CONF-9509263--1
BNL-62345

Measuring Dopamine Release in the Human Brain with PET

N.D. Volkow[ac], J.S. Fowler[b], G.-J. Wang[a], J. Logan[b],

[a]Medical and [b]Chemistry Departments Brookhaven National Laboratory, Upton, New York, NY 11973

[c]Department of Psychiatry, State University of New York at Stony Brook, Stony Brook, New York 11794-8101

INTRODUCTION

The dopamine system is involved in the regulation of brain regions that subserve motor, cognitive and motivational behaviors [1,2,3]. Disruptions of dopamine (DA) function have been implicated in neurological and psychiatric illnesses including substance abuse, as well as on some of the deficits associated with aging of the human brain [4,5,6]. This has made the DA system an important topic in research in the neurosciences and neuroimaging as well as an important molecular target for drug development.

Dopamine cells reside predominantly in the mesencephalon in three neuronal groups, the retrobulbar, the Substantia Nigra, and the Ventral Tegmental area [7,8,9,10,11]. The Substantia Nigra projects predominantly to the dorsal striatum and is mainly concerned with initiation and execution of movements. The Ventral Tegmental area projects to nucleus accumbens, orbital and cingulate cortices, amygdala and hippocampus and is involved with reinforcement, motivation, mood and thought organization. From within the DA cells dopamine is released into the synapse in response to an action potential and interacts with postsynaptic DA receptors. The concentration of DA in the synapse is regulated primarily by its reuptake by the DA transporters, to maintain low (nanomolar) steady-state concentrations [12].

Positron Emission Tomography (PET), was the first technology that enabled direct measurement of components of the DA system in the living human brain [13]. Imaging studies of DA in the living brain have been indirect, relying on the development of radiotracers to label DA receptors, DA transporters, precursors of DA or chemical compounds which have specificity for the enzymes which degrade synaptic DA [14]. Additionally, through the use of tracers that provide information on regional brain activity (ie brain glucose metabolism and cerebral blood flow) and of appropriate pharmacological interventions, it has been possible to assess the functional consequences of changes in brain DA activity. DA specific ligands have been useful in the evaluation of patients with neuropsychiatric illnesses as well as to investigate receptor blockade by antipsychotic drugs [15,16,17,18].

A limitation of strategies that rely on the use of DA specific ligands is that the measures do not necessarily reflect the functional state of the dopaminergic system and that there use to study the effects of drugs is limited to the investigation of receptor or transporter occupancy. Newer strategies have been developed in an attempt to provide with information

on dopamine release and on the functional responsivity of the DA system in the human brain [19]. This in turn allows to investigate the effects of pharmacological agent in an analogous way to what is done with microdialysis techniques [20].

PET Strategies To Measure DA Release

It is possible to assess changes in intrasynaptic DA with PET using DA D2 receptor ligands such as [11C]raclopride which have a relatively low affinity for the DA D2 receptor so that they compete with endogenous DA for binding to the receptor site [21,22]. The competition of endogenous DA with D2 receptor radioligands presents the opportunity to measure changes in synaptic DA in vivo by observing the degree of reduction in the binding of a D2 receptor radiotracer by pharmacological agents [23,24,25,26,27].

The strategy involves two studies with [11C]raclopride one is done at baseline and the other is done after administration of 0.25 mg/kg iv or 0.5 mg/kg iv methylphenidate. Methylphenidate (MP) significantly decreases binding of [11C]raclopride in striatum. The reductions with methylphenidate were dose dependent and were larger for the 0.5 mg/kg iv dose than for the 0.25 mg/kg iv dose. Because [11C]raclopride is highly reproducible [28-29] the reductions after methylphenidate most likely reflect changes in synaptic DA.

Methylphenidate induced change in [11C]raclopride were quantified using the distribution volume (DV) in striatum to that in cerebellum. Distribution volumes were calculated using graphical analyses [30]. The ratio of the DV in striatum to that in cerebellum is a function of Bmax/Kd + 1. Changes in the model parameter Bmax/Kd after methylphenidate (0.5 mg/kg iv) were obtained in 15 healthy male controls; five of the subjects were also tested with a 0.25 dose of methylphenidate. Methylphenidate significantly decreased binding of [11C]raclopride in striatum but not in cerebellum (Figure 1). Methylphenidate-induced changes in [11C]raclopride binding were dose dependent and were larger for the 0.5 mg/kg iv dose than for the 0.25 mg/kg iv dose. Percent change in Bmax/Kd for the 0.5 mg/kg iv dose was -23.0 $\pm$ 15 and for the 0.25 mg/kg iv dose was -16.7 $\pm$ 17.

The responses to methylphenidate were quite variable among the subjects; both with respect to its behavioral effects as well as its effects on [11C]raclopride binding. While half of the subjects reported the effects of methylphenidate as pleasurable, 30% reported them as unpleasent and 20% as neutral. Similarly the pattern of changes in mental state were quite variable inducing in some subjects increases in anxiety while relaxing others. The reductions in [11C]raclopride binding as assessed with the model parameter Bmax/Kd were also quite variable and ranged between 0 and 45%. Changes in Bmax/Kd were associated with the subjective rating for the intensity of the experience of methylphenidate (Figure 2). Subjects who rated very intense sensation after the drug were the ones that showed the largest changes in Bmax/Kd after methylphenidate and subjects who had minimal or no behavioral effects were the one who showed changes in [11C]raclopride binding within the range of test retest resproducibility for this tracer (-5% to + 5%). There were no correlations with specific behavioral effects such as high, anxiety or alertness. On the other hand the [11C]raclopride responses were positively correlated with methylphendate induced restlessness.

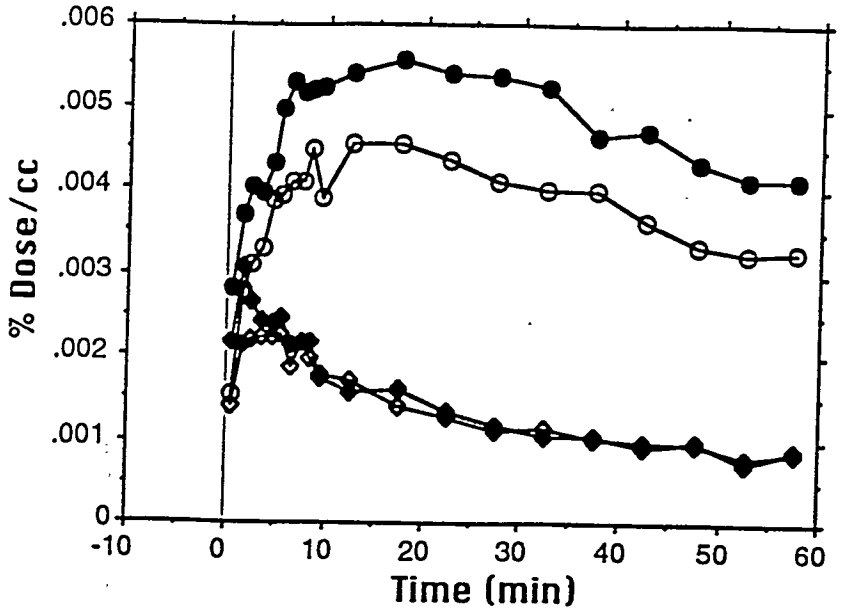

Figure 1. Time activity curve for [11C]raclopride in striatum (circles) and in cerebellum *rhombi) at baseline (closed) and after administration of 0.5 mg/kg iv methylphenidate (open). Notice that methylphenidate significanlty decreased binding in striatum but not in cerebellum.

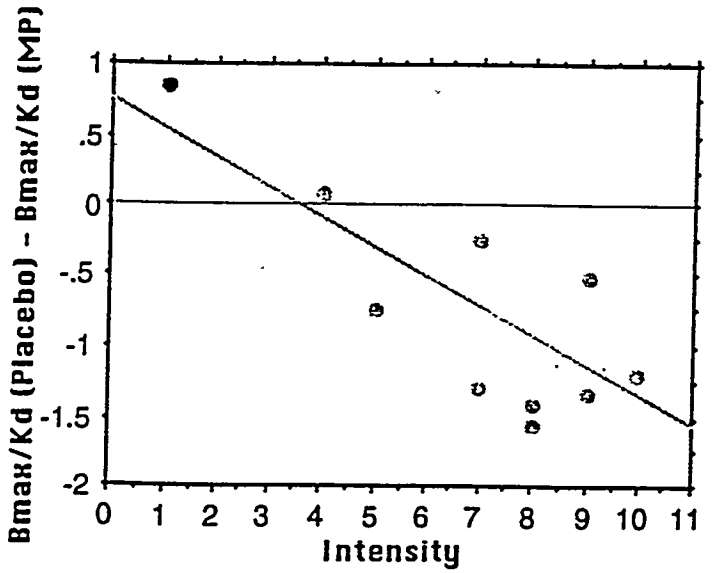

Figure 2. Relation between metylphenidate (MP) induced changes in [11C]raclopride and the intensity of the subjective experience to metylphenidate ($r = 0.76$, $p < 0.007$)

The reductions in [11C]raclopride binding after administration of methylphenidate were also found to decrease with age (Figure 3). Older subjects showed less of a response than younger ones. The decreased responses to methylphenidate in older subjects is likely to reflect age associated decreases in dopamine transporter sites [31-32]. Decreases in presynaptic DA transporters with age would make drugs that act

at the DA transporter level such as methylphenidate less effective. This in turn would have implications in understanding for example the decrease in substance abuse with aging. This finding is also of relevance in understanding differences in medication effectiveness among elderly subjects. Though most of the interest in sensitivity to drugs in aging concentrates in differences in drug metabolism with age this study illustrates that differences could also be the resultant of neurochemical changes which could make a drug less effective because there are less binding sites with which the drug can interact. This finding is also interesting in that it differs from most studies previously done with aging which have mainly concentrated on the measurement of DA transporter decline with age in that it provides with a functional index of the ability of the DA cells to respond to a pharmacological challenge. It is the first direct documentation in human subjects that there is a decline in dopaminergic responsivity with age. Notice also that this decline appear to occur relatively early in life since it is already apparent in subjects in their mid thirties and early forties.

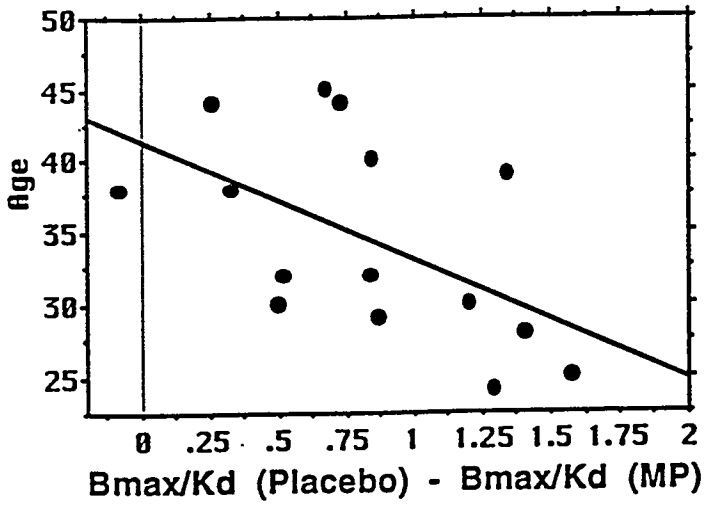

Figure 3. Relation between metylphenidate induced changes in [11C]raclopride and age ($r = -0.53$, $p < 0.03$).

The magnitude of the changes in DA in response to MP were significantly correlated with the baseline mental state of the subjects in particular with anxiety. The subjects who reported the highest scores in anxiety during baseline were those which showed the most robust responses to methylphenidate (Figure 4).

Because the measurements were obtained during the placebo scan, the anxiety scores probably reflect the responses to the PET experience. The anxiety response during the PET procedure could therefore be considered analogous to the response of an animal to novel stimulus, for whom higher responsivity is associated with increased psychostimulant sensitivity [33,34,35]. Hence we postulate that, in human subjects, heightened sensitivity to novel stimuli and/or unfamiliar situations, may also be linked with a more responsive DA system.

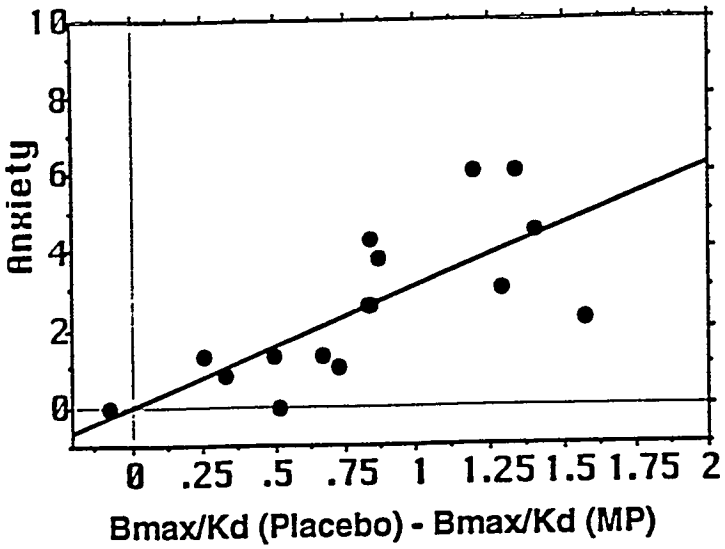

Figure 4. Relation between metylphenidate induced changes in [11C]raclopride and the subjective rating for anxiety during baseline ($r = 0.74$, $p < 0.002$).

These findings show that the response to a drug is not only a function of the pharmacological properties of the drug but also of the intrinsic characteristics of the subject. That the particular neurochemical state of the individual affects their response to a drug is demonstrated by studies which have shown that the increases in DA concentration induced by cocaine are decreased or abolished by manipulating GABAergic activity in brain using drugs such as benzodiazepine agonists [36]. In this respect it is interesting to note that drugs that enhance GABAergic neurotransmission have anxiolitic properties [37].

SUMMARY

Investigating DA release in response to drug administration *in vivo* in the human brain is a new tool in human neuropharmacology which will enable to evaluate correlations between changes in neurotransmitter concentration and behavioral effects. The methodology may also be of help in the early detection of dopaminergic dysfunction that would be undetected when studying patients during baseline conditions.

ACKNOWLEDGMENTS

This research was supported in part by the US. Department of Energy under Contract DE-ACO2-76CH00016 and NIDA Grant No. 5RO1-DA06891.

DISCLAIMER

REFERENCES

1 Goldman-Rakic P. Circuitry of the prefrontal cortex. In: F. Plum, ed. Handbook of Psychology Bethesda MD: American Physiological Society, 1987,373-417.

2 LeMoal M, Simon H. Mesocorticolimbic dopamine network: Functional and regulatory roles. Physiol Rev 1991; 71:155-234.

3 Koob GF, Bloom FE. Cellular and molecular mechanisms of drug dependence. Science 1988; 242:715-723.

4 Kopin IJ. The pharmacology of Parkinson's disease therapy: An update. Ann Rev Pharmacol Toxicol 1993; 32:467-495.

5 Creese I, Burt DR, Snyder SH. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science 1976; 192:481-483.

6 McGeer PL, McGeer EG, Suzuki JS. Aging and extrapyramidal function. Arch Neurol 1977; 34: 33-35.

7 Di Chiara G, Morelli M, Acquas E, Carboni E. Functions of dopamine in the extrapyramidal and limbic systems. Arzneim-Forsch Drug Res 1992; 42:231-237

8 Willner P, Muscat R, Papp M, Sampson D. In: Willner P, Scheel-Kruger J, eds. The Mesolimbic Dopamine System: From Motivation to Action, New York: John Wiley and Sons, 1992 pp 387-400.

9 Glowinski J, Tassin JP, Thierry AM. The mesocortical-prefrontal dopaminergic neurons. TINS 1984; 451-418.

10 Selemon LD, Goldman Rackic PS. Longitudinal topography and interdigitations of corticostriatal projections in the rhesus monkey. J Neurosci 1984; 5, 776-794.

11 Stuss DT, Benson DF. The Frontal Lobes, New York: Raven Press, 1986 pp 12-38.

12 Garris PA, Ciolkowski EL, Pastore P, Wightman RM. Efflux of dopamine from the synaptic cleft in the nucleus accumbens of the rat brain. J Neurosci 1994; 14:6084-6093.

13 Fowler JS, Wolf AP. New directions in positron emission tomography. Chapter 30.In: Bristol JA ed. Annual Reports in Medicinal Chemistry 1989; 24:277-286.

14 Volkow ND, Fowler JS, Gatley JS, et al. Evaluation of the Human Brain Dopamine System With PET: Review and Update of Tracers. J Nucl Med (in press).

15 Andreasen NC, Carson R, Diksic M, et. al. Workshop on schizophrenia, PET and the dopamine D2 receptors in the human neostriatum. Schiz Bull 1988; 14: 471-484.

16 Farde L, Nordstrom A-L, Wiesel FA, et. al. Positron emission tomography analysis of central D1 and D2 recepotr occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side ffects. Arch Gen Psychiatry 1992; 49:538-544.

17 Smith M, Wolf AP, Brodie JD, et. al. Serial ^{18}F-N- methylspiroperidol PET studies to measure changes in antipsychotic drug D2 receptor occupancy inschizophrenic patients. Biol Psyciatry 1988; 23:653-663.

18 Farde L, Nordstrom A, Nyberg S, Halldin C, Sedvall G. D1, D2, and 5HT2 occupancy in clozapine treated patients. J Clin Psychiatry 1994; 55(Suppl B):67-69.

19 Volkow ND, Wang G-J, Fowler JS, et. al. Imaging endogenous dopamine competition with [^{11}C]raclopride in the human brain. Synapse 1994; 16:255-262.

20 Deterding LJ, Dix K, Burka LT, Tomer KB. On-line coupling of in vivo microdialysis with tandem mass spectrometry. Anal Chem 1992; 64:2636-2641

21 Seeman P, Guan C, Niznik HB. Endogenous dopamine lowers the dopamine D2 receptor density as measured by 3H raclopride: Implications for positron emission tomography of the human brain. Synapse 1989; 3:96-97.

22 Ross SB, Jackson DM. Kinetic properties of the accumulation of 3H raclopride in the mouse in vivo. Naunyn-Schmied Arch Pharmacol 1989; 340:6-12.

23 Dewey SL, Smith GW, Logan J, et. al. GABAergic inhibition of endogeneous dopamine release measured in vivo with ^{11}C-raclopride and positron emission tomography. J Neurosci 1992; 12:3773-3780.

24 Dewey SL, Smith GS, Logan J, et. al. Striatal binding of the PET ligand ^{11}C-raclopride is altered by drugs that modify synaptic dopamine levels. Synapse 1993; 13; 350-356.

25 Hume SP, Myers R, Bloomfield PM, et. al. Quantitation of carbon-11-labeled raclopride in rat striatum using positron emission tomography. Synapse 1992; 12:47-54.

26 Dewey SL, Logan J, Wolf AP, et. al. Amphetamine induced decreases in [^{18}F] N-methylspiroperidol binding in baboon brain using positron emission tomography (PET) Synapse 1991; 7: 324-327.

27 Logan J, Dewey SL, Wolf AP, et. al. Effects of endogenous dopamine on measures of [^{18}F]N-methylspiroperidol binding in the basal ganglia: Comparison of simulations and experimental results from PET studies in baboons. Synapse 1991; 9: 195-207.

28 Nordstrom AL, Farde L, Pauli S, Litton JE, Halldin C. PET analysis of central [^{11}C]raclopride binding in healthy young adults and schizophrenic patients, reliability and age effects. Human Psychopharmacology 1992; 7:157-165.

29 Volkow ND. Fowler JS, Wang G.-J, et. al. Reproductibility of repeated measures of ^{11}C raclopride binding in the human brain. J Nucl Med 1993; 34:609-613.

30 Logan J, Fowler JS, Volkow ND, et. al. Graphical analysis of reversible radioligand binding from time-activity measurements applied to [N-^{11}C-methyl]-(-)-cocaine PET studies in human subjects. J Cereb Blood Flow Metab 1990; 10:740-747.

31 Volkow ND, Fowler JS, Wang G-J, et. al. Decreased dopamine transporters with age in healthy human subjects. Annals Neurology 1994; 36: 237-239.

32 Van Dick CH, Seibyl JP, Malison RT, et. al. Age-related decline in dopamine transporter binding in human striatum with [I-123]b-CIT SPECT. J Nucl Med 1995; 36:1175-1181.

33 Piazza PV, Deminiere JM, Le Moal M, Simon H. Factors that predict individual vulnerability to amphetamine self-administration. Science 1989; 245:1511-1513.

34 Hooks MS, Jones GH, Smith AD, Neill DB, Justice JB. Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. Synapse 1991; 9:121-128.

35 Jones GH, Marsden CA, Robbins TW. Increased sensitivity to amphetamine and reward-related stimuli following social isolation in rats: possible disruption of dopamine dependent mechanisms in the nucleus accumbens. Psychopharmacology 1990; 102:364-372.

36 Chen CR, Straughter-Moore RM, et al. Pharacologic modualtion of cocaine-induced dopmaine release and locomotor activity: a potential therapeutic strategy for cocaine abuse. Soc Neuroscience Abstracts Vol 21 1995; 767.5.

37 Woods JH, Katz JL, Winger G. Benzodiazepines: use, abuse and consequences. Pharm Rev 1992; 44:154-347.