16. Sapin E, Lapray D, Bérod A, Goutagny R, Léger L, Ravassard P, et al. Localization of the brainstem GABAergic neurons controlling paradoxical (REM) sleep. PLoS One 2009;4:e4272
17. Arrigoni E, Chen MC, Fuller PM. The anatomical, cellular and synaptic basis of motor atonia during rapid eye movement sleep: neural circuitry regulating REM atonia. J Physiol 2016;594:5391–5414.
18. Sampaio-Baptista C, Johansen-Berg H. White matter plasticity in the adult brain. Neuron 2017;96:1239–1251.
19. Unger MM, Belke M, Menzler K, Heverhagen JT, Keil B, Stiasny-Kolster K, et al. Diffusion tensor imaging in idiopathic REM sleep behavior disorder reveals microstructural changes in the brainstem, substantia nigra, olfactory region, and other brain regions. Sleep 2010;33:767–773.
20. Scherfler C, Frauscher B, Schocke M, Iranzo A, Gschliesser V, Seppi K, et al. White and gray matter abnormalities in idiopathic rapid eye movement sleep behavior disorder: a diffusion-tensor imaging and voxel-based morphometry study. Ann Neurol 2011;69:400–407.
21. García-Lorenzo D, Longo-Dos Santos C, Ewenczyk C, Leu-Semenescu S, Gallea C, Quattrocchi G, et al. The coeruleus/subcoeruleus complex in rapid eye movement sleep behaviour disorders in Parkinson's disease. Brain 2013;136:2120–2129.
22. Pyatigorskaya N, Yahia-Cherif L, Valabregue R, Gaurav R, Gargouri F, Ewenczyk C, et al. Parkinson disease propagation using MRI biomarkers and partial least squares path modeling. Neurology 2021;96:e460–e471.
23. De Marzi R, Seppi K, Högl B, Müller C, Scherfler C, Stefani A, et al. Loss of dorsolateral nigral hyperintensity on 3.0 tesla susceptibility-weighted imaging in idiopathic rapid eye movement sleep behavior disorder: loss of dorsolateral nigral hyperintensity in iRBD. Ann Neurol 2016;79:1026–1030.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Adenosine A_{2A} Receptor Occupancy by Caffeine After Coffee Intake in Parkinson's Disease

CME

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ABSTRACT: Background: Coffee intake can decrease the risk for Parkinson's disease (PD). Its beneficial effects are allegedly mediated by caffeine through adenosine A_{2A} receptor (A_{2A}R) antagonist action.
Objective: We aimed to calculate occupancy rates of striatal A_{2A}Rs by caffeine after coffee intake in PD.
Methods: Five patients with PD underwent ^{11}C-preladenant positron emission tomography scanning at baseline and after intake of coffee containing 129.5 mg (n = 3) or 259 mg (n = 2) of caffeine. Concurrently, serum caffeine levels were measured.
Results: The mean serum caffeine level (μg/mL) was 0.374 at baseline and increased to 4.48 and 8.92 by 129.5 and 259 mg of caffeine, respectively. The mean occupancy rates of striatal A_{2A}Rs by 129.5 and 259 mg of caffeine were 54.2% and 65.1%, respectively.
Conclusions: A sufficient A_{2A}R occupancy can be obtained by drinking a cup of coffee, which is equivalent to approximately 100 mg of caffeine. © 2022 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: adenosine A_{2A} receptor; coffee; caffeine; Parkinson's disease; ^{11}C-preladenant PET

Epidemiological studies have consistently demonstrated that coffee intake can decrease the risk for development of Parkinson's disease (PD).[1,2] Because decaffeinated coffee is not protective against PD,[1] caffeine in coffee is believed to be the essential pharmacological factor contributing to its beneficial effects in PD. Caffeine mainly works as a nonselective blocker of all four adenosine receptor subtypes: A_1 (K_D = 12 μM), A_{2A} (K_D = 2.4 μM), A_{2B} (K_D = 13 μM), and A_3 (K_D = 80 μM).[3] Of these subtypes, adenosine A_{2A} receptors (A_{2A}Rs) are believed to underlie most of the beneficial effects of caffeine in PD,[4] although its mechanism is unclear.

A_{2A}Rs are predominantly distributed in the putamen, caudate, nucleus accumbens, and external globus pallidus, and they interact with dopamine D_2 receptors in the indirect basal ganglia pathway.[5-7] Because of these features, A_{2A}Rs have been recognized as a therapeutic target to modulate motor symptoms in PD. Istradefylline, a selective A_{2A}R antagonist (K_i = 12.4 nM),[8] was then launched in

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Japan in 2013 as an adjunct to levodopa to alleviate *off* episodes in PD and was subsequently approved by the US Food and Drug Administration in 2019.[9,10] Currently, once-daily oral administration of istradefylline 20 or 40 mg is recommended. We found that occupancy rates of striatal A_{2A}Rs after single administration of istradefylline 20 and 40 mg were 39.5% and 52.1%, respectively,[11] and that the corresponding rates after long-term administration of istradefylline 20 and 40 mg increased to 72.1% and 86.5%, respectively.[12]

We hypothesized that if the beneficial effects of coffee in PD are mediated by caffeine through A_{2A}R antagonist action, a substantial amount of A_{2A}R should be occupied by caffeine after coffee intake, similar to that observed after administration of istradefylline.[11,12] This study aimed to test the hypothesis by calculating occupancy rates of striatal A_{2A}Rs after coffee intake in patients with PD using ^{11}C-preladenant positron emission tomography (PET) for measurement of A_{2A}R availability. Concurrently, the amount of caffeine in coffee was verified, and the serum caffeine levels were measured.

Materials and Methods

Research Participants

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Tokyo Metropolitan Institute of Gerontology (R19-19). Written informed consent was obtained from all five patients with PD (three men and two women) aged 61 to 76 years (Table 1). All patients were taking at least one antiparkinsonian drug other than istradefylline. Two patients regularly consumed at least one cup of coffee per day. Two other patients occasionally drank coffee. The remaining one patient rarely drank coffee. None of the patients had a history of smoking after middle age.

Study Protocol, Coffee Intake, and Serum Caffeine Level

Commercially available "canned coffee" (Suntory Premium Boss; Suntory Holdings Limited, Osaka, Japan) was used for caffeine loading by drinking coffee. One can of coffee (185 g) contained 129.5 mg of caffeine (70 mg/100 g). The five patients with PD were classified into either the low-caffeine-loading group or the high-caffeine-loading group according to their requests. The two patients in the high-caffeine-loading group consumed two cans of coffee containing 259 mg of caffeine. The other three patients in the low-caffeine-loading group consumed one can of coffee containing 129.5 mg of caffeine. To calculate A_{2A}R occupancy rates by caffeine after coffee intake, each patient underwent a total of two ^{11}C-preladenant PET scans in two conditions:

TABLE 1 *Characteristics of the patients with Parkinson's disease*

	Patient No.				
Characteristics	**1**	**2**	**3**	**4**	**5**
Dose of caffeine, mg	259	259	129.5	129.5	129.5
Age, y	74	61	71	69	61
Sex	Male	Male	Male	Female	Female
Weight, kg	60.1	47.5	61.5	52.3	48.2
Coffee consumption	1 cup/day	1 cup/day	Occasionally	Occasionally	Rarely
Duration, y	6	13	3	5	3
Hoehn & Yahr stage	3	3	3	3	2
Medication	L-Dopa pramipexole	L-Dopa pramipexole	L-Dopa	L-Dopa pramipexole	Ropinirole
Serum caffeine level, μg/mL					
Baseline	0.56	0.29	0.06	0.96	0.00
Caffeine loading	8.94	8.90	4.51	4.58	4.36
BP_{ND} in the striatum[a]					
Baseline	4.34	3.89	3.16	3.06	4.16
Caffeine loading	1.68	1.21	1.50	1.42	1.79
Occupancy, %	61.3	68.9	52.4	53.4	57.0

Patients 1–5 correspond to Fig. 1A–E, respectively.
L-Dopa, levodopa.
[a]Binding potential (BP_{ND}) was calculated using the volume-of-interest-based method.[11]

caffeine restricted (ie, baseline) and caffeine loading. The interval between the two PET scans was less than 3 months.

In both caffeine-restricted and caffeine-loading conditions, all patients were instructed to avoid consuming caffeine-containing products such as coffee, tea, energy drinks, or chocolate from the evening before undergoing PET. We also instructed them not to withhold any antiparkinsonian drugs before the PET scan. On the day of the examination, all patients visited the PET center after taking breakfast and their antiparkinsonian drugs. In the caffeine-restricted condition, the PET scan began at about 13:00 after blood samples were collected immediately before the injection of ^{11}C-preladenant. In the caffeine-loading condition, each patient drank one can or two cans of coffee at about 12:15. The PET scan was then started at about 13:00 immediately after the collection of blood samples.

The collected blood samples were transferred to the Tsukuba Research Institute (BoZo Research Center, Tokyo, Japan), and serum caffeine levels were measured using liquid chromatography mass spectrometry. The pharmacokinetics of caffeine have been established.[13] After oral administration of a single 250-mg dose of caffeine, the peak plasma caffeine level reaches approximately 10 μg/mL in an hour, and the plasma elimination half-lives ($t_{1/2}$) range from 3 to 7 hours. Therefore, the ^{11}C-preladenant PET scan in the caffeine-loading condition was performed approximately 45 minutes after coffee intake; as such, serum caffeine level reached a peak during PET scanning.

PET and Data Analysis

^{11}C-preladenant PET scanning and image processing were conducted basically as described previously.[11,12] In brief, after a bolus injection of approximately 500 MBq of ^{11}C-preladenant, emission data were acquired for 60 minutes. Binding potential (BP_{ND}) in the whole striatum was calculated to measure $A_{2A}R$ availability using the Simplified Reference Tissue Model,[14] after the cerebellum was set as a reference region. In addition, BP_{ND} maps were generated using the Simplified Reference Tissue Model 2.[15]

The $A_{2A}R$ occupancy was calculated using the following equation: Occupancy (%) = $100 \times [(BP_{ND}$ in caffeine restricted) − (BP_{ND} in caffeine loading)]/(BP_{ND} in caffeine restricted). The relationships between $A_{2A}R$ occupancy and serum caffeine levels (μg/mL) or dose of caffeine (mg) were modeled using the following equation: occupancy (%) = $\alpha \times [D/(D + ED_{50})]$, where α refers to the maximal receptor occupancy, D refers to serum caffeine levels or dose of caffeine, and ED_{50} refers to the level resulting in 50% of maximal receptor occupancy.[16-18] The two parameters, α and ED_{50}, were estimated with a nonlinear regression analysis, using SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA).

Results

The serum caffeine levels and striatal BP_{ND} values are shown in Table 1. The mean serum caffeine level (μg/mL) was 0.374 in the caffeine-restricted condition (n = 5) and increased to 4.48 and 8.92 in the low-caffeine-loading (129.5 mg: n = 3) and high-caffeine-loading (259 mg: n = 2) conditions, respectively. The mean $A_{2A}R$ occupancy rates in the low-caffeine and high-caffeine groups were 54.2% and 65.1%, respectively. The changes in the striatal BP_{ND} values after coffee intake are displayed in BP_{ND} maps (Fig. 1A–E).

The relationships between $A_{2A}R$ occupancy and serum caffeine levels or doses of caffeine are depicted (Fig. 1F,G). The two estimated parameters, maximal receptor occupancy and ED_{50}, in the relationship between $A_{2A}R$ occupancy and serum caffeine levels were 81.1% (standard error [SE], 10.0%) and 2.2 μg/mL (SE, 1.0 μg/mL), respectively. The corresponding values in the relationship between $A_{2A}R$ occupancy and dose of caffeine were 81.3% (SE, 9.4%) and 64.7 mg (SE, 27.2 mg), respectively.

Discussion

This study found that the mean occupancy rates of striatal $A_{2A}Rs$ by 129.5 and 259 mg of caffeine were 54.2% and 65.1%, respectively. Meanwhile, the corresponding rates after single administration of istradefylline 20 and 40 mg are 39.5% and 52.1%, respectively,[11] and those after long-term administration of istradefylline 20 and 40 mg are 72.1% and 86.5%, respectively.[12] These findings suggest that striatal $A_{2A}R$ occupancy by caffeine after coffee intake is comparable with that by the administration of the approved dose of istradefylline (20–40 mg) and strongly support the hypothesis that a substantial amount of $A_{2A}R$ is occupied by caffeine after coffee intake.

Zhou et al.[19] assessed the suitability of ^{11}C-preladenant PET for the quantification of striatal $A_{2A}Rs$ and calculated occupancy rates of striatal $A_{2A}R$ by caffeine in conscious monkeys. They demonstrated that occupancy rates after intravenous injections of caffeine at doses of 2.5, 5.0, and 10.0 mg/kg were 64%, 74%, and 81%, respectively. Meanwhile, the average body weight of five patients in our study was 54 kg. Applying this mean value to 129.5 and 259 mg of caffeine, our results restated that occupancy rates of striatal $A_{2A}Rs$ after administration of 2.4 and 4.8 mg/kg caffeine were 54.2% and 65.1%, respectively. Given the methodological differences, our results from human

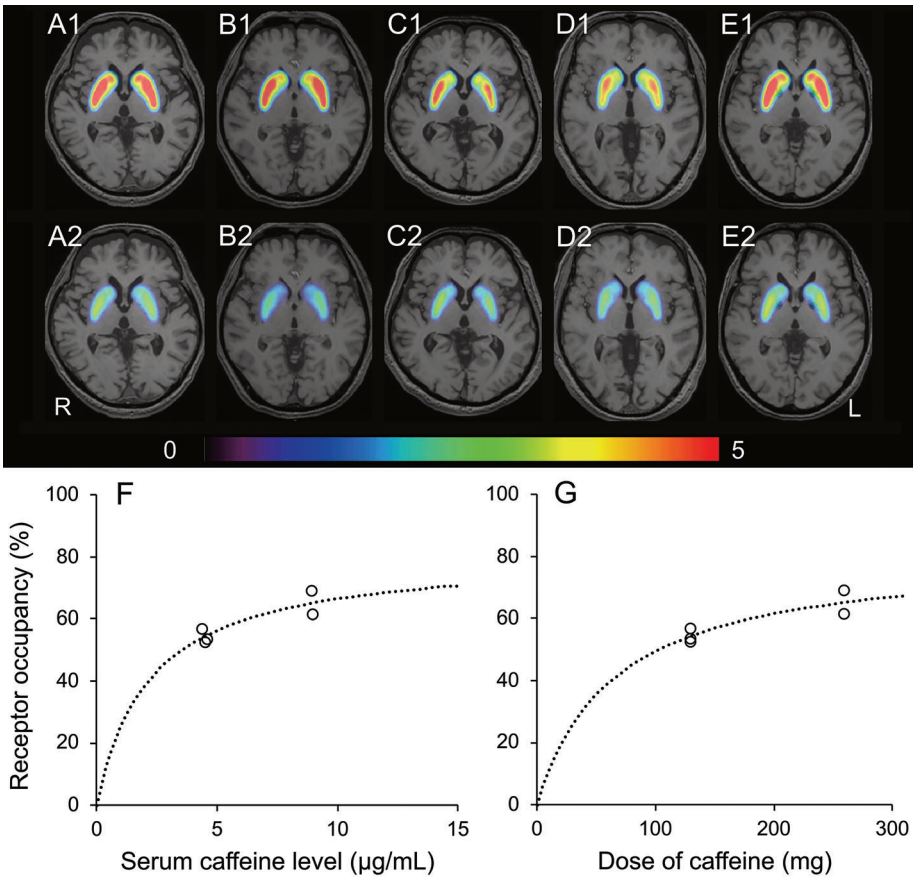

FIG. 1. Changes in binding potential (BP_{ND}) maps after caffeine intake in five patients with Parkinson's disease (**A–E**) and the relationships between adenosine A_{2A} receptor occupancy and serum caffeine levels (**F**) or caffeine dose (**G**). BP_{ND} maps of adenosine A_{2A} availability in patients 1 (A), 2 (B), 3 (C), 4 (D), and 5 (E) are displayed on structural magnetic resonance imaging as follows: at baseline (A1, B1, C1, D1, and E1) and after intake of coffee containing 259 mg (A2 and B2) or 129.5 mg (C2, D2, and E1) of caffeine. The rainbow-colored scale represents the magnitude of BP_{ND} values. Patients 1–5 correspond to the numbers of the five patients in Table 1. The dashed curve was modeled using the following equation: occupancy (%) $= \alpha \times [D/(D + ED_{50})]$, where α refers to the maximal receptor occupancy, D refers to serum caffeine levels (**F**) or caffeine dose (**G**), and ED_{50} refers to the level resulting in 50% of maximal receptor occupancy. L, left; R, right. [Color figure can be viewed at wileyonlinelibrary.com]

patients seem to agree well with those carried out by Zhou et al.[19] involving animals.

The ED_{50} values were estimated to be 2.2 μg/mL for serum caffeine levels and 64.7 mg for doses of caffeine. A cup of coffee generally contains approximately 100 mg of caffeine. Therefore, after drinking a cup of coffee (ie, intake of 100 mg of caffeine), serum caffeine level can exceed its ED_{50} value (ie, 2.2 μg/mL). According to the National Coffee Association, USA, the average American coffee drinker drinks about three cups per day, which is equivalent to approximately 300 mg of caffeine per day. Considering the ED_{50} (64.7 mg) and $t_{1/2}$ (3–7 hours) of caffeine, it is quite possible that at least approximately 50% of striatal A_{2A}Rs is constantly blocked by caffeine in coffee drinkers. This estimated occupancy rate is novel and is an important finding to help understand the impact of caffeine on health and disease in coffee drinkers.[4,20]

Recently, a randomized controlled trial reported that compared with administration of placebo, consumption of caffeine-containing capsules 200 mg twice daily did not improve motor manifestations in PD.[21] This result appears to conflict with epidemiological links between coffee intake and lower PD risk.[1,2] One possible reason for this contradiction is that in the placebo group, daily intake of 92.17 ± 50.30 mg of caffeine was allowed during the trial.[21] Considering the ED_{50} (64.7 mg) and $t_{1/2}$ (3–7 hours) of caffeine, 92.17 mg of caffeine can occupy a substantial amount of A_{2A}Rs, and it is possible that daily caffeine intake in the placebo group[21] might already exert some symptomatic effects in PD. Therefore, further studies are required to investigate the symptomatic effects of caffeine in patients with PD who have no or less caffeine consumption. In addition, this study recommends measuring blood caffeine concentration or at least avoiding the consumption of caffeine-containing products when investigating human A_{2A}Rs.

In conclusion, this study shows that caffeine binds to striatal A_{2A}Rs in a dose-dependent manner. A sufficient A_{2A}Rs occupancy can be obtained by drinking one cup of coffee, which is equivalent to approximately 100 mg of caffeine.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Palacios N, Gao X, McCullough ML, et al. Caffeine and risk of Parkinson's disease in a large cohort of men and women. Mov Disord 2012;27(10):1276–1282.
2. Hernan MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann Neurol 2002;52(3):276–284.
3. Froestl W, Muhs A, Pfeifer A. Cognitive enhancers (nootropics). Part 1: drugs interacting with receptors. Update 2014. J Alzheimer's Dis 2014;41(4):961–1019.
4. Rivera-Oliver M, Diaz-Rios M. Using caffeine and other adenosine receptor antagonists and agonists as therapeutic tools against neurodegenerative diseases: a review. Life Sci 2014;101(1–2):1–9.
5. Svenningsson P, Hall H, Sedvall G, Fredholm BB. Distribution of adenosine receptors in the postmortem human brain: an extended autoradiographic study. Synapse 1997;27(4):322–335.
6. Mori A. International review of neurobiology. Adenosine receptors in neurology and psychiatry.Preface. Int Rev Neurobiol 2014;119: xv–xvi.
7. Pinna A, Serra M, Morelli M, Simola N. Role of adenosine A2A receptors in motor control: relevance to Parkinson's disease and dyskinesia. J Neural Transm 2018;
8. Kase H, Aoyama S, Ichimura M, et al. Progress in pursuit of therapeutic A2A antagonists: the adenosine A2A receptor selective antagonist KW6002: research and development toward a novel nondopaminergic therapy for Parkinson's disease. Neurology 2003; 61(11 Suppl 6):S97–S100.
9. Mizuno Y, Kondo T. Japanese Istradefylline study G. adenosine A2A receptor antagonist istradefylline reduces daily OFF time in Parkinson's disease. Mov Disord 2013;28(8):1138–1141.
10. Chen JF, Cunha RA. The belated US FDA approval of the adenosine A2A receptor antagonist istradefylline for treatment of Parkinson's disease. Purinergic Signal 2020;16(2):167–174.
11. Ishibashi K, Miura Y, Wagatsuma K, Toyohara J, Ishiwata K, Ishii K. Occupancy of adenosine A2A receptors by istradefylline in patients with Parkinson's disease using (11)C-preladenant PET. Neuropharmacology 2018;143:106–112.
12. Ishibashi K, Miura Y, Wagatsuma K, Toyohara J, Ishiwata K, Ishii K. Adenosine A2A receptor occupancy by long-term Istradefylline Administration in Parkinson's disease. Mov Disord 2021;36(1):268–269.
13. Nehlig A. Interindividual differences in caffeine metabolism and factors driving caffeine consumption. Pharmacol Rev 2018;70(2): 384–411.
14. Lammertsma AA, Hume SP. Simplified reference tissue model for PET receptor studies. Neuroimage 1996;4(3 Pt 1):153–158.
15. Wu Y, Carson RE. Noise reduction in the simplified reference tissue model for neuroreceptor functional imaging. J Cereb Blood Flow Metab 2002;22(12):1440–1452.
16. Kapur S, Zipursky RB, Jones C, et al. The D2 receptor occupancy profile of loxapine determined using PET. Neuropsychopharmacology 1996;15(6):562–566.
17. Remington G, Mamo D, Labelle A, et al. A PET study evaluating dopamine D2 receptor occupancy for long-acting injectable risperidone. Am J Psychiatry 2006;163(3):396–401.
18. Ishikawa M, Ishiwata K, Ishii K, et al. High occupancy of sigma-1 receptors in the human brain after single oral administration of fluvoxamine: a positron emission tomography study using [11C] SA4503. Biol Psychiatry 2007;62(8):878–883.
19. Zhou X, Boellaard R, Ishiwata K, et al. In vivo evaluation of (11)C-Preladenant for PET imaging of adenosine A2A receptors in the conscious monkey. J Nucl Med 2017;58(5):762–767.
20. Nieber K. The impact of coffee on health. Planta Med 2017;83(16): 1256–1263.
21. Postuma RB, Anang J, Pelletier A, et al. Caffeine as symptomatic treatment for Parkinson disease (cafe-PD): a randomized trial. Neurology 2017;89(17):1795–1803.

Dairy Intake and Parkinson's Disease: A Mendelian Randomization Study

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