Decreased GABA-A Receptor Binding in Association With β-Lactam Antibiotic Use

DOI:
10.1097/RLU.0000000000002811

Document Version
Accepted author manuscript

Link to publication record in Manchester Research Explorer

Citation for published version (APA):

Published in:
Clinical Nuclear Medicine

Citing this paper
Please note that where the full-text provided on Manchester Research Explorer is the Author Accepted Manuscript or Proof version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version.

General rights
Copyright and moral rights for the publications made accessible in the Research Explorer are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Takedown policy
If you believe that this document breaches copyright please refer to the University of Manchester’s Takedown Procedures [http://man.ac.uk/04Y6Bo] or contact uml.scholarlycommunications@manchester.ac.uk providing relevant details, so we can investigate your claim.
Decreased GABA-A receptor binding in association with β-lactam antibiotic use

Flaus A\textsuperscript{a, b}, Riano Barros DA\textsuperscript{c, d}, Hinz R\textsuperscript{e}, Myers JF\textsuperscript{c}, Lingford-Hughes A\textsuperscript{f}, Koepp MJ\textsuperscript{e, b}, Hammers A\textsuperscript{b, c, d, i}, McGinnity CJ\textsuperscript{b, c, d}.

\textsuperscript{a} Department of Nuclear Medicine, University Hospital, Saint-Etienne, France
\textsuperscript{b} School of Biomedical Engineering & Imaging Sciences, King’s College London, London, UK and Guy’s and St Thomas’ PET Centre, St Thomas’ Hospital, London, UK
\textsuperscript{c} Centre for Neuroscience, Department of Medicine, Imperial College London, London, UK
\textsuperscript{d} MRC Clinical Sciences Centre Hammersmith Hospital, London, UK
\textsuperscript{e} Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK
\textsuperscript{f} Neuropsychopharmacology Unit, Department of Medicine, Imperial College London, London, UK
\textsuperscript{g} Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, UK
\textsuperscript{h} Epilepsy Society, Chalfont St Peter, UK
\textsuperscript{i} Neurodis Foundation, CERMEP, Imagerie du Vivant, Lyon, France

Corresponding author:
Flaus Anthime
Service de Médecine Nucléaire, Hopital Nord, CHU de St Etienne
42055 Saint-Etienne Cedex 2 FRANCE.
Email address: anthime.flaus@gmail.com – Telephone number: +33477828318
16-digit ORCID identifier is 0000-0001-5877-2159

Compliance with Ethical Standards

- The authors declare that they have no conflict of interest.
- Informed consent was obtained from all individual participants included in the study.
- All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
Decreased GABA-A receptor binding in association with β-lactam antibiotic use
Abstract: β-lactam antibiotics are proconvulsive. In laboratory animals, this effect appears to be predominantly mediated through inhibition of GABA-A receptors, but it has not been demonstrated in humans in vivo. We report images of a $[^{11}C]$Ro15-4513 PET from a 40 years old male who had completed a one week course of flucloxacillin before it. Relative to healthy controls, the participant had significantly lower mean grey matter binding. These novel data suggest that in humans, the proconvulsive effect of β-lactam antibiotics is mediated via either competition for the same benzodiazepine binding site as $[^{11}C]$Ro15-4513, or downregulation of GABA-A receptor expression.

Keywords: PET; Ro15-4513; β-lactam; GABA-A
**FIGURE 1.** β-lactam antibiotics such as flucloxacillin are proconvulsive, and seizures are a well-recognized manifestation of penicillin neurotoxicity[1,2]. In laboratory animals, this effect appears to be predominantly mediated through inhibition of GABA-A receptors[3–5]. However, to our knowledge, the effect of β-lactam antibiotics on GABA-A receptor binding has not been demonstrated in humans *in vivo*.

[11C]Ro15-4513 was used to acquire positron emission (PET) data from a 40-year-old male who had completed a one-week course of flucloxacillin 250mg q.i.d. one day before the scan. Data were acquired as described previously[6]. [11C]Ro15-4513 volume-of-distribution (Vr; i.e. binding) reflects the availability of GABA-A receptor subunit: total, α1 (most fast), and α5 (most slow) components [7]. We corrected for partial volume effects using SFS–RR[8].

Relative to 23 unmedicated healthy controls, the participant had significantly lower mean grey matter total Vr (-30% [3.39 vs. mean ± standard deviation 4.86 ± 0.51], p=0.002). The reduction was of similar magnitude for both fast and slow mean grey matter Vr s (fast: -29% [2.10 vs. 2.94 ± 0.29], p=0.002; slow: -31% [1.24 vs. 1.81 ± 0.60], p=0.174). The participant’s injectate had contained 17.05 µg of ligand, whereas 3.44 ± 1.34 µg was typical for the healthy controls. This cannot explain our findings, as α5 subunit occupancy was ~11.9%, and α1 occupancy only ~1.0%, with a near-identical reduction for both components.

These novel data suggest that in humans, the proconvulsive effect of β-lactam antibiotics is mediated via either competition for the same benzodiazepine binding site as [11C]Ro15-4513, or downregulation of GABA-A receptor expression.

Slow component VT
Healthy Controls
Participant Flucloxacillin

Total $V_T$
Fast component $V_T$
Slow component $V_T$