI Functional magnetic resonance imaging
FDG Fluo-2-rodeoxy-D-glucose
FOV Field of view
g Gram
GBq Gigabecquerel
GCF Global correction factor
GDNF Glial cell line-derived neurotrophic factor
GPe Globus pallidus pars externa
GPi Globus pallidus pars interna
HCl Hydrogen chloride
HD Huntington’s disease
HIV Human immunodeficiency virus
HPLC High performance liquid chromatography
Hz Herz
ICC Intra-class correlation coefficient
ICRP International Commission on Radiological Protection
keV Kiloelectronvolt
$K_1$-$k_n$ Rate constant ‘n’
kBq Kilobecquerel
kDa Kilodalton
$K_d$ Dissociation constant
kg Kilo gram
$K_i$ Inhibition constant
$K_i$ Metabolic rate constant
L-DOPA Levodopa
LGA Logan graphical analysis
LID Levodopa-induced dyskinesia
LogD_{7.4} Octanol water partition coefficient at pH7.4
mg Minigram
min Minute
mL Minilitre
mm Minimitre
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>mmol</td>
<td>Minimole</td>
</tr>
<tr>
<td>mM</td>
<td>Minimolar</td>
</tr>
<tr>
<td>M</td>
<td>Molar concentration (1 M = 1 mole/litre)</td>
</tr>
<tr>
<td>MBq</td>
<td>Mega becquerel</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MRTM</td>
<td>Ichise’s multilinear reference tissue model</td>
</tr>
<tr>
<td>MS</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>nm</td>
<td>Namometre</td>
</tr>
<tr>
<td>nM</td>
<td>Nanomolar</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>$\text{Occ}_{\text{max}}$</td>
<td>Maximum occupancy</td>
</tr>
<tr>
<td>6-OHDA</td>
<td>6-Hydroxydopamine</td>
</tr>
<tr>
<td>OSEM3D/MAP</td>
<td>Ordered set expectation maximization-3-Dimension/maximum a posteriori</td>
</tr>
<tr>
<td>PBS</td>
<td>Phosphate-buffered saline</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>PEG400</td>
<td>Polyethylene glycol 400</td>
</tr>
<tr>
<td>PET</td>
<td>Positron-emission tomography</td>
</tr>
<tr>
<td>PVE</td>
<td>Partial volume effect</td>
</tr>
<tr>
<td>QC</td>
<td>Quality control</td>
</tr>
<tr>
<td>RLogan</td>
<td>Reference tissue Logan plot</td>
</tr>
<tr>
<td>ROI</td>
<td>Regions of interest</td>
</tr>
<tr>
<td>RP</td>
<td>Reverse-phase</td>
</tr>
<tr>
<td>RT</td>
<td>Residence time</td>
</tr>
<tr>
<td>s</td>
<td>Second</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SNc</td>
<td>Substantia nigra pars compacta</td>
</tr>
<tr>
<td>SNr</td>
<td>Substantia nigra pars reticulate</td>
</tr>
<tr>
<td>SPM</td>
<td>Statistical parametric mapping</td>
</tr>
<tr>
<td>SPMS</td>
<td>Secondary progressive multiple sclerosis</td>
</tr>
<tr>
<td>SRTM</td>
<td>Simplified reference tissue model</td>
</tr>
<tr>
<td>STN</td>
<td>Subthalamic nucleus</td>
</tr>
<tr>
<td>SUV</td>
<td>Standardized uptake value</td>
</tr>
<tr>
<td>SUV$_r$</td>
<td>Standardized uptake value ratio</td>
</tr>
<tr>
<td>Sv</td>
<td>Sievert</td>
</tr>
<tr>
<td>Symbol</td>
<td>Term</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>t</td>
<td>Time</td>
</tr>
<tr>
<td>t_{1/2}</td>
<td>Half-life</td>
</tr>
<tr>
<td>T</td>
<td>Tesla</td>
</tr>
<tr>
<td>TAC</td>
<td>Time-activity curve</td>
</tr>
<tr>
<td>TAT</td>
<td>Trans-activator of transcription</td>
</tr>
<tr>
<td>nTCM</td>
<td>n-Tissue compartment model</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin-layer chromatography</td>
</tr>
<tr>
<td>TM</td>
<td>Transmembrane</td>
</tr>
<tr>
<td>TRV</td>
<td>Test-retest variability</td>
</tr>
<tr>
<td>TSPO</td>
<td>Translocator protein 18 kDa</td>
</tr>
<tr>
<td>UPLC</td>
<td>Ultra-high performance liquid chromatography</td>
</tr>
<tr>
<td>v/v</td>
<td>Volume per volume</td>
</tr>
<tr>
<td>V_B</td>
<td>Fractional blood volume</td>
</tr>
<tr>
<td>V_{ND}</td>
<td>Non-displaceable volume of distribution</td>
</tr>
<tr>
<td>VOI</td>
<td>Volume of interest</td>
</tr>
<tr>
<td>V_T</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>YFP</td>
<td>Yellow fluorescent protein</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
<tr>
<td>μL</td>
<td>Microlitre</td>
</tr>
<tr>
<td>μM</td>
<td>Micromolar</td>
</tr>
<tr>
<td>μm</td>
<td>Micrometre</td>
</tr>
<tr>
<td>μSv</td>
<td>Microsievert</td>
</tr>
</tbody>
</table>