PET Imaging of the P2X7 Ion Channel with a Novel Tracer [18F]JNJ-64413739 in a Rat Model of Neuroinflammation

Tamara Berdyyeva*[1a], Chunfang Xia[1b], Natalie Taylor[1c], Yingbo He[1d], Gang Chen[1e], Chaofeng Huang[1f], Wei Zhang[1g], Hartmuth Kolb[1h], Michael Letavic[1i], Anindya Bhattacharya[1j], Anna Katrin Szardenings[1k]

[1]Janssen Research & Development LLC, 3210 Merryfield Row, San Diego, CA 92121, USA

*Corresponding author

[a] tberdyy6@its.jnj.com; [b] cxia1@its.jnj.com; [c] ntaylo23@its.jnj.com; [d] yhe50@its.jnj.com; [e] gchen43@its.jnj.com; [f] chuang64@its.jnj.com; [g] wzhan110@its.jnj.com; [h] hkolb1@its.jnj.com; [i] mletavic@its.jnj.com; [j] abhatta2@its.jnj.com; [k]aszarden@its.jnj.com

Running Title: P2X7 PET in rat LPS model

Materials and Methods

[^{18}F]JNJ-64413739 Preparation and Characteristics

[^{18}F]JNJ-64413739 was synthesized from the precursor JNJ-64410047 using [^{18}F]F-/KHCO$_3$/K-222 in dimethyl sulfoxide (DMSO) at 120 °C for 10 min. After completion of the reaction, the crude labeling mixture was purified by semi-preparative reverse phase high-performance liquid chromatography (RP-HPLC) to yield the product (decay corrected yield, DCY = 8.9 ± 1.8%) with a radiochemical purity of ≥ 99% and molar activity 9.88 ± 3.2 GBq/µmol at the end of synthesis. The product was confirmed by analytical HPLC by co-injection of standard compound.

Drugs and Formulations

LPS-EB (Lot# LEB-38-02, InvivoGen) was freshly prepared in sterile PBS (GE Healthcare Life Sciences, HyClone) at 4 µg/µl.

JNJ-54175446 was freshly prepared in 20% 2-Hydroxypropyl)-β-cyclodextrin (HP-β-CD) and 20% polyethylene glycol 400 (PEG-400) in acetate buffer at a concentration of 1 mg/ml and dosed at 2.25 ml/kg (i.v.) to achieve 2.25 mg/kg dose. The blank formulation ("vehicle") was dosed with the same volume.

Animals

Adult (10-15 weeks at the start of the experiments) male socially housed Sprague Dawley rats (HSD Livermore) were used in these experiments. The rats had access to food and water ad libitum and were kept under a 12-h light-dark cycle. All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals (US National Institutes of Health) and the research protocol was approved by the Institutional Animal Care and Use Committee (IACUC).

Animal Procedures

Animals underwent stereotactic surgery for the intracerebral injections of LPS or PBS. On the day of the surgical procedure, the animals were deeply anesthetized with Isoflurane (in a medical oxygen carrier) and placed into a stereotaxic device (Kopf ® David Kopf Instruments, Tujunga, USA) equipped with atraumatic ear bars. The Isoflurane (typically 4.5-5% at the start, 2-3% during the surgery) was delivered to the nose of the animal via a face mask that integrates with the stereotaxic apparatus; the body temperature was maintained at 37 °C by a homeothermic blanket (Harvard Apparatus, Holliston, USA). The surgical site was prepared in compliance with aseptic procedures; then a small hole was manually drilled in the skull with the sterile 18G needle at following stereotaxic coordinates corresponding to striatum: 0.8 mm in anterioposterior, 2.7 mm lateral, and 5.5 mm dorsoventral (measured from Bregma, [S1]). Unless indicated otherwise, 20 micrograms of LPS (freshly prepared in sterile PBS at 4 µg/µl) in a total volume of 5 µl/rat were infused at a flow rate of 500 nl/min (Pump 11 Elite, Harvard Apparatus, Holliston, USA) via microsyringe (NanoFil Syringe; World Precision Instruments, Sarasota, USA) mounted on the stereotaxic arm. Control animals were injected with PBS in a similar manner except the PBS solution contained no LPS. After the microinjection, the syringe was kept in place for 5-10 min to avoid backflow of the solution. Following administration, the injection syringe was withdrawn, and the skin was sutured.

All scanning procedures were performed while rats were anesthetized using Isoflurane gas in O_2 carrier (3.0%–4.5% for induction and 1.0%–3% for maintenance). During the scan, heat was continually supplied via a heating blanket, and the breathing rate was continuously monitored by a scanner-integrated physiological monitoring system (BioVet, m2m Imaging Corp, Cleveland, USA).

Imaging Procedures

Images were acquired on a microPET/CT hybrid Inveon MM scanner (Siemens, Knoxville, USA). On the day of the imaging experiment, [^{18}F]JNJ-64413739 was produced. Shortly after the quality control for the compound's radioactivity and purity, doses for animal studies were calculated by measuring the activity in the vial by a PET dose calibrator (AtomLab 400, Biodex Medical Systems, New York, USA). PET scan was performed first, followed by computer tomography (CT) scan which was used for attenuation correction, anatomical images to locate anatomical landmarks (Bregma and Lambda), and for scatter correction. Acquisition parameters for CT were 80 kVp beam energy with a current of 500 μA and an exposure time of 245 ms; 220-degree rotation; 440 projections. The data were reconstructed using ordered-subsets expectation maximization (OSEM) algorithm (no down sampling, low noise reduction, Hounsfield Units (HU) scaling factor of 3.4002 applied, beam-hardening correction optimized for rats applied) into 1024 × 1024 × 992 reconstruction volume size (4 x 4 binning, low magnification), corresponding to a voxel size of 102.966 × 102.966 × 102.966 micrometers.

[^{18}F]JNJ-64413739 (12.95±2.96MBq) was administered intravenously (i.v.) via a bolus tail vein injection on the scanner bed and PET acquisition was started at the same time. The energy window was set between 350 and 650 KeV, 3.438 ns timing window. The head was centered in the axial field of view (FOV) of the scanner (127 mm axial length) to maximize sensitivity and resolution. Emission data were collected in list mode for 60 min. When *ex vivo* ARG experiments were performed after the PET scan, a shorter scanning time of 20 min was used.

PET images were reconstructed with iterative 2-dimensional ordered-subsets expectation maximization (OSEM2D) algorithm (4 OSEM2D–iterations, with Fourier rebinning) into 17 time frames (10 × 1 min, 4 x 5 min, 3 × 10 min) for 60 min scans, and into 14 time frames (10 × 1 min, 4 x 5 min) for 20 min scans. The data were reconstructed into 128 × 128 matrix size images. Time-activity curves (TAC) were generated using Inveon Research Workspace software (ver.4.2, Siemens Medical Solutions USA). The reconstructed images were examined in axial, coronal and sagittal planes. Reconstructed PET

images of each rat were checked for artefacts or CT/PET misalignments and averaged over time. The images were resliced and manually co-registered to the canonical CT rat brain template image.

Volumes of interest (VOI) for this study were: 1) Injection site: right (injected with LPS) hemispheric elliptical volume centered on the position of the tip of the injection needle (recorded for each animal during the surgery) and extending 6 mm along the anteroposterior axis and 4.5 mm along the dorsoventral and mediolateral axes; 2) Control site: left (intact, control) corresponding region with parameters equivalent to (1); and 3) Cerebellum (reference area). The VOIs were manually drawn using the Inveon Research Workplace software and an anatomical image (with Bregma and Lambda positions identified on the CT images). The resulting transformation matrix was applied to the entire dynamic PET series.

A standard volume of interest (VOI) drawn in the CT space was applied to the normalized PET images to extract time-activity curves (TACs) in units of SUV (standardized uptake value), calculated as

$$SUV(t) = c_{img}(t)/(ID/BW)$$

where c_{img} is the image derived radioactivity concentration in MBq/cc, ID is the injected radioactivity, and BW is the body weight; all values were decay-corrected.

The SUV values (mean SUV, upper bound, lower bound, standard deviation) for each time frame in each VOI were exported as .csv files. For the figures, custom-written Matlab scripts were used to produce the summary plots and perform statistical analysis to compare tracer retention (measured by calculating the average SUV values in each region during the entire scan or specified period (e.g., 30-60 min post-tracer injection) across VOIs. SUVRs values were calculated as a ratio of SUV value for the injected or control VOI to the reference area (cerebellum).

To produce the example PET/CT images shown in Fig. 1-2, the greyscale CT image (displayed on a scale of -1000 to +2500 HU) was overlaid with PET data (shown on a "Jet" color scale) summed over the entire scan period.

For the results presented in Table 1, SUVR values were compared by one-tailed, two-sample t-test with unequal variance (Excel, Version 1708, Build 8431.2153)

Ex vivo Autoradiography and Immunohistochemistry

To determine the distribution of the tracer in the brain, *ex vivo* autoradiography (ARG) was performed. [18F]JNJ-64413739 (14.8MBq) was injected i.v. into rats injected 2 days prior with LPS (20 μg, n = 2) or PBS (n = 2). All rats were scanned (20 min PET scan) and sacrificed 10 min after the scan. The brains were extracted and immediately frozen on dry ice. Coronal brain sections were cut with 10 or 20-μm thickness at the LPS/PBS injection site. The 20 μm sections were exposed to a phosphor screen in a cassette and kept in darkness overnight. On the next day the screen was scanned on a Fuji Bio-Imaging System FLA-7000 (Tokyo, Japan). Autoradiographic images were obtained and signal intensity measured using a Multi Gauge program from Fuji (Tokyo, Japan).

Iba1 IHC was performed on adjacent 10-μm sections. The frozen sections were air dried. After fixing in paraformaldehyde fixative solution (Alfa Aesar, MA), sections were permeated with 3% H_2O_2 and then blocked with 10% goat serum in 0.01 M PBS for 1 h. The sections were then incubated with rabbit anti-Iba1 antibody (WAKO, Richmond, VA) overnight at 4 °C. Iba1 immunoreactivity was visualized using an Alexa-488-labeled goat anti-rabbit secondary antibody (Invitrogen, CA) under an Axio Imager 2 microscope (Carl Zeiss, Inc, Jena, Germany).

RNA Extraction, Reverse Transcription PCR and Quantitative Real-Time PCR

To determine the expression levels of genetic biomarkers of neuroinflammation, brain samples (injected hemisphere, contralateral hemisphere and cerebellum) from rats injected 2 days prior with LPS (20 μg, n = 2) or PBS (n = 2) were collected and fresh frozen immediately after a PET/CT scan performed to confirm uptake of the [18F]JNJ-64413739 at the LPS-injected site. Brain samples were homogenized

and total Ribonucleic Acid (RNA) was extracted using RNeasy plus mini kit (Qiagen). Total RNA concentrations were measured using NanoDrop ND-1000 spectrophotometer. RNA was then reverse-transcribed into complementary deoxyribonucleic acid (cDNA) using Superscript III reverse transcriptase (Invitrogen) with random hexamer primers. Transcript abundance was determined by quantitative PCR using SYBR Green PCR mix (Applied Biosystems). The following primer pairs were used for quantitative real-time PCR:

Gapdh: 5' AACCCATCACCATCTTCCAG 3' (F) and 5' CCAGTAGACTCCACGACATAC 3' (R)

P2rx7: 5' GACAAACAAAGTCACCCGGAT 3' (F) and 5' CGCTCACCAAAGCAAAGCTAAT 3' (R)

Tspo: 5' CAG CGC AGT GTC CTT CA 3' (F) and 5' GTA CCC AGG ATT GAG ACATAGTG 3' (R)

Nos2: 5' TGTCTGTGACTTTGTGCTTCT (F) and 5' GACTGGACTTTTAGAGACGCTT 3' (R)

Aif1: 5' TCGATATCTCCATTGCCATTCAG 3' (F) and 5' GATGGGATCAACAAGCACTTC 3' (R)qPCR

Supplementary Results

Selection of LPS dose and timepoints: longitudinal pilot PET imaging studies with [^{18}F]JNJ-64413739

Since P2X7 tracers have not been evaluated in a rat model of local neuroinflammation induced with intracerebral injection of LPS, we first conducted a pilot imaging study with [^{18}F]JNJ-64413739 to select the optimal dose of LPS and time point post-LPS injection for subsequent imaging experiments. Groups of rats (n = 2 in each group) were injected with 0, 5, 20 and 50 µg of LPS (dissolved in 5 µl of sterile PBS) and imaged after 1 day (0, 5 and 20 µg groups), 2 days (all groups), 3 days (all groups) and 4 days (20 µg group only) post-injection. The averaged (across animals in each group and across all timepoints during each imaging session, 0-60 min post-tracer injection) measurements of SUV, SUVR and normalized SUV difference between the injected and control site

$$\Delta_{ic} = (\text{SUV at Injected Site} - \text{SUV at Control Site})/ \text{SUV at Control Site}*100\%$$

are summarized in Table 1.

At any given day post-LPS injection, the uptake of the [^{18}F]JNJ-64413739 at the LPS-injected site had increased in a dose-dependent manner. However, for each given dose of LPS, the difference between the LPS injected site and control site varied in a time-dependent manner (Table 1). Control rats injected with 0 µg of LPS did not show any significant difference (p>0.05, one-sided t-test) in [^{18}F]JNJ-64413739 uptake between injected and control site at any time point. Rats injected with 5 µg and 20 µg of LPS showed the highest difference at day 2 post-LPS administration. Representative examples of PET images of rats injected with 0 µg of LPS (PBS control) and 20 µg of LPS, respectively, at day 1, 2, 3 and 4 post-injection are shown in Fig. 1. While the difference in [^{18}F]JNJ-64413739 uptake between injected and control site can be driven even higher by injecting higher LPS doses (50 µg) and waiting longer (day 3 post-LPS), the magnitude of the increase (31.6% ± 0.4% for 20 µg at day 2 vs 36.3% ± 0.1% for 50 µg at day 3) did not warrant higher doses and longer timepoints.

Based on the results of this pilot experiment, 20 µg of LPS and day 2 post-LPS were selected as the dose and timepoint to be used in all subsequent PET imaging experiments with [^{18}F]JNJ-64413739.

Displacement with JNJ-54175446 PET imaging study

To further demonstrate that binding of [^{18}F]JNJ-64413739 was displaceable, we also performed a displacement study with JNJ-54175446. Rats injected 2 days prior with LPS (20 µg) were administered intravenously with JNJ-54175446 (2.25 mg/kg, n = 5) or vehicle (blank formulation, n = 5) 25 min after injection of the tracer [^{18}F]JNJ-64413739. As illustrated in Suppl. Fig 1a and 1b, uptake of [^{18}F]JNJ-64413739 was higher at the LPS-injected site throughout the imaging session in both groups of animals. As expected in a case of displaceable binding, the administration of JNJ-54175446 (2.25 mg/kg) reduced tracer retention relative to control animals treated with vehicle. An "SUV drop rate" was calculated as a

difference between SUV measured at the end of the scan (60 min after injection of the tracer [^{18}F]JNJ-64413739) and SUV measured at the time of the blocker administration (JNJ-54175446 or vehicle, 25 min after injection of the tracer), normalized to SUV values measured at the time of blocker administration. The SUV drop rate was significantly higher in the group treated with JNJ-54175446 than in the vehicle control group (injected side: 30% vs 10%, p = 0.002, t-test; control side: 26% vs 4%, p = 0.003).

Supplementary Discussion

Our team has recently characterized [^{18}F]JNJ-64413739 as a potent brain-penetrant PET ligand to image P2X7 receptors *in vivo* [S2]. To demonstrate the potential utility of this tracer to image neuroinflammation, we studied this tracer in a well-validated pre-clinical model of neuroinflammation. We have selected a model of intracerebral injection of LPS in rats [S3] because it is a reliable, replicable and dose-dependent way of inducing local neuroinflammation [S4]. This model also seems to induce changes thought to recapitulate some cellular and molecular deficits seen in Alzheimer Disease, aging and other neurodegenerative conditions [S5]. In contrast to other pre-clinical models of neuroinflammation (such as systemic LPS administration and experimental autoimmune encephalitis (EAE) rat models), intracerebral LPS injection induces a spatially localized neuroinflammatory response, which allows measuring difference between injected and contralateral site in the same animal. This is an important advantage of this model as no true reference region exists for P2X7 receptors. Importantly, this feature won't be critical for P2X7 imaging in humans as arterial blood sampling is available during PET scans to enable volume of distribution (V_t) quantification. We used a PBS injection as a control to account for possible vasculature or inflammatory effects from the surgery, which otherwise could have confounded interpretation of increased uptake and retention of the tracer at the LPS injected site.

Studies reported in the literature often utilize local LPS rat models for pre-clinical evaluation of PET tracers to image neuroinflammation [S6-S12]. However, the amount of injected LPS varies from 0.5 µg [S13] to 50 µg [S8, S9, S14] and post-LPS timepoints used to demonstrate increased tracer uptake range from 1 day [S13] to 30 days [S14]. Importantly, selecting an inadequate dose or timepoint may lead to negative results [S7, S11, S13]. Since P2X7 tracers have not been evaluated in this model of neuroinflammation, we first conducted a pilot imaging study with [^{18}F]JNJ-64413739 to select the optimal dose of LPS and post-LPS timepoints suitable for the subsequent imaging experiments. We have explored different doses (0-50 µg) and different timepoints (1-4 days) post-LPS administration. We found that at any given day post-LPS injection, the uptake of the [^{18}F]JNJ-64413739 at the LPS-injected site had increased in a dose-dependent manner. For each given dose of LPS, the magnitude of increased uptake at the LPS injected site relative to the control site varied in a time-dependent manner. Control rats injected with 0 µg of LPS did not show any significant difference in [^{18}F]JNJ-64413739 uptake between injected and control site at any time point. Based on the results of this pilot experiment (Table 1, Figure 1), 20 µg of LPS and day 2 post-LPS injection were selected for all subsequent PET imaging experiments with [^{18}F]JNJ-64413739.

Table 1. Selection of LPS dose and time post-LPS for subsequent evaluation of [^{18}F]JNJ-64413739.

Averaged (across animals) measurements of SUV, SUVR (reference area: cerebellum) or normalized

differences between the injected and control site Δ_{ic} = (SUV at Injected Site – SUV at Control Site)/ SUV

at Control Site*100% are shown ± s.e.m. SUV and SUVRs are averaged across all timepoints during the

entire scan time (0-60 min post-tracer injection).

*: p<0.05; **: p<0.01; t-test, one-tailed, two-sample

TABLE 1	0 µg of LPS (PBS)	5 µg of LPS	20 µg of LPS	50 µg of LPS
Day 1, Injected Site	0.629±.050 (SUV) 1.084±.013 (SUVR)	0.64±.030 (SUV) 1.149±.029 (SUVR)	0.893±.004 (SUV) 1.307±.013 (SUVR)	N/A
Day 1, Control Site	0.601±.050 (SUV) 1.036±.031 (SUVR)	0.537±.004 (SUV) 0.965±.038 (SUVR)	0.754±.006 (SUV) 1.104±.015 (SUVR)	N/A
Day 1, Δ_{ic}	**4.7%±0.4%** n = 2	**6.9%±2.8%** n = 2	**18.5%±0.4%*** n = 2	N/A
Day 2, Injected Site	0.743±.006 (SUV) 1.066±.024 (SUVR)	0.708±.022 (SUV) 1.166±.019 (SUVR)	0.924±.004 (SUV) 1.451±.012 (SUVR)	1.211±.012 (SUV) 1.325±.024 (SUVR)
Day 2, Control Site	0.724±.003 (SUV) 1.034±.028 (SUVR)	0.565±.018 (SUV) 0.932±.014 (SUVR)	0.703±.005 (SUV) 1.103±.013 (SUVR)	0.914±.003 (SUV) 1.000±.005 (SUVR)
Day 2, Δ_{ic}	**2.7%±0.5%** n = 2	**25.2%±0.1%*** n = 2	**31.6%±0.4%**** n = 2	**32.5%±1.8%*** n = 2
Day 3, Injected Site	0.729±.006 (SUV) 1.072±.046 (SUVR)	0.715±.023 (SUV) 1.102±.035 (SUVR)	0.863±.016 (SUV) 1.291±.038 (SUVR)	1.209±.012 (SUV) 1.298±.022 (SUVR)
Day 3, Control Site	0.720±.011 (SUV) 1.056±.039 (SUVR)	0.640±.027 (SUV) 0.975±.001 (SUVR)	0.735±.004 (SUV) 1.100±.019 (SUVR)	0.887±.009 (SUV) 0.952±.017 (SUVR)
Day 3, Δ_{ic}	**1.4%±0.6%** n = 2	**12.9%±3.4%** n = 2	**18.5%±0.4%** n = 2	**36.3%±0.1%*** n = 2
Day 4, Injected Site	0.665 (SUV) 1.08 (SUVR)	N/A	0.890±.003 (SUV) 1.245±.021 (SUVR)	N/A
Day 4, Control Site	0.658 (SUV) 1.067 (SUVR)	N/A	0.832±.024 (SUV) 1.166±.051 (SUVR)	N/A
Day 4, Δ_{ic}	**1.1%** n = 1	N/A	7.2%±2.8% n = 2	N/A
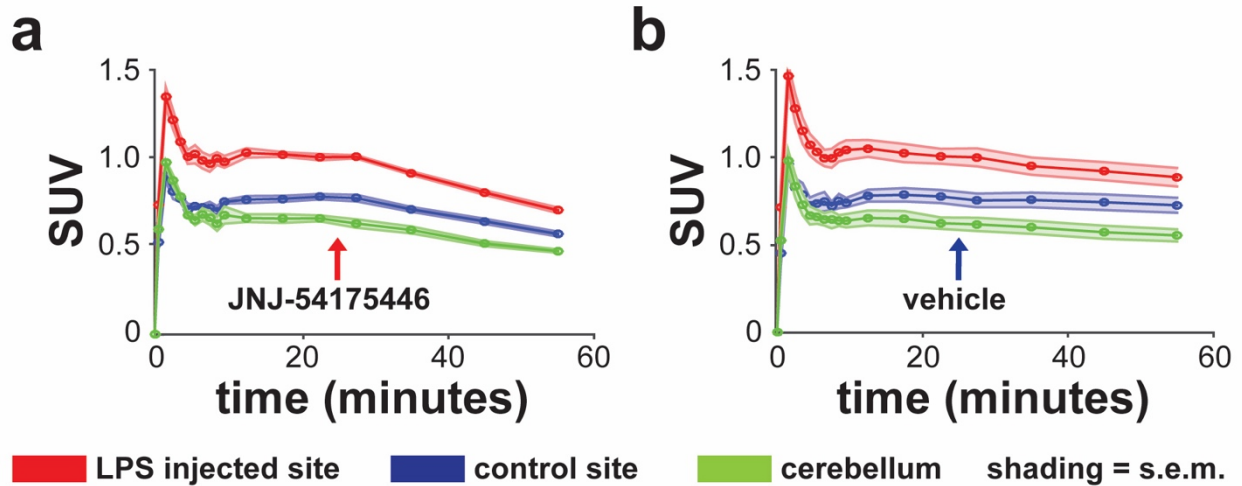
Suppl. Figure 1. TACs of SUV values of [^{18}F]JNJ-64413739 in in three VOIs (LPS injected site, red line; control site, blue line; and cerebellum as a reference area, green line; the shading around the lines indicates s.e.m.) in two groups of LPS-injected rats (n = 5 in each group) plotted over time. Time of intravenous injection of **a** JNJ-54175446 (2.25 mg/kg) or **b** vehicle (blank formulation, 0 mg/kg) is indicated by the red and blue arrow correspondingly.

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