Semba J., Wakuta M., Suhara T.	Long-term suppression of methamphetamine-induced c-Fos expression in rat striatum by the injection of c-fos antisense oligodeoxynucleotides absorbed in water-absorbent polymer	Psychiatry Clin Neurosci	58	531-535	2004
Takano A., Suhara T.	The necessary parameters for estimating the time-course of receptor occupancy	Int J Neuropsychopharmacol	8	143-144	2004
Matsuda T., Matsuura M., Ohkubo T., Ohkubo H., Matsushima E., Inoue K., Taira M., Kojima T.	Functional MRI mapping of brain activation during visually guided saccades and antisaccades	Psychiatry Research: Neuroimaging	131	147-155	2004
Ohtsuki T., Tanaka S., Ishiguro H., Noguchi E., Arinami T., Tanabe E., Yara K., Ohkubo T., Takahashi S., Matsuura M., Sakai T., Muto M., Kojima T., Matsushima E., Toru M., Inada T.	Failure to find association between PRODH deletion and schizophrenia	Schizophrenia Research	67	111-113	2004
Moriyama Y., Muramatsu T., Kato M., Kashima H., Mimura M.	Repeated clinical episodes of Wernicke-Korsakoff syndrome	Australian and New Zealand Journal of Psychiatry	38	653	2004
Kato A., Kato M., Ishii H., Ichimiya Y., Suzuki K., Kawasaki H., Yamamoto S., Kumashiro R., Yamamoto K., Kawamura N., Hayashi N., Matsuzaki S., Terano A., Okita K., Watanabe A.	Development of quantitative neuropsychological tests for diagnosis of subclinical hepatic encephalopathy in liver cirrhosis patients and establishment of diagnostic criteria—multicenter collaborative study in Japanese	Hepatology Research	30	71-78	2004
Yahata N., Takahashi H., Okubo Y.	Pharmacological modulations on the Human cognitive processes: an fMRI study	J Nippon Med Sch	72 (1)	2-3	2005
Zhang M.-R., Maeda J., Ito T., Ogawa M., Noguchi J., Suhara T., Halldin C., Suzuki K.	Synthesis and evaluation of N-(5-fluoro-2-phenoxyphenyl)-N-(2-[^{18}F]fluoromethoxy-d(2)-5-methoxybenzyl)acetamide: a deuterium-substituted radioligand for peripheral benzodiazepine receptor	Bioorg Med Chem	13	1811-1818	2005
成重竜一郎、舘野周、大久保善朗	非定型抗精神病薬投与中clonazepam減量に伴いParkinson症候群を呈した1症例	精神医学	46 (10)	1113-1115	2004
関根瑞保、鈴木博子、竹沢健司、舘野周、朝山健太郎、大久保善朗	救命救急センターに搬送された自殺未遂症例の検討	総合病院精神医学	16 (3)	257-263	2004

伊藤敬雄、葉田道雄、 木村美保、黒川顕、 黒澤尚、大久保善朗	高次救命救急センターに入院した 自殺未遂患者とその追跡調査 －精神科救急対応の現状を踏まえた 1考察－	精神医学	46 (4)	389-396	2004
伊藤敬雄，大久保善朗	アルツハイマー型痴呆患者における メラトニン療法	Geriatric Medicine	42 (9)	1201- 1206	2004
小泉淳、須原哲也、 西條朋行、高野晶寛、 安野史彦、生駒洋子、 大久保善朗	PETによる気分障害患者の病態と 治療法の作用機序に関する研究	INNERVISION	7	18	2004
大久保善朗、伊藤逸生、 織田健司	精神疾患の脳形態画像	精神神経学雑誌	106 (7)	900-905	2004
須原哲也	画像から見た薬物治療の評価	精神神経学雑誌	106 (7)	916-920	2004
松浦雅人、松田哲也、 大久保起延、大久保博美、 根本安人、松田玲子、 鹿中紀子、小島卓也、 福本真衣、松島英介、 泰羅雅登	統合失調症の眼球運動異常の 機能的MRI	精神経誌	106 (7)	906-909	2004
根本安人、松田哲也、 松浦雅人、本下真衣、 大久保起延、大久保博美、 鈴木正泰、鹿中紀子、 松島英介、小島卓也	探索眼球運動の神経機構	日大医誌	63 (7)	352-359	2004
松浦雅人	道路交通法改正後のてんかんを もつ人における運転免許，精神科医 からみた問題点と課題	てんかん研究	22 (1)	64-65	2004
松浦雅人	てんかんと抑うつ症状	ともしび	3	4-13	2004
松浦雅人	てんかんのメンタルヘルス，診断を めぐって	波	9	279-280	2004
小島卓也、大久保起延、 大久保博美、鹿中紀子、 根本安人、鈴木正泰、 松田哲也、本下真衣、 松島英介、松浦雅人	統合失調症の基本障害と眼球 運動異常	脳精神医学	15 (4)	421-426	2004
加藤元一郎	失行の発現機序と責任病巣	臨床神経学	44	839-841	2004
春原則子、宇野彰、 金子真人、加藤元一郎、 吉野文浩	英語学習の困難さを主訴とした中学 生・高校生の認知機能	神経心理学	20	264-271	2004
加藤元一郎、青柳裕、 阿内謙吉、小野寺晋志	アルツハイマー病に類似した症状を 呈する疾患の脳機能画像統計解析	臨床放射線	49	1203- 1210	2004
加藤元一郎、梅田聡、 秋根良英	虚記憶に関する神経心理学的障害と 機能的脳画像所見	精神神経学雑誌	106 (7)	910-915	2004
鈴木博子、成重竜一郎、 大久保善朗	Milnacipranが有効であったrapid cyclerの2症例	精神科治療学	20 (2)	203-210	2005
大久保善朗、浅井邦彦	精神科病床と脱施設化への道	最新精神医学	10 (2)	143-150	2005

大久保善朗、須原哲也	脳イメージングによる抗精神病薬の薬効評価	Human Science	16 (2)	22-25	2005
大久保善朗、須原哲也	画像診断からみた薬物療法の評価	カレントテラピー	23 (1)	69-72	2005

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書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
Kurihara T. & Kato M.	Emotional environment of patients with schizophrenia:A cross-cultural Study between Baland Tokyo	Clark AV.	Mood State and Health	Nova Science Publishers, Inc.	New York	2005	121-155
ドロンベコフ・タラント、ケネショウィッチ、安野史彦、須原哲也	統合失調症、うつ病の神経伝達物質受容体イメージング	福田寛	脳の形態と機能-画像医学の進歩	振興医学出版社	東京	2005	89-104
荒川亮介、伊藤浩、高野晶寛、森本卓也、高橋英彦、須原哲也	テーラーメード治療に向けての脳機能画像と遺伝多型での評価		精神科 7(5)	科学評論社	東京	2005	413-417
松浦雅人	神経系の基礎	森本武利、彼末一之	やさしい生理学	南江堂	東京	2005	155-170
松浦雅人	統合失調症	松本紘一	研修医必携・薬物療法と禁忌	東京医学社	東京	2005	638-641
加藤元一郎	カテゴリー特異的意味障害	笹沼澄子	言語コミュニケーション障害の新しい視点と介入理論	医学書院	東京	2005	33-56
加藤元一郎	前頭葉と高次脳機能	山浦晶	脳神経外科学体系　1 神経科学	中山書店	東京	2006	281-299
穴水幸子、加藤元一郎、斎藤文恵、鹿島晴雄	右前頭葉背外側損傷に対する遂行機能リハビリテーション	認知リハビリテーション研究会	認知リハビリテーション 2005	新興医学出版社	東京	2005	51-58
南雲祐美、加藤元一郎、梅田聡、鹿島晴雄	左右の前頭葉損傷例におけるミニデー課題の学習経過について	認知リハビリテーション研究会	認知リハビリテーション 2005	新興医学出版社	東京	2005	65-69

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Koeda M., Takahashi H., Yahata N., Asai K., Okubo Y., Tanaka H.	An fMRI study: cerebral laterality for lexical-semantic processing and human voice perception	Am J Neuroradiolgy		in press	
Koeda M., Takahash H., Yahata N., Matsuura M., Asai K., Okubo Y., Tanaka H.	Language Processing and Human Voice Perception in Schizophrenia: An fMRI study	Biol Psychiatry		in press	
Oda K., Matsushima E., Okubo Y., Ohta K., Murata Y., Koike R., Miyasaka N., Kato M.	Abnormal regional cerebral blood flow in systemic lupus erythematosus patients with psychiatric symptoms	J Clin Psychiatry	66	907-13	2005
Yahata N., Takahashi H., Okubo Y.	Pharmacological modulations in human cognitive processes: an fMRI study	J Nippon Med Sch	30	197-207	2005
Takahashi H., Yahata N., Koeda M., Takano A., Asai K., Suhara T., Okubo Y.	Effects of dopaminergic and serotonergic manipulation on emotional processing: a pharmacological fMRI study.	Neuroimage	27	991-1001	2005
Takano A., Suhara T., Yasuno F., Suzuki K., Takahashi H., Morimoto T., Lee Y-J., Kusuhara H., Sugiyama Y., Okubo Y.	The antipsychotic sultopride is overdosed: a PET study of drug-induced receptor occupancy in comparison with sulpiride.	Int J Neuropsychopharmacol	9	1-7	2005
Inaji M., Okauchi T., Ando K.,Maeda J., Haneda E., Nagai Y., Yoshizaki T., Okano H., Nariai T.,Ohno K., ObayashiS., Suhara T.	Correlation between quantitative imaging and behavior in unilaterally 6-OHDA-lesioned rats.	Brain Res	1064	136-145	2005
Ji B.,Maeda J., Higuchi M., Inoue K., Akita H., Harashima H., Suhara T.	Pharmacokinetics and brain uptake of lactoferrin in rats	Life Sci.	78	851-855	2005

Lee Y-J.,Maeda J.,Kusuhara H., Okauchi T., Inaji M.,Nagai Y., Obayashi S., Nakao R.,Suzuki K., Sugiyama Y., Suhara T.	In vivo evaluation of P-glycoprotein function at the blood-brain barrier in nonhuman primates using [^{11}C]verapamil.	J Pharmacol Exp Ther	316	647-653	2005
Fujimura Y., Ikoma Y., Yasuno F., Suhara T., Ota M., Matsumoto R., Nozaki S., Takano A., Kosaka J., Zhang M.-R., Nakao R., Suzuki K., Kato N., Ito H.	Quantitative analyses of [^{18}F]FEDAA1106 binding to peripheral benzodiazepine receptors in living human brain.	J Nucl Med	47	43-50	2006
Obayashi S., Matsumoto R., Suhara T., Nagai Y., Iriki A., Maeda J.	Functional organization of monkey brain for abstract operation	Cortex		in press	
Takano A., Suhara T., Ichimiya T., Yasuno F.	Time course of in vivo 5-HT transporter occupancy by fluvoxamine.	J Clin Psychopharmcol		in press	
Takano A., Suzuki K., Kosaka J., Ota M., Nozaki S., Ikoma Y., Tanada S., Suhara T.	A dose-finding study of duloxetine based on serotonin transporter occupancy	Psychopharmacology		in press	
Tanaka Y., Obata T., Sassa T., Yoshitome E., Asai Y., Ikehira H., Suhara T., Okubo Y., Nishikawa T.	Quantitative magnetic resonance spectroscopy of schizophrenia: relationship between decreased N-acetylaspartate and frontal lobe dysfunction	Psychiatry Clin Neurosci	60(3)	in press	
Ota M., Yasuno F., Ito H., Seki C., Nozaki S., Asada T., Suhara T.	Age-related decline of dopamine synthesis in the living human brain measured by positron emission tomography with L-[β-^{11}C]DOPA	Life Sci.		in press	
Kuroda Y., Motohashi N., Ito H., Ito S., Takano A., Nishikawa T., Suhara T.	Effects of repetitive transcranial magnetic stimulation on [11C]raclopride binding and cognitive function in patients with depression	J Affect Dis.		in press	

Matsumoto R., Kitabayashi Y., Narumoto J., Wada Y., Okamoto A., Ushijima Y., Yokoyama C., Takahashi H., Yasuno F., Suhara T., Fukui K.	Regional cerebral blood flow change in process of recovery from anorexia nervosa.	Prog NeuroPsychopharmacol Biol Psychiatry		in press	
Takahashi H., Higuchi M., Suhara T.	The role of extrastriatal dopamine D2 receptor in schizophrenia	Biological Psychiatry		in press	
Rusjan P., Hussey D., Mamo D., Ginovart N., Yasuno F., Suhara T., Houle S., Kapur S.	An Automated Method for the Extraction of Regional Data from PET Images.	Psychiatry Research neuroimaging		in press	
Higuchi M., Saido T.C., Suhara T.	Animal models of tauopathies	Neuropathology		in press	
Matsuura M., Adachi N., Muramatsu R., Kato M., Onuma T., Okubo Y., Oana Y., Hara T.	Intellectual disability and psychotic disorders of adult epilepsy.	Epilepsia	46	11-14	2005
Koyama S., Sasaki Y., Tootell RBH., Andersen GJ., Matsuura M., Watanabe T.	Separate processing of different global motion structures in visual cortex revealed by fMRI.	Curr Biol	15	2027-2032	2005
Kamei S., Oga K., Matsuura M., Tanaka N., Kojima T., Arakawa Y., Matsukawa Y., Mizutani T., Sakai T., Ohkubo H., Matsumura H., Moriyama M., Hirayanagi K.	Correlation between quantitative-EEG alterations and age in patients with interferon-alpha-treated hepatitis C.	J Clin Neurophysiol	22	49-52	2005
Higuchi M., Suhara T.	Aggregating interests in aggregates: mechanistic, diagnostic and therapeutic implications of brain amyloidosis in neurodegenerative disorders among the elderly	Psychogeriatrics	5(4)	117-121	2005

Mimura M., Watanabe R., Kato M., Kashima. H.	Selective memory impairment for personally familiar colors following encephalitis	Psychiatry and Clinical Neuroscience	59	215-218	2005
Fujinaga N., Muramastu T., Ogano M., Kato M.	A 3-year follow-up study of 'orientation agnosia'	Neuropsychologia	43	1222-1226	2005
Umeda S., Akine Y., Kato M., Muramatsu T., Mimura M., Kandatsu S., Tanada S., Obata T., Ikehira H., Suhara T.	Functional network in the prefrontal cortex during episodic memory retrieval	NeuroImage	26	932-940	2005
Kurihara T., Kato M., Reverger R., Tirta GR., Kashima H.	Eleven-year clinical outcome of schizophrenia in Bali	Schizophrenia Research	79	307-313	2005
Kurihara T., Kato M., Reverger R., Tirta GR., Kashima H.	Never-treated patients with schizophrenia in the developing country of Bali	Acta Psychiatrica Scandinavica	112	456-462	2005
Emori A., Matsushima E., Aihara O., Ohta K.,Koike R., Miyasaka N., Kato M.	Cognitive dysfunction in systemic lupus erythematosus	Psychiatry and Clinical Neurosciences	59	584-589	2005
Mimura M., Komatsu S., Kato M., Yoshimasu H., Moriyama Y., Kashima H.	Further evidence for a memory advantage of self-performed tasks in person with alcoholic Korsakoff's syndrome	Journal of the International Neuropsychological Society	11	545-553	2005
Sugita K., Kato Y.,Sugita K.,KatoM., Tanaka Y.	Magnetoencephalographic analysis in children with Panayiotopoulos syndrome	Journal of Child Neurology	20	616-618	2005
Akiyama T., Kato M., Muramatsu T., Saito F., Nakachi, R., Kashima H.	A deficit in discriminating gaze direction in a case with right superior temporal gyrus lesion	Neuropsychologia	44	161-170	2006
Moriyama Y., Muramatsu T., Kato M., Mimura M., Kashima H.	Familiy history of alcoholism and cognitive recovery in subacute withdrawal state	Psychiatry and Clinical Neuroscience	60	85-89	2006

Kato Y., Muramatsu T., Kato M., Shibukawa Y., Shintani M., Yoshino F.	Cortical reorganization and somatic delusional psychosis: An MEG study	Psychiatry Research : Neuroimaging	146	91-95	2006
Kurihara T., Kato M., Takebayashi T., Reverger R., Tirta GR., Kashima H.	Excess mortality of schizophrenia in a developing country	Schizophrenia Research	83	103-105	2006
Umeda S., Nagumo Y., Kato M.	Dissociative contributions of the medial temporal region and frontal cortex to prospective remembering	Reviews in the Neurosciences		in press	
Kurihara T., Kato M., Reverger R., Tirta GR.	Pathway to psychiatric care in Bali	Psychiatry and Clinical Neuroscience		in press	
Moriyama Y., Mimura M., Kato M., Kashima H.	Primary alcoholic dementia and alcohol-related dementia	Psychogeriatrics		in press	
Kurihara T., Kato M., Reverger R., Tirta GR.	Causal belief of schizophrenia described by family members: A community-based survey in Bali	Psychiatric Services		in press	
Akiyama T., Kato M., Muramatsu T., Saito F., Umeda S., Kashima H.	Gaze but not arrows – a dissociative impairment after right superior temporal gyrus damage	Neuropsychologia		in press	
大久保善朗、須原哲也	画像診断からみた薬物療法の評価	カレントテラピー	23	69-72	2005
大久保善朗、浅井邦彦	精神科病床と脱施設化への道	最新精神医学	10	143-150	2005
大久保善朗	画像検査と精神科診断	精神医学	47	1162-1163	2005
大久保善朗	新しい抗てんかん薬の開発動向	臨床精神医学	34	1551-1555	2005
舘野周、大久保善朗、須原哲也	双極性障害の最近の脳画	HUMAN SCIENCE	16	1263-1271	2005
太田深秀、須原哲也	精神疾患の病態解明-神経伝達物質の画像化	薬の知識	56	26-28	2005
大久保善朗、須原哲也	脳イメージングによる抗精神病薬の薬効評価	HUMAN SCIENCE	16	22-25	2005
福田寛、工藤幸司、篠遠仁、須原哲也	脳機能の分子イメージング	臨床放射線	50	375-382	2005
黒田裕子、須原哲也	PET による精神疾患の研究	最新医学	60	994-999	2005

松本良平、 須原哲也	PET による生体内発現タンパクの評価	日本神経精神薬理学雑誌	25	137-141	2005
高橋英彦、 須原哲也	ゲノム研究に役立つ高次脳機能テストバッテリー	分子精神医学	5	48-52	2005
須原哲也、 森本卓哉	向精神薬の臨床試験における PET の有用性	精神神経学雑誌	107	704-711	2005
徳永正希、 須原哲也	ポジトロン CT(PET) アルツハイマー病やパーキンソン病に関する分子レベルの情報を得る	化学と教育	53 (12)	690-693	2005
高橋英彦、 須原哲也	分子イメージングでみた精神疾患の病態と治療 特集 第 40 回脳のシンポジウム	脳の分子イメージング神経研究の進歩	49 (6)	949-957	2005
高橋英彦、 須原哲也	分子イメージングでみた精神疾患の病態と治療	神経進歩	4(6)	949-957	2005
永井裕司、 大林茂、 須原哲也、 安東潔	ポジトロン CT を用いたパーキンソン病モデルサルにおけるドーパミントランスポーター機能評価	INNERVISION	20 (別冊付録)	14-15	2005
前田純、 樋口真人、 須原哲也	末梢型ベンゾジアゼピン受容体 PET リガンドを用いたグリア細胞のイメージング	日本神経精神薬理学雑誌	26 (1)	17-21	2006
丸山将浩、樋口真人、岩田修永、須原哲也、西道隆臣	アルツハイマー病の画像診断	BIO Clinica	21 (4)	361-365	2006
小島卓也、高橋栄、大久保起延、大久保博美、鈴木正泰、安芸竜彦、松島英介、松浦雅人、松田哲也	統合失調症の新しい診断装置の開発	総合臨床	54	3034-3037	2005
森山泰、加藤元一郎、三村將、村松太郎、鹿島晴雄	潜在性肝性脳症における遂行機能 障害の検討	日本アルコール 精神医学雑誌	12	3-7	2005
福永篤志、大平貴之、加藤元一郎, 鹿島晴雄、河瀬斌	後出しじゃんけん時の補足運動野の役割	高次脳機能研究	25	242-250	2005
高野晴成、稲垣中、渡邊衡一郎、 加藤元一郎、 鹿島晴雄	うつ病における通電療法の脳機能に与える影響	精神薬療研究年報	37	238-243	2005
吉村元、 内山健志、 加藤元一郎	MEG による発音運動想起における大脳皮質活動の解析	音声言語医学	46	179-184	2005
秋山知子、 加藤元一郎、 鹿島晴雄	扁桃体の機能画像研究 特に顔、表情、視線の認知について	精神科治療学	20	263-269	2005
加藤元一郎	ADHD の脳科学 ①ADHD の脳 MRI 研究について	LD&ADHD14	4月号	44-45	2005

加藤元一郎	ADHDの脳科学 ②ADHD の脳機能画像について	LD&ADHD14	7月号	44-45	2005
前田貴記、 加藤元一郎	広汎性発達障害（自閉性障害、アスペルガー障害）の診断	治療　増刊号	87	1324-1328	2005
田渕肇、 加藤元一郎	うつ状態の鑑別	治療　増刊号	87	1339-1341	2005
加藤元一郎	遂行機能	臨床精神医学 増刊号 「精神科臨床評価検査マニュアル」		450-457	2005
加藤元一郎	前頭前野と注意、時間認知	Clinical Neuroscience	23	632-635	2005
加藤元一郎	高次脳機能障害	愛知作業療法	13	40-50	2005
加藤元一郎	Q&A 2つの異なる行為を同時に行う時の脳のメカニズム	Clinical Neuroscience	23	837	2005
加藤元一郎	アルコール依存症の概念と症候論	治療	87	2409-2415	2005
加藤元一郎、 梅田聡	前頭前野と記憶活動 －特に false memory について	神経研究の進歩	49	619-625	2005
加藤元一郎	器質性精神障害の診断に役立つ神経心理学	精神科	7	8-13	2005
加藤　隆、 加藤元一郎、 鹿島晴雄	衝動制御の神経心理学 －前頭葉眼窩部損傷例における行動異常の側面から	臨床精神医学	34	195-201	2005
加藤元一郎	高次脳機能障害のテストとスケール	脳と循環	10	221-225	2005
加藤元一郎	ADHDの脳科学 ③ADHD の神経心理学的研究について	LD&ADHD15	10月号	44-45	2005
加藤元一郎	器質性健忘症候群	精神科治療学	20	33-35	2005
栗原稔之、 加藤元一郎	Family History Research Diagnostic Criteria (FH-RDC)	分子精神医学	5	424-427	2005
加藤隆、加藤元一郎、鹿島晴雄	統合失調症の認知機能評価 －Gambling Task	Schizophrenia Frontier	6	301-306	2005
加藤元一郎	ADHDの脳科学 ④ADHD の神経心理学的研究について－覚醒状態と時間認知について	LD&ADHD16	1月号	44-45	2005
加藤元一郎、 穴水幸子	精神障害リハビリテーションの目標とゴール－生物学的視点から	精神科治療学	21	27-35	2006
加藤元一郎、 秋山知子	他者知覚プロセスの脳基盤 －特に視線と右上側頭溝領域の役割について	神経心理学	22	53-61	2006
加藤元一郎	今、リハビリテーション医学・医療に求められるもの －「精神医学の立場から」	第12回高度先進リハビリテーション医学研究会講演集	第12巻	33-39	2006

Ⅲ. 研究成果の刊行物・別刷

（主要な論文のみ）

ORIGINAL ARTICLE

High Levels of Serotonin Transporter Occupancy With Low-Dose Clomipramine in Comparative Occupancy Study With Fluvoxamine Using Positron Emission Tomography

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Context: Serotonin transporters (5-HTT) are regarded as one of the major therapeutic targets of antidepressants. However, there have only been a few studies about 5-HTT occupancy, and in particular, data concerning classical antidepressants are still limited.

Objective: To investigate the relationship between 5-HTT occupancy and a wide range of antidepressant dosing protocols.

Design, Setting, and Participants: Antidepressant occupancies of 5-HTT were measured using positron emission tomography (PET) with [^{11}C](+)McN5652. Twenty-seven healthy volunteers were measured with and without pretreatment with single low doses of antidepressants, and long-term doses were evaluated in 10 patients. Scan data were collected between December 12, 1995, and August 7, 2002, and data were analyzed during the 2001-2002 period at the National Institute of Radiological Sciences (Chiba, Japan).

Intervention: Four different doses of clomipramine hydrochloride (5-50 mg) and 3 different doses of fluvoxamine maleate (12.5-50 mg) were used for single administration. Long-term doses were 20 to 250 mg per day for clomipramine hydrochloride, and 25 to 200 mg per day for fluvoxamine maleate.

Main Outcome Measure: Occupancies in the thalamus were calculated using the individual baseline of [^{11}C](+)McN5652 for single-dose studies and 2 long-term–dose studies, and the mean value of healthy volunteers as the baseline for 8 long-term–dose studies. The average data from inactive enantiomers [^{11}C](−)McN5652 were used for the estimation of nonspecific binding.

Results: Occupancy of 5-HTT increased in a curvilinear manner. Even 10 mg of clomipramine hydrochloride showed approximately 80% occupancy, which was comparable with that of 50 mg of fluvoxamine maleate. Estimated median effective dose (ED_{50}) of clomipramine hydrochloride was 2.67 mg for oral dose and 1.42 ng/mL for plasma concentration; those of fluvoxamine maleate were 18.6 mg and 4.19 ng/mL, respectively.

Conclusions: Clinical doses of clomipramine and fluvoxamine occupied approximately 80% of 5-HTT, and dose escalation would have minimal effect on 5-HTT blockade. Ten milligrams of clomipramine hydrochloride was enough to occupy 80% of 5-HTT in vivo.

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SEROTONIN TRANSPORTERS (5-HTT) are located at presynaptic serotonergic neurons and have a key role in the regulation of serotonin concentration in the synapse. They are believed to be the primary target for selective serotonin reuptake inhibitors (SSRIs) and several tricyclic antidepressants such as clomipramine hydrochloride.[1] In clinical practice, SSRIs are commonly used, and clomipramine is also one of the most widely used antidepressants and drugs for obsessive compulsive disorders.[2-4]

The recent neuroimaging techniques of positron emission tomography (PET)[5-7] and single photon computed emission tomography (SPECT)[8,9] have introduced several ligands for the measurement of 5-HTT in vivo. However, there have been limited data about the effect of antidepressants on 5-HTT in the living human brain.[8-11] Occupancy of 5-HTT as the percentage reduction of specific binding during the treatment of SSRIs has been reported in 2 SPECT studies[8,9] and 1 PET study.[12] Using β-CIT labeled with iodine 123, 40% to 50% of 5-HTT occupancies were reported during the treatment with 60 mg/d of fluoxetine hydrochloride[9] or 20 to 60 mg/d of citalopram hydrobromide.[8] However, the detectability of oc-

cupancy by less selective ligands of 5-HTT, such as [^{123}I]β-CIT, requires some circumspection,[5] and the baseline of the calculation of occupancy also needs to be addressed with some caution because of the possible difference in nonspecific binding.[11,13] A recent study using [^{11}C]DASB [3-^{11}C-amino-4-(2-dimethylaminomethylphenylsulphanyl)benzonitrile] reported approximately 80% 5-HTT occupancy during treatment with 10 to 20 mg/d of paroxetine hydrochloride and 20 mg/d of citalopram hydrobromfide.[12] However, the relationship with low doses is not yet clear, and no data are as yet available on 5-HTT occupancy with classic tricyclic antidepressants like clomipramine.

McN5652 (trans-1,2,3,5,6, 10-β-hexahydro-6-[4 (methylthio) phenyl] pyrrolo [2,1-a] isoquinoline) is a selective serotonin reuptake inhibitor that has nanomolar affinity for serotonin 5-HT transporters. Its pharmacologically active enantiomer, (+)McN5652, has at least 2 orders of magnitude with higher affinity than its pharmacologically inactive enantiomer, (–)McN5652.[6,14] [^{11}C](+)McN5652 is currently being used as a PET tracer for 5-HTT, with good test-retest reproducibility.[6,10,11,15] However, a relatively high fraction of nonspecific binding and possible differences in nonspecific binding among regions has made it difficult to evaluate specific bindings and occupancies accurately.[11] Nevertheless, by the use of [^{11}C](–)McN5652, we have been able to calculate 5-HTT occupancy despite the regional differences of nonspecific binding.[11]

As for pharmacological evidence regarding the clinical dose of antidepressants, there have been only limited in vivo data, especially in relationship to 5-HTT occupancy. The purpose of this study was to investigate the precise relationship between 5-HTT occupancy and the dose of the classic tricyclic antidepressant clomipramine, or one of the SSRIs, fluvoxamine maleate, with a wide range of dosing protocols using [^{11}C](+) McN5652.

METHODS

SUBJECTS

Twenty-seven healthy male volunteers (mean±SD age, 22.0±2.3 years; range, 20-29 years) participated in single low-dose studies, and 10 patients (mean±SD age, 35.7±12.1 years; range, 21-55 years) with psychiatric disorders who were receiving long-term treatment with antidepressants were included in this study (**Table 1** and **Table 2**). All healthy volunteers were recruited from among university students and hospital employees. They filled out a questionnaire about their medical history and medications, and were then interviewed by a medical staff member. They had no history of present or past psychiatric, neurological, or somatic disorders, and no alcohol- or drug-related problems. They had not taken any kind of medication for at least 2 weeks prior to the start of the study. Six patients (age range, 21-50 years) had been taking clomipramine, 4 patients (age range, 24-55 years) had been taking fluvoxamine, and 6 of the 10 patients were also taking 1 or 2 benzodiazepines as anxiolytic or hypnotic treatments. The doses, duration of treatment, and diagnoses are presented in Table 2.

This study was approved by the ethics and radiation safety committees of the National Institute of Radiological Sciences (Chiba, Japan). Written informed consent was obtained from each subject.

PET MEASUREMENT

[^{11}C](+)McN5652 and [^{11}C](–)McN5652 were synthesized by S-methylation of the corresponding desmethyl precursor, which was stabilized by adding a protecting agent for mercapto groups, dithiothreitol, into the reaction medium immediately after the demethylation of McN5652 by an automated procedure.[16] The radiochemical purity was higher than 95%.

For 34 of the 37 subjects, PET scans were performed using a Siemens ECAT47 system (CTI-Siemens, Knoxville, Tenn), which provides 47 slices with 3.375-mm (center-to-center) thickness. Radioactivity was measured in 2-dimensional mode, and the data were reconstructed with a ramp filter with a cut-off frequency of 0.5 (full-width half-maximum [FWHM], 6.3 mm). The other 3 subjects were measured using an EXACT HR+scanner (CTI-Siemens, Knoxville, Tenn), which pro-

Table 1. Summary of Single-Dose Studies

Drug	Dose, mg	No. of Doses	Mean (SD) Occupancy, %
Clomipramine hydrochloride	5	2	67.2 (8.3)
	10	2	81.1 (6.9)
	25	3	84.9 (12.3)
	50	6	94.0 (4.7)
Fluvoxamine maleate	12.5	3	28.4 (31.2)
	25	7	56.8 (18.9)
	50	4	84.9 (2.2)

Table 2. Summary of Long-term Dose Studies With Patients

Drug	Doses, mg/d	Duration of Treatment	Concentration, ng/mL	Diagnosis	Occupancy, %
Clomipramine hydrochloride	250 (qid)	3 mo	660	OCD	100.0
	100 (qid)	8 mo	84	MDD	83.9
	70 (tid)	3 mo	53	OCD	100.0
	55 (qid)	2 mo	NA	MDD	86.4
	20 (bid)	2 wk	17	AD	97.1
	20 (qd)	1 wk	11	AD	89.3
Fluvoxamine maleate	200 (bid)	6 mo	143	MDD	86.8
	100 (bid)	3 wk	NA	MDD	79.7
	75 (tid)	6 mo	54	BPD	93.6
	25 (qd)	3 wk	NA	AD	76.6

Abbreviations: AD, anxiety disorder; bid, twice daily; BPD, bipolar disorder; MDD, major depressive disorder; NA, not applicable; OCD, obsessive-compulsive disorder; qd, daily; qid, 4 times daily; tid, 3 times daily.

vides 63 planes and a 15.5-cm field-of-view, and the data were reconstruicted with a Hanning filter cut-off frequency 0.4 (FWHM, 7.5 mm). The subjects were placed in the supine position with eyes closed and ears unplugged. To minimize head movement during each scan, head fixation devices (Fixster Instruments, Stockholm, Sweden) and thermoplastic attachments made to fit the individuals were used. A transmission scan of 10 minutes with a germanium 68–gallium 68 source was followed by a dynamic scan for 90 minutes with a bolus injection of 581 to 20.51 mCi (215-759 MBq) of [^{11}C](+)McN5652. The specific radioactivities ranged from 0.31 to 5.25 Ci/μmol (11.6-194.3 GBq/μmol) (mean±SD radioactivity, 2.61±1.19 Ci/μmol [96.4±44.1 GBq/μmol]) at the time of injection. A dynamic scan for 90 minutes with a bolus injection of 12.30 to 19.86 mCi (455-735 MBq) (mean±SD injection, 18.11±2.68 mCi [670-99 MBq]) of [^{11}C](−)McN5652 was performed on 14 healthy volunteers. The specific radioactivities were 0.69 to 3.66 Ci/μmol (25.6-135.6 GBq/μmol) (mean, 2.11±0.95 [77.9±35.2]) at the time of injection.

To measure the occupancy by a single administration of antidepressants, 13 healthy volunteers took part in the clomipramine study. Initial PET scans were carried out to establish the baseline data. Second PET scans were performed 5 hours after orally taking 5 mg to 50 mg of clomipramine hydrochloride (2 volunteers for 5 mg; 2 for 10 mg; 3 for 25 mg; and 6 for 50 mg) (Table 1). Blood samples (10 mL) were taken to measure the plasma concentration of clomipramine just before tracer injection. Fourteen healthy volunteers took part in the fluvoxamine occupancy study. Initial PET scans were carried out to attain the baseline data. Second PET scans were performed 5 hours after oral administration of different doses of fluvoxamine maleate (3 volunteers at 12.5 mg; 7 at 25 mg; 4 at 50 mg) (Table 1). Three subjects were scanned with the EXACT HR+ scanner for first and second scans having been given 25 mg of fluvoxamine maleate. Blood samples (10 mL) were taken to measure the plasma concentration of fluvoxamine just before tracer injection.

The plasma concentration of clomipramine was measured using high-performance liquid chromatography (HPLC) with ultraviolet detection, and that of fluvoxamine was measured by HPLC and a mass spectrometer.

To measure 5-HTT occupancy by long-term doses of antidepressants, the 10 patients were measured for 5-HTT binding during long-term treatment with clomipramine or fluvoxamine (Table 2). The PET scans were performed 7 hours after intake of fluvoxamine for 2 patients; 4 hours for 1 patient; 1 hour for 1 patient. Scans were performed 10 hours after intake of clomipramine for 1 patient; 4 hours for 3 patients; and 1 hour for 2 patients. Blood samples (10 mL) were taken to measure their plasma concentrations just before tracer injection. One of the patients taking clomipramine and 2 of the patients taking fluvoxamine refused the blood sampling.

DATA ANALYSIS

Positron emission tomographic images summated for 90 minutes were coregistered to magnetic resonance imaging (MRI) data with SPM99 (Wellcome Department of Cognitive Neurology, London, England), and regions of interest were defined over the cerebellum and thalamus based on these coregistered MRI and PET images. Because the specific binding of [^{11}C](+)McN5652 in the cerebral cortex is too low for quantitative analysis,[10,11] we focused on the thalamus to quantify its specific binding. Binding potential (BP) was used for the quantification that is expressed as k_3/k_4 in compartment models. In the 3-compartment model, K_1 was used to describe the uptake of the tracer across the blood-brain barrier; k_2 represented back diffusion from tissue to the vascular space; and k_3 and k_4 described the binding and dissociation of the radioligand at the specific binding site. The ratio k_3/k_4 is expressed by the equation

$$(1) \qquad k_3/k_4 = \mathrm{DVR} - 1,$$

where DVR is the distribution volume ratio based on the assumption that K_1/k_2 in the target tissue is equal to that in the reference tissue. However, the amount of nonspecific binding in the target tissue (the thalamus) was different from that in the reference tissue (cerebellum) with [^{11}C](+)McN5652.[11] The DVR of the target tissue to the reference tissue is given by the following equations for [^{11}C](+)McN5652 and the pharmacologically inactive enantiomer [^{11}C](−)McN5652:

$$(2) \qquad \mathrm{DVR}(+) = \frac{\dfrac{K_1^+}{k_2^+}\left(1 + \dfrac{k_3^+}{k_4^+}\right)}{\dfrac{K_1^{r+}}{k_2^{r+}}},$$

$$(3) \qquad \mathrm{DVR}(-) = \frac{\dfrac{K_1^-}{k_2^-}}{\dfrac{K_1^{r-}}{k_2^{r-}}},$$

respectively, where K_1^+, k_2^+, k_3^+, and k_4^+ are the estimated parameters of [^{11}C](+)McN5652 for the target tissue; K_1^{r+} and k_2^{r+} are the estimated parameters of [^{11}C](+)McN5652 for the reference tissue without a specific binding site, and K_1^-, k_2^-, K_1^{r-} and k_2^{r-} are those of [^{11}C](−)McN5652. Then k_3^+/k_4^+ is expressed as

$$(4) \qquad \frac{k_3^+}{k_4^+} = \frac{\mathrm{DVR}(+)}{\dfrac{K_1^+/k_2^+}{K_1^{r+}/k_2^{r+}}} - 1$$

If it is assumed that $(K_1^+/k_2^+)/(K_1^{r+}/k_2^{r+})$ is equal to DVR(−), then BP can be derived from the equation

$$(5) \qquad \mathrm{BP} = \mathrm{DVR}(+)/\mathrm{DVR}(-) - 1,$$

where the DVR of the thalamus to the cerebellum was calculated without arterial input function by the graphical method.[11,16] This assumption is based on the result that the value of DVR(+) in the saturation study of [^{11}C](+)McN5652 was almost equal to DVR(−).[11]

CALCULATION OF 5-HTT OCCUPANCY

Serotonin transporter occupancy (Occu [%]) using [^{11}C](+)McN5652 is expressed as

$$(6) \quad \mathrm{Occu}\,(\%) = 100 \cdot (\mathrm{BP}_{\mathrm{baseline}} - \mathrm{BP}_{\mathrm{drug}})/\mathrm{BP}_{\mathrm{baseline}} = 100 \cdot [1 - (\mathrm{DVR}(+)_{\mathrm{drug}} - \mathrm{DVR}(-))/(\mathrm{DVR}(+)_{\mathrm{baseline}} - \mathrm{DVR}(-))],$$

where DVR(+) and DVR(−) are the distribution volume ratios of [^{11}C](+)McN5652 and [^{11}C](−)McN5652 as estimated by graphical method with the reference tissue[17]; the test-retest variability and reliability (intraclass correlation coefficient) of [^{11}C](+)McN5652 for this graphical method were 10.8% and 0.83, respectively, based on

the 10-subject data (unpublished data). In this study, the mean±SD value of DVR(−) was estimated as 1.16±0.06 based on the data of 14 healthy volunteers (mean±SD age, 23.4±4.1 years), and it was used as a fixed value for the calculation of occupancy since not all subjects underwent the PET scans with [^{11}C](−)McN5652.

In 8 of the 10 patients studied, the mean±SD value of DVR(+)$_{baseline}$ for the 27 healthy volunteers (1.89±0.21 [range, 1.59-2.40]) was used for the calculation because the individual DVR(+)$_{baseline}$ values were not available for these 8 patients.

The relationship between 5-HTT occupancy and the dose or plasma concentration of antidepressants was modeled by the equation

$$(7) \qquad 5\text{-HTT}_{occu} = 100 \cdot D/(ED_{50} + D),$$

where 5-HTT$_{occu}$ is 5-HTT occupancy, ED_{50} (the in vivo median effective dose) is a constant, and D is the concentration of the drug near the 5-HTT. Dose and plasma concentration were used as functional surrogates of D.[18]

RESULTS

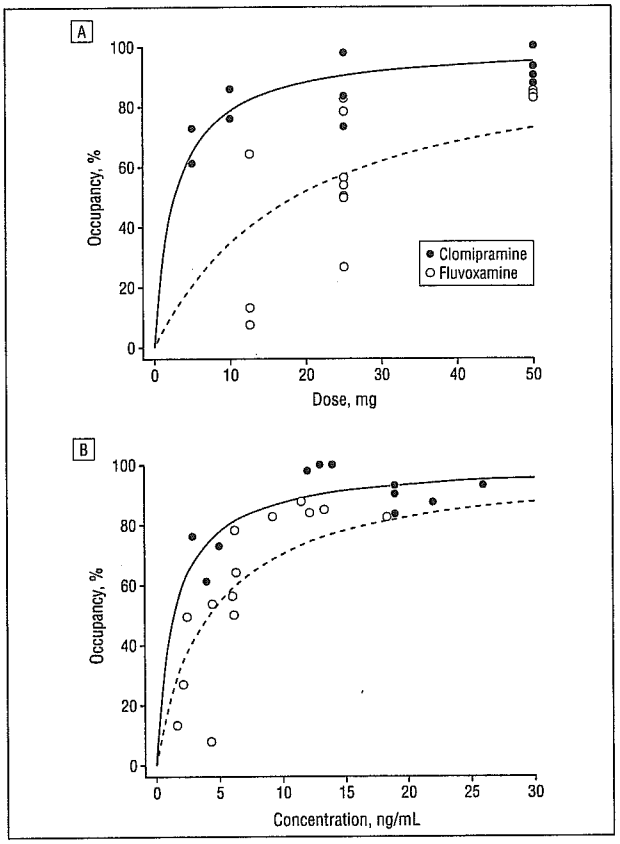
The occupancy of 5-HTT in the thalamus was dose-dependently increased both by clomipramine and fluvoxamine (Table 1, **Figure**). In the single-dose studies, clomipramine occupied more than 60% of 5-HTT even with the lowest dose of 5 mg (Table 1 and Figure). The ranges of occupancy were from 61.3% to 100% between 5 mg and 50 mg of clomipramine hydrochloride and from 7.7% to 87.7% between 12.5 mg and 50 mg of fluvoxamine maleate. There were hyperbolic relationships between 5-HTT occupancy and oral dose (r=0.780) and plasma concentration of clomipramine (r=0.752) (Figure) (2 of the plasma samples were under the detection limit and are not shown in the Figure). There were also hyperbolic relationships between 5-HTT occupancy and oral dose (r=0.686) and plasma concentration of fluvoxamine (r=0.808) (Figure). The calculated ED_{50} was 2.67 mg for oral dose and 1.42 ng/mL for plasma concentration of clomipramine, and that of fluvoxamine was 18.6 mg for oral dose and 4.19 ng/mL for plasma concentration.

In this study, we used the patient data with long-term dose to estimate 5-HTT occupancy. The occupancies from long-term dose ranged from 83.9% to 100% for clomipramine and 76.6% to 93.6% for fluvoxamine (Table 2). Including the patient data, the saturation curves did not significantly deviate against the dose or plasma concentration (clomipramine: r=0.724; fluvoxamine: r=0.722) or plasma concentration (clomipramine: r=0.726; fluvoxamine: r=0.835). The calculated ED_{50} including the patient data was 2.62 mg for oral dose and 1.40 ng/mL for plasma concentration of clomipramine. The calculated ED_{50} of fluvoxamine was 17.4 mg for oral dose and 4.20 ng/mL for plasma concentration including the patient data.

COMMENT

The present results demonstrated that 5-HTT was occupied by clomipramine or fluvoxamine in dose-dependent manners (Table 1), and curvilinear functions against drug concentration were clearly demonstrated (Figure). The present results showed marked high 5-HTT occupancy even with a small dose of clomipramine (Table 1 and Figure). Approximately 80% of 5-HTT was occupied with 10 mg of clomipramine hydrochloride (Table 1 and Figure). On the other hand, the 5-HTT occupancy of fluvoxamine increased slowly compared with that of clomipramine. The ED_{50} values of fluvoxamine were several times larger than those of clomipramine. Although several different values using different methods have been reported, this order of ED_{50} was generally consistent with the binding parameters in vitro.[19,20] However, the daily clinical doses of those antidepressants were not so different between clomipramine hydrochloride (at 75-300 mg/d [50-100 mg/d in Japan]) and fluvoxamine maleate (at 100-300 mg/d [50-100 mg/d in Japan]).[4]

The present results indicated that the variations in 5-HTT occupancy with low doses (12.5 mg and 25 mg) of fluvoxamine maleate were relatively large, but 50 mg of fluvoxamine maleate consistently occupied approximately 80% of 5-HTT (Table 1 and Figure). This suggested that at least 50 mg of fluvoxamine maleate was necessary to obtain certainly high 5-HTT occupancy (Table 2). These results of 5-HTT occupancy were concordant with those reporting that a dose of 50 to 150 mg of fluvoxamine maleate per day was therapeutically effective and that the minimally effective dose was 50 mg/d.[21]



Serotonin transporter occupancy of healthy volunteers by single oral administration of clomipramine hydrochloride and fluvoxamine maleate. Occupancies are plotted against oral dose (A) and plasma concentration (B) of clomipramine and fluvoxamine.

A recent study indicated that the clinical doses of paroxetine and citalopram occupy 70% to 80% of 5-HTT in living human brain.[12] It seems that close to 80% of 5-HTT occupancy is necessary to obtain therapeutic effects. That is a value of occupancy similar to that reported for the dopamine D2 receptor with a clinical dose of antipsychotics.[22] Furthermore, saturated 5-HTT with high-doses of antidepressants (Table 2) can explain the fact that there was no relationship between the plasma concentration of fluvoxamine and clinical response during the treatment with a relatively high oral dose (200-300 mg/d[23] or 150-300 mg/d[24]).

On the other hand, ED_{50} of clomipramine was much smaller compared with the usual clinical dose. The present results showed that 10 mg of clomipramine hydrochloride would be enough for nearly 80% of 5-HTT occupancy. It has been reported that there was no relationship between clinical effects and plasma concentration of clomipramine at a fixed dose of 150 mg/d[25,26] or different doses between 30 and 75 mg/d.[27-29] These reports support the present results that clomipramine occupied close to 80% of 5-HTT with an oral dose of 10 mg and that only a minimal increase in 5-HTT occupancy could be expected with a high dose. However, some reports have suggested a relationship between clinical response and dose (25-200 mg[30]) or plasma concentration of clomipramine and its metabolite desmethylclomipramine.[30,31] Other studies showed a relationship between clinical response and the plasma concentration of desmethylclomipramine only.[25,32] Since desmethylclomipramine is a potent noradrenaline reuptake inhibitor and clomipramine has relatively high affinities to several receptors,[33] mechanisms other than 5-HTT blockade can be supposed after sufficient saturation of 5-HTT.

Although the clinical merits of therapeutic drug monitoring of SSRIs are controversial,[34] 5-HTT occupancy correlates well with the plasma concentration as compared with the dose especially in the case of fluvoxamine (Figure). This suggested the possible use of therapeutic drug monitoring of SSRIs. If a patient does not respond well to an SSRI despite a high plasma concentration, this would be a good reason to switch antidepressants since there are many SSRI nonresponders.[35] There would be no merit in a dose escalation in a highly saturated dose range.[36] The beneficial alternative would be switching to a non-SSRI with different pharmacological properties.[35,37,38] Clomipramine has been reported to show a better clinical outcome compared with citalopram or paroxetine in severely depressed hospitalized patients.[39,40] A high dose of clomipramine can work on multiple neurotransmitter systems.

There are several limitations to the present study, especially with regard to the 5-HTT occupancy of the 8 patients being treated with antidepressants long-term. We used the mean $DVR(+)_{baseline}$ of the 27 healthy volunteers as the baseline. The variance of the calculated occupancy of 83.9% would be 73.3% to 90.7% using the extreme values of DVR(+) (1.59 and 2.40). This variance was similar to that of dopamine receptor occupancy using the average value as a baseline.[22] However, since BPs of [^{11}C](+)McN5652 in the thalamus were higher in patients with mood disorders[41] and no data are available for the 5-HTT of obsessive-compulsive disorders in vivo, some of the occupancy values calculated in this study might be underestimated or overestimated. In addition, the age effect of BPs was not considered in this study, since the effect of age[42] in these different diseases was not clear. In this study we used the mean value of DVR(−) (1.16±0.06) from 14 healthy volunteers as an estimate of nonspecific binding. The estimation of nonspecific binding can affect the absolute value of occupancy.[11] For example, the calculated occupancy of 82.6% can vary between 78.9% and 86.7% based on the deviation of DVR(−) value. Furthermore, if the nonspecific binding of the patients was different from that of the healthy volunteers, the estimated value of occupancy might be inaccurate.

In this study we have demonstrated that clinical doses of clomipramine and fluvoxamine occupied about 80% of 5-HTT, and that a small dose (such as 10 mg) of clomipramine can occupy about 80% of 5-HTT in vivo. However, further studies are needed to investigate the relation between clinical effects and occupancy especially for the use of a long-term small dose of clomipramine.

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REFERENCES

1. Schloss P, Williams DC. The serotonin transporters: a primary target for antidepressant drugs. *J Psychopharmacol.* 1998;12:115-121.
2. Koran LM, McElroy SL, Davidson JRT, Rasmussen SA, Hollander E, Jenike MA. Fluvoxamine versus clomipramine for obsessive compulsive disorder: a double-blind comparison. *J Clin Psychopharmacol.* 1996;16:121-129.
3. DeWilde JE, Doogan DP. Fluvoxamine and chlorimipramine in endogenous depression. *J Affect Disord.* 1982;3:249-259.
4. Rush JA. Mood disorders: treatment of depression. In: Sadock BJ, Sadock VA, eds. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry.* 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2000:1377-1385.
5. Farde L, Halldin C, Muller L, Suhara T, Karlsson P, Hall H. PET study of [^{11}C]β-CIT binding to monoamine transporters in the monkey and human brain. *Synapse.* 1994;16:93-103.
6. Szabo Z, Kao PF, Scheffel U, Suehiro M, Mathews WB, Ravert HT, Musachio JL, Marenco S, Kim SE, Ricaurte GA, Wong DF, Wagner HN Jr, Dannals RF. Positron emission tomography imaging of serotonin transporters in the human brain using [^{11}C](+)McN5652. *Synapse.* 1995;20:37-43.
7. Houle S, Ginovart N, Hussey D, Meyer J, Wilson A. Imaging the serotonin transporter with positron emission tomography: initial human studies with [^{11}C]DAPP and [^{11}C]DASB. *Eur J Nucl Med.* 2000;27:1719-1722.

8. Pirker W, Asenbaum S, Kasper S, Walter H, Angelberger P, Koch G, Pozzera A, Deecke L, Podreka I, Brücke T. βk-CIT SPECT demonstrates blockade of 5-HT-uptake site by citalopram in the human brain in vivo. *J Neural Transm Gen Sect.* 1995;100:247-256.
9. Tauscher J, Pirker W, De Zwaan M, Asenbaum S, Brücke T, Kasper S. In vivo visualization of serotonin transporters in the human brain during fluoxetine treatment. *Eur Neuropsychopharmacol.* 1999;9:177-179.
10. Parsey RV, Kegeles LS, Hwang DR, Simpson N, Abi-Dargham A, Mawlawi O, Slifstein M, Van Heertum RL, Mann JJ, Laruelle M. In vivo quantification of brain serotonin transporters in human using [^{11}C]McN5652. *J Nucl Med.* 2000;41:1465-1477.
11. Ikoma Y, Suhara T, Toyama H, Ichimiya T, Takano A, Sudo Y, Inoue M, Suzuki K. Quantitative analysis for estimating binding potential of brain serotonin transporters with [^{11}C]McN5652. *J Cereb Blood Flow Metab.* 2002;22:490-501.
12. Meyer JH, Wilson AA, Ginovart N, Goulding V, Hussey D, Hood K, Houle S. Occupancy of serotonin transporters by paroxetine and citalopram during treatment of depression: a [^{11}C]DASB PET imaging study. *Am J Psychiatry.* 2001; 158:1843-1849.
13. Logan J, Volkow N, Fowler JS, Wang G-J, Fischman MW, Foltin RW, Abumrad NN, Vitkun S, Gatley SJ, Pappas N, Hitzemann R, Shea CE. Concentration and occupancy of dopamine transporters in cocain abusers with [^{11}C]cocaine and PET. *Synapse.* 1997;27:347-356.
14. Shank RP, Vaught JL, Pelley KA, Setler PE, McComsey DF, Maryanoff BE. McN5652: a highly potent inhibitor of serotonin uptake. *J Pharmacol Exp Ther.* 1988;247: 1032-1038.
15. Lombardo I, Parsey RV, Hwang DR, Huang Y, Hashimoto T, Simpson N, Mawlawi O, Slifstein M, Arevalo A, Van Heertum R, Mann JJ, Laruelle M. Test/retest reproducibility of measurement of 5-HT transporter parameters in humans with (+) [^{11}C]McN5652: comparison between methods [abstract]. *J Nucl Med.* 2000;41:211.
16. Sasaki M, Suhara T, Kubodera A, Suzuki K. An improved automated synthesis and in vivo evaluation of PET radioligand for serotonin re-uptake sites: [^{11}C]McN5652X. *Kaku Igaku.* 1996;33:1319-1327.
17. Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL. Distribution volume ratios without blood sampling from graphical analysis of PET data. *J Cereb Blood Flow Metab.* 1996;16:834-840.
18. Kapur S, Zipursky RB, Jones C, Remington GJ, Wilson AA, DaSilva J, Houle S. The D2 receptor occupancy profile of loxapine determined using PET. *Neuropsychopharmacology.* 1996;15:562-566.
19. Tatsumi M, Groshan K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur J Pharmacol.* 1997;340:249-258.
20. Hyttel J. Pharmacological characterization of selective serotonin reuptake inhibitors (SSRIs). *Int Clin Psychopharmacol.* 1994;9(suppl 1):19-26.
21. Walczak DD, Apter JT, Halikas JA, Borison RL, Carman JS, Post GL, Patrick R, Cohn JB, Cunningham LA, Rittberg B, Preskorn SH, Kang JS, Wilcox CS. The oral dose-effect relationship for fluvoxamine: a fixed-dose comparison against placebo in depressed outpatients. *Ann Clin Psychiatry.* 1996;3:139-151.
22. Farde L, Nordström A-L, Wiesel F, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. *Arch Gen Psychiatry.* 1992;49:538-544.
23. Kasper S, Dotsch M, Kick H, Vieira A, Moller HJ. Plasma concentrations of fluvoxamine and maprotiline in major depression: implications on therapeutic efficacy and side effects. *Eur Neuropsychopharmacol.* 1993;3:13-21.
24. De Wilde JEM, Doogan DP. Fluvoxamine and clomipramine in endogenous depression. *J Affect Dis.* 1982;4:249-259.
25. Broadhurst AD, James HD. Clomipramine plasma level and clinical response. *Postgrad Med J.* 1977;53(suppl 4):139-145.
26. Montgomery SA, Montgomery DB, McAuley R, Dawling S, Braithwaite RA. Plasma concentration of clomipramine and clinical response in depressed patients. *Postgrad Med J.* 1980;56(suppl 1):130-133.
27. Gringras M. A comparison of a low and high dosage regime of clomipramine (Anafranil). *J Int Med Res.* 1975;3(suppl 1):47-54.
28. Frank P. Comparisons of various clomipramine (Anafranil) dosage regimes. *J Int Med Res.* 1977;5(suppl 1):11-15.
29. Miller P, Luscombe DK, Jones RB, Seldrup J, Beaumont G, John V. Relationships between clinical response, plasma levels, and side-effects of clomipramine (Anafranil) in general practitioner trials. *J Int Med Res.* 1977;5(suppl 1): 108-118.
30. Danish University Antidepressant Group (DUAG). Clomipramine dose-effect study in patients with depression: clinical end points and pharmacokinetics. *Clin Pharmacol Ther.* 1999;66:152-165.
31. Faravelli C, Ballerini A, Ambonetti A, Broadhurst AD, Das M. Plasma levels and clinical response during treatment with clomipramine. *J Affect Dis.* 1984;6:95-107.
32. Corte LD, Broadhurst AD, Sgaragli GP, Filippini S, Heeley AF, James HD, Faravelli C, Pazzagli A. Clinical response and tricyclic plasma levels during treatment with clomipramine. *Br J Psychiatry.* 1979;134:390-400.
33. Mctavish D, Benfield P. Clomipramine: an overview of its pharmacological properties and a review of its therapeutic use in obsessive compulsive disorder and panic disorder. *Drugs.* 1990;39:136-153.
34. Lundmark J, Bengtsson F, Nordin C, Reis M, Wålinder J. Therapeutic drug monitoring of selective serotonin reuptake inhibitors influences clinical dosing strategies and reduces drug costs in depressed elderly patients. *Acta Psychiatr Scand.* 2000;101:354-359.
35. Fredman JS, Fava M, Kienke AS, White CN, Nierenberg AA, Rosenbaum JF. Partial response, nonresponse, and relapse with selective serotonin reuptake inhibitors in major depression: a survey of current "next-step" practices. *J Clin Psychiatry.* 2000;61:403-408.
36. Benkert O, Azegedi A, Wetzel H, Staab HJ, Meister W, Philipp M. Dose escalation vs continued dose of paroxetine and maprotiline: a prospective study in depressed out-patients with inadequate treatment response. *Acta Psychiatr Scand.* 1997;95:288-296.
37. Fava M. Management of nonresponse and intolerance: switching strategies. *J Clin Psychiatry.* 2000;61(suppl 2):10-12.
38. Withersty DJ, Vanin JR. Guidelines for treating depression using non-selective serotonin reuptake inhibitors. *W V Med J.* 1999;95:20-23.
39. Danish University Antidepressant Group. Citalopram: clinical effect profile in comparison with clomipramine: a controlled multicenter study. *Psychopharmacology.* 1986;90:131-138.
40. Danish University Antidepressant Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *J Affect Disord.* 1990;18:289-299.
41. Ichimiya T, Suhara T. Sudo Y, Okubo Y, Nakayama K, Nankai M, Inoue M, Yasuno F, Takano A, Maeda J, Shibuya H. Serotonin transporter binding in patients with mood disorders: a PET study with [^{11}C](+)McN5652. *Biol Psychiatry.* 2002;51:715-722.
42. Yamamoto M, Suhara T, Okubo Y, Sudo Y, Ichimiya T, Sudo Y, Inoue M, Takano A, Yasuno F. Age-related decline of serotonin transporter binding in living human brain measured by PET with [^{11}C] (+)McN5652. *Life Sci.* 2002;71:751-757.

[11C]PE2I: a highly selective radioligand for PET examination of the dopamine transporter in monkey and human brain

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Abstract. The aim of this study was to explore the potential of a new selective dopamine transporter (DAT) compound as a radioligand for positron emission tomography (PET) examination of DAT in the human brain. The high affinity DAT compound *N*-(3-iodoprop-2*E*-enyl)-2β-carbomethoxy-3β-(4-methylphenyl)nortropane (PE2I) was radiolabelled by the O-methylation approach and the binding was characterised by PET in cynomolgus monkeys and a healthy man. Metabolite levels in plasma were measured by gradient high-performance liquid chromatography. O-methylation of the corresponding free acid precursor with [11C]methyl triflate gave high radiochemical yield (80%) and specific radioactivity (55 GBq/μmol). [11C]PE2I binding in cynomolgus monkeys was nine times higher in the striatum than in the cerebellum at peak equilibrium, which appeared 55–65 min after injection. Displacement and pretreatment measurements using unlabelled β-CIT, GBR 12909, cocaine, citalopram and maprotiline confirmed that [11C]PE2I binds selectively to DAT. In a preliminary study in one human subject the radioactivity ratios of the striatum and substantia nigra to the cerebellum were 10 and 1.8, respectively, at peak equilibrium, which appeared at 40–50 min and 20 min, respectively, after injection. The fraction of the total radioactivity in monkey and human plasma representing unchanged [11C]PE2I was 15–20% at 40 min after injection. The present characterisation of binding in monkey and man suggests that [11C]PE2I is a suitable PET radioligand for quantitative regional examination of DAT in man.

Keywords: Brain – Dopamine transporter – Striatum – Substantia nigra – PE2I – PET

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Introduction

The neuronal dopamine transporter (DAT) is a membrane-bound presynaptically located protein that regulates the synaptic concentration of dopamine at nerve terminals. Positron emission tomography (PET) and single-photon emission tomography (SPET) imaging of DAT in the human brain has been applied for the examination of degenerative brain disorders such as Parkinson's disease, for depression, for attention deficit hyperactive disorder and for studies on effects of psychostimulants in brain [1, 2, 3, 4, 5, 6, 7, 8].

DAT radioligands applied in clinical PET and SPET studies include [11C]cocaine, [11C]methylphenidate and tropane-type derivatives of cocaine [9]. The cocaine congener β-CIT [2β-carbomethoxy-3β-(4-iodophenyl)tropane] (Fig. 1) labelled with iodine-123 has been widely used as a SPET radioligand for in vivo studies of DAT [10, 11]. The structure of β-CIT also allows labelling with 11C in the *N*-methyl group for PET studies by using [11C]methyl iodide [12] or [11C]methyl triflate [13]. However, β-CIT is not selective for DAT, having relatively high affinity for the serotonin transporter (SERT) and noradrenaline transporter. Another problem with the quantitation of [11C]β-CIT binding to DAT is that the uptake of radioactivity in the dopamine transporter-rich striatum increases with time and does not reach equilibrium within the duration of a PET examination [14].

There is a need for selective PET radioligands that are suitable for quantitation of DAT in the human brain. Among series of *N*-fluoroalkyl analogues of β-CIT [15] the *N*-fluoropropyl- and *N*-fluoroethyl analogues, β-CIT-FP and β-CIT-FE, have been labelled with 11C, 18F and 123I [16, 17, 18, 19, 20, 21]. β-CIT-FE (Fig. 1) has been evaluated as a PET radioligand for quantitation of DAT

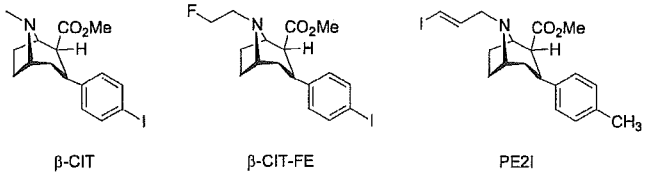

Fig. 1. Structural formulae for β-CIT, β-CIT-FE and PE2I

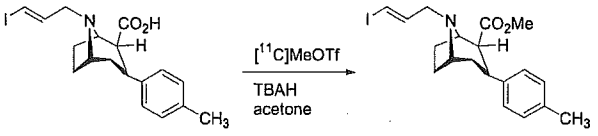

Fig. 2. Incorporation of [^{11}C]methyl triflate to [^{11}C]PE2I

in monkey and human [20, 21]. Specific binding reaches peak equilibrium within 1 h in human subjects after i.v. injection. However, β-CIT-FE is not sufficiently selective for detailed mapping of the distribution of DAT in the human brain [22].

Another fluorinated analogue, β-CFT, is a more selective DAT ligand and has been labelled with either ^{11}C or ^{18}F [23, 24]. In vivo, [^{11}C/^{18}F]β-CFT reaches peak striatal uptake at 225 min in humans, which makes the ^{18}F analogue suitable whereas the ^{11}C-labelled version has limited potential for imaging of DAT. The *N*-3-iodoallyl derivative of β-CFT, altropane, can principally be labelled with either ^{123}I or ^{11}C and has been reported in preliminary studies to be useful in humans with SPET [25]. SPET images in healthy volunteers showed that [^{123}I]altropane accumulated rapidly and selectively in the striatum and yielded excellent quality images within 1 h after administration.

Recently a new compound, *N*-(3-iodoprop-2*E*-enyl)-2β-carbomethoxy-3β-(4-methylphenyl)nortropane (PE2I, Fig. 1) [26, 27, 28] has been proven to be a ligand that binds with high affinity for DAT in vitro (K_i: 17 n*M*) and with much (>30-fold) lower affinity to the other monoamine transporters. In initial studies, ^{123}I-labelled PE2I has been used for SPET analysis of DAT in the monkey [29] and human brain [30]. An excellent specific to non-specific ratio of this SPET tracer has been obtained, with a peak uptake at about 60 min in the striatum of human subjects [30].

The aim of this work was to develop the selective DAT compound PE2I as a new radioligand for PET. The specificity and selectivity of binding was examined by displacement and pretreatment experiments in cynomolgus monkeys. Radioligand metabolism was measured in plasma by gradient high-performance liquid chromatography (HPLC). The anatomical distribution of [^{11}C]PE2I binding in the human brain was illustrated by a preliminary study in a control subject.

Materials and methods

General chemistry. *N*-(3-iodoprop-2*E*-enyl)-2β-carbomethoxy-3β-(4-methylphenyl)nortropane (PE2I) and its corresponding acid precursor were prepared as described in detail previously [28]. Silver trifluoromethane sulphonate (silver triflate) and Graphac GC (80–100 mesh) were obtained from Sigma-Aldrich Sweden AB and Alltech, respectively. Other chemicals were obtained from commercial sources and were of analytical grade wherever possible. Silver triflate-impregnated graphitised carbon was prepared according to a previously described method [31]. Carbon dioxide was produced at the Karolinska Hospital with a Scanditronix RNP 16 cyclotron using 16-MeV protons during the ^{14}N(p, α)^{11}C reaction. The synthesis and purification of [^{11}C]PE2I was performed in a fully automated hepa-filtered air controlled system for methylation that has been described in detail elsewhere [32]. The system contains a GEMS MeI PETtrace MicroLab as an integrated part. [^{11}C]Methyl iodide was prepared from [^{11}C]carbon dioxide via [^{11}C]methane by catalytic gas-phase iodination. Sweeping the [^{11}C]methyl iodide vapour through a glass column, containing silver triflate-impregnated graphitised carbon and being heated at 150–200°C, produced [^{11}C]methyl triflate. [^{11}C]methyl triflate was trapped at room temperature in a reaction vessel containing the precursor, solvent and base.

Purification of [^{11}C]PE2I was performed in a built-in semi-preparative reversed phase HPLC system using a Kontron 420 pump, an automatic sample injector (Type VICI with a 1-ml loop), a Waters μ-Bondapak-C-18 column (300×7.8 mm, 10 μm) and a Kontron 432 UV-detector (wavelength =254 nm) in series with a GM tube for radiation detection. [^{11}C]PE2I was purified using acetonitrile, water, triethyl amine (60/40/0.1) as the mobile phase with a flow rate of 6.0 ml/min. The radiochemical purity of [^{11}C]PE2I was analysed by reversed-phase HPLC using a Kontron 420 pump, a Rheodyne injector (7125 with a 100-μl loop) equipped with a Waters μ-Bondapak-C18 column (300×4.6 mm, 10 μm) and an LDC-Milton Roy 300 UV-spectrophotometer (254 nm) in series with a Beckman 170 radioactivity detector. Acetonitrile and 0.01 *M* phosphoric acid (35/65) were used as the mobile phase with a flow rate of 2.0 ml/min.

Preparation of [11C]PE2I. [^{11}C]Methyl triflate, prepared as described in detail elsewhere [32], was trapped at room temperature in a reaction vessel (1.0-ml mini-vial, Alltech) containing PE2I acid precursor (0.5 mg), aqueous tetrabutylammonium hydroxide (0.4 *M*, 4 μl) and acetone (400 μl) (Fig. 2). No extra reaction time after trapping was needed for [^{11}C]methyl triflate. Mobile phase (500 μl) was added before injection onto the semi-preparative HPLC column. [^{11}C]PE2I eluted after 7–9 min with a retention time identical to a standard reference sample (Fig. 3). After evaporation of the mobile phase, the residue was dissolved in 8 ml sterile physiological phosphate-buffered saline (pH=7.4) and filtered through a Millipore filter (0.22 mm), yielding a solution which was sterile and free from pyrogens.

Positron emission tomography. The PET system Siemens ECAT EXACT HR 47 was run in the three-dimensional mode. The in-plane and axial resolution is about 3.8 mm and 4 mm FWHM, respectively [33]. The reconstructed volume was displayed as 47 transaxial sections with a section thickness of 3.125 mm.