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Dynamic Neurotransmitter Interactions Measured with PET

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INTRODUCTION

Positron emission tomography (PET) has become a valuable interdisciplinary tool for understanding physiological, biochemical and pharmacological functions at a molecular level in living humans, whether in a healthy or diseased state. The utility of tracing chemical activity through the body transcends the fields of cardiology, oncology, neurology and psychiatry. In this, PET techniques span radiochemistry and radiopharmaceutical development to instrumentation, image analysis, anatomy and modeling. PET has made substantial contributions in each of these fields by providing a venue for mapping dynamic functions of healthy and unhealthy human anatomy.

As diverse as the disciplines it bridges, PET has provided insight into an equally significant variety of psychiatric disorders. Using the unique quantitative ability of PET, researchers are now better able to non-invasively characterize normally occurring neurotransmitter interactions in the brain. With the knowledge that these interactions provide the fundamental basis for brain response, many investigators have recently focused their efforts on an examination of the communication between these chemicals in both healthy volunteers and individuals suffering from diseases classically defined as neurotransmitter specific in nature. In addition, PET can measure the biochemical dynamics of acute and sustained drug abuse. Thus, PET studies of neurotransmitter interactions enable investigators to describe a multitude of specific functional interactions in the human brain. This information can then be applied to understanding side effects that occur in response to acute and chronic drug therapy, and to designing new drugs that target multiple systems as opposed to single receptor types. Knowledge derived from PET studies can be applied to drug discovery, research and development (for review, see (Fowler *et al.*, 1999) and (Burns *et al.*, 1999)).

Here, we will cover the most substantial contributions of PET to understanding biologically distinct neurochemical systems that interact to produce a variety of behaviors and disorders. Neurotransmitters are neither static nor isolated in their distribution. In fact, it is through interactions with other neurochemically distinct systems that the central nervous system (CNS) performs its vital role in sustaining life. Exclusive quantitative capabilities intrinsic to PET make this technology a suitable experimental tool to measure not only the regional distribution of specific receptors and their subtypes, but also the dynamic properties of neuroreceptors and their inherent influence on related neurotransmitter pathways. The ability to

investigate dynamic properties in a non-invasive and reproducible manner provides a powerful tool that can extend our current knowledge of these interactions. Coupled with innovative paradigms including pharmacologic manipulations, physiologic models and reconstruction theories, knowledge derived from PET studies can greatly advance our understanding of normal and abnormal brain function.

TECHNICAL ATTRIBUTES SPECIFIC TO NEUROTRANSMITTER MAPPING WITH PET

Neurotransmitter mapping with PET is based on the principle that labeled compounds can be designed to compete with endogenous neurochemical activity at receptor sites on both pre- and post-synaptic terminals. In this, radiotracers can be targeted at a number of physiological functions, from pre-synaptic release and reuptake to post-synaptic uptake. In the midst of disease states, this information provides vital insight into the development of potential pharmacologic interventions (Ding *et al.*, 1995; Ginovart *et al.*, 1997; Frey *et al.*, 1996; Meyer *et al.*, 1999). Further, neurochemical mapping with PET can be carefully controlled, so that depending on the kinetic properties of the tracer molecule, varying degrees of competition interfere with normal neurotransmitter activity and occupy all receptor sites, or less competitively occupy only a few of the receptor sites. Several concepts are fundamental to understanding the general foundation of mapping dynamic neurochemical interactions with PET. These are the choice of a ligand and target neurotransmitter system, kinetic modeling of chosen radioligands, and specific to multi-neurotransmitter investigations, the design of a challenge paradigm. From this, we can assay the effects of pharmaceuticals on interrelated neurotransmitter systems as well as gather information about regular and irregular endogenous states.

The Ligand

The freedom implied by the ability to label a variety of compounds might lead one to raise the possibility of labeling the neurotransmitters themselves, but this is impossible for several reasons. Primarily, neurotransmitters do not cross the blood-brain barrier. Because labeled compounds must be injected or inhaled, blood-brain barrier permeability is necessary.

Second, the binding affinity of all amino acid and amine neurotransmitters to their specific receptors is low. In this, the fate of neurotransmitters themselves cannot be controlled (i.e. presynaptic reuptake or enzymatic degredation), but the action of a molecule designed to bind to a specific receptor, or ligand, can be reliably predicted depending on the kinetics of the labeled molecule. Therefore, it is necessary to use molecules that bind to the receptor under investigation with a known affinity.

The choice of a ligand should be clinically relevant, and its actions should be well documented. In this, ligands should have a known affinity for specific receptor subtypes to minimize the possibility of confounding effects or untraceable radioligand activity from promiscuous ligand delivery. Second, ligands should have a biological half-life long enough to remain in systemic circulation for the duration of the scanning period (although kinetic modeling parameters can compensate for this). Finally, it is important that ligands have a conformation that can be readily labeled while retaining blood-brain barrier permeability.

By using a competitive ligand with a high affinity, the amount of neurotransmitter bound to receptor sites will be insignificant compared with the amount of ligand bound to identical sites. Theoretically, noncompetitive ligands with moderate affinity do not interfere with endogenous neurotransmitter activity (Seeman *et al.*, 1990). Investigations that use competitive ligands identify fundamental neuroreceptor arrangement, and typically differentiate basal receptor physiology in healthy and unhealthy psychiatric conditions. For example, the high affinity D_2 receptor radiotracer ^{11}C-N-methylspiroperidol (^{11}C-NMSP) demonstrated a two- to three-fold increase in ligand competition in schizophrenic patients when compared to normal controls (Wong *et al.*, 1986), while the noncompetitive D_2 radiotracer ^{11}C-raclopride demonstrated no change in competition between schizophrenic patients and controls (Farde *et al.*, 1987). A later discovery was that endogenous dopamine (DA) released into the synapse competes with ^{11}C-raclopride for D_2 receptor binding sites (Seeman *et al.*, 1990), whereas ^{11}C-NMSP is less sensitive to the influence of endogenous dopamine (Logan *et al.*, 1992) and possibly a more effective tool for measuring receptor physiology. Further, while Farde *et al.*, demonstrated no change in the binding characteristics of ^{11}C-raclopride between schizophrenic patients and normal controls, Breier et al. (1997) recently demonstrated amphetamine-induced increases in dopamine release produce less ^{11}C-raclopride binding in schizophrenic patients when compared to healthy controls given the same challenge (Breier *et al.*, 1997). Together,

these studies support the existence of similar endogenous dopamine activity between schizophrenic patients and controls, while demonstrating substantially different responses to a challenge of the dopamine system. In this, measurement of dynamic neurotransmitter activity may be more informative about the plasticity of neurochemical activity in the brain than about a single physiological trait like receptor concentration.

Kinetic Modeling

The scientific progression from investigations of static neuroreceptor concentration to dynamic neurotransmitter activity also instigated marked innovations in the methods by which we process and statistically manipulate data from PET cameras. Specifically, the initial receptor mapping studies by Wong (Wong *et al.*, 1986) and Farde (Farde *et al.*, 1987) used the same radioactive label on two compounds with different pharmacokinetic properties. ^{11}C-raclopride, used by Farde *et al.*, reaches equilibrium during the time of the scan and allows the quantification of binding parameters via a Scatchard plot. ^{11}C-NMSP, however, does not reach equilibrium within the period of the scan and requires kinetic modeling (Tune *et al.*, 1993). It is now possible to estimate changes in endogenous dopamine following a pharmacologic challenge in each PET study with a mathematical approach (for example, see (Dewey *et al.*, 1992a)). Since extracting absolute measures of neurotransmitter concentrations requires knowledge of both receptor concentration (B_{max}) and the *in vivo* receptor-ligand dissociation constant, k_d, and estimations of B_{max} are crude and difficult to measure (Logan *et al.*, 1997), results from most dynamic PET studies are expressed as relative change between baseline (radiotracer alone) and challenge scans (i.e. pretreatment + challenge drug + radiotracer). Studies in our laboratory were designed to examine changes in receptor availability by determining parameters that are linearly related to free receptors, rather than the actual number of free receptors targeted by conventional neuroreceptor investigations.

For noncompetitive, moderate affinity radiotracers, two such modeling parameters are the distribution volume (DV) and B_{max}/K_d. The distribution volume is a graphical method of analysis applied to ligands that bind reversibly to receptors or enzymes. A method for determining DV was developed for the kinetic analysis of ^{11}C-cocaine data and has been applied to the analysis of ^{11}C-benztropine and ^{11}C-raclopride data used in our investigations of neurotransmitter activity (Logan *et al.*, 1990); (Dewey *et al.*, 1990c). Alternatively, the DV can

also be calculated from the kinetic parameters determined from a non-linear least squares fit of the data using a compartmental model. For a three compartment model, the steady state DV (K_R) is given by $K_1/k_2(1+k_3/k_4)$. For a two compartment model, the ratio K_R is expressed by K_1/k_2. For the analysis of ^{11}C-cocaine data, kinetic parameters determined using the graphical technique are consistent with estimates from a nonlinear least squares method. In addition, the ratio B_{max}/K_d is similar to that found *in vitro* (Logan *et al.*, 1990).

One of the advantages of applying the DV approach is that it represents a linear function of free receptor concentration and does not depend on blood flow, since the variables containing blood flow cancel in the ratio K_1/k_2. Specifically, if we calculate the ratio of the DV for a region containing few or no target receptors to the DV for a receptor-rich region, the K_1/k_2 ratio can be eliminated, giving a parameter more closely related to B_{max}/K_d. As a validation of the DV ratio approach, Koeppe *et al.*, (Koeppe *et al.*, 1991) established that focal alterations in blood flow produced by visual stimulation coincided with a 21% increase in ligand delivery (K_1) to the visual cortex. In this investigation, the DV for ^{11}C-flumazenil in the visual cortex or other regions was unaltered, supporting the insensitivity of the DV parameter to focal alterations in blood flow. The DV parameter is also easily computed and less sensitive to noise than the individual kinetic parameters, which often have large standard errors associated with their determination. This technique is conceptually similar to the two-compartment model approach used by Frey *et al.*, (Frey *et al.*, 1990) to study muscarinic receptors with ^{11}C-tropanyl benzilate and by Koeppe *et al.*, (Koeppe *et al.*, 1991) to study benzodiazepine receptors with ^{11}C-flumazenil. In sum, our investigations estimate the free concentration of tracer in tissue and the concentration of nonspecifically bound tracer from a reference region of the brain that contains few or no target receptors. For ^{11}C-raclopride and ^{11}C-benztropine, the cerebellum provides a reference region containing few or no dopamine or cholinergic terminals or receptors, so ligands for these receptors distribute only to the compartments of free ligand and nonspecifically bound ligand. Data from PET studies reported here is expressed as the percentage change relative to the baseline DV ratio of radiotracer binding.

NEUROTRANSMITTER INTERACTIONS MEASURED WITH PET

Neurodevelopmental models support the involvement of large numbers of discrete neurons involved in adaptive plasticity, and contend that these processes underlie psychopathology (Olney and Farber, 1995). It is also likely, however, that many diverse neurotransmitter systems contribute to maintain a certain level of homeostasis. Whether a healthy or unhealthy state, there remains a dynamic interplay between endogenous systems to sustain the organism.

Noncompetitive receptor ligands have been established as successful markers of endogenous neurotransmitter activity, and are sensitive to pharmacologic challenges that either increase or decrease synaptic concentrations of the target neurotransmitter. Our laboratory and others have taken this paradigm one step further to explore the functional interactions between isolated neurotransmitter systems. To do this, we measured the acute response of one neurotransmitter system to a challenge targeting a discrete, related system. Prior to evaluating the feasibility of PET as an accurate measure of simultaneous neurotransmitter interactions, it was essential to select for study a well-defined neurotransmitter system whose function is dependent on interactions between at least two chemically different neurotransmitter systems. Furthermore, the target system should be particularly sensitive to alterations in either of these endogenous neurotransmitters and their site of interaction must be localized to neurochemical factors that are within the resolution of the machine itself. Within the confines of these requirements, the extra-pyramidal motor system provides a multi-neurotransmitter region within the window of PET resolution.

Interconnections of the extra-pyramidal motor system have been extensively documented in animal and human postmortem studies using a wide variety of neuroanatomical, neurophysiological and behavioral methods. The principle components of this system involve interactions between acetylcholine, dopamine, gamma aminobutyric acid (GABA) and serotonin. Disruptions in any single component of this system present a discrete clinical picture. For example, therapeutically relevant blockade of dopamine D_2 receptors produces movement disorders, which can be alleviated by decreasing cholinergic activity. Studies using a variety of methods have demonstrated that these neurochemical systems interact in the corpus striatum through reciprocal inhibitory and excitatory connections with the substantia nigra and medial raphe nucleus (Arnfred and Randrup, 1968; Bloom *et al.*, 1965; Costall and Olley, 1971; Ehlert *et al.*, 1981; Lehmann and Langer, 1982). The corpus striatum, consisting of the caudate nucleus

and putamen, is well within the resolution of modern PET scanners and contains a large number of dopamine D_2 and cholinergic muscarinic receptors. While each of these neurotransmitters is involved in maintaining the necessary input required for the normal day-to- day operation of the extra-pyramidal motor system, each has been implicated in other physiological roles that may or may not be directly linked to the neuronal systems mentioned above. These other roles may contribute to disease states of the CNS and/or conditions that predispose or maintain drug addiction.

Modulation of dopaminergic activity studied with ^{11}C-raclopride and ^{18}F-NMSP

The interpretation of neurotransmitter interaction studies is dependent on the ability of each radiotracer to demonstrate receptor specific binding and reproducibility, and also on the ability of each radiotracer to reflect fluctuations in receptor availability secondary to drug-induced changes in endogenous neurotransmitter activity. Therefore, in a series of PET studies, we utilized a multi-mechanistic approach to investigate the effects of increases in endogenous dopamine on the binding of ^{11}C-raclopride. Using *d*-amphetamine and GBR-12909, drugs that alter synaptic dopamine concentrations by different mechanisms, we addressed the question of whether ^{11}C-raclopride binding is sensitive to changes in endogenous dopamine. In the first set of studies, we used *d*-amphetamine to increase synaptic dopamine levels by releasing cytostolic stores into the synapse. Following *d*-amphetamine administration, the ratio of striatal to cerebellar DV for ^{11}C-raclopride decreased by an average of 16%. Parallel studies using *in vivo* microdialysis techniques in freely moving rats demonstrate *d*-amphetamine significantly increases extracellular striatal DA release. GBR-12909, a potent dopamine reuptake inhibitor, decreased the same ratio by an average of 22%. Again, this investigation was confirmed by microdialysis studies indicating an increase in extracellular dopamine release following GBR-12909 pretreatment (Dewey *et al.*, 1993b). Together, these studies demonstrated that our system was capable of measuring changes in synaptic dopamine concentrations, and prompted the utility of this strategy to quantify changes in dopamine activity secondary to pharmacologic modulation of related, upstream neurotransmitter systems. For a summary of each investigation and the result, please see Table 1.

Cholinergic modulation of dopamine

Initially, our investigations of dynamic neurochemical interactions measured with PET looked at the cholinergic/dopaminergic system, with the outcome measure being changes in endogenous dopamine activity. The cholinergic system has demonstrated an essential role in many memory and cognitive functions (Davies and Verth, 1977; Meltzer and Stahl, 1976). Some studies have hypothesized that cholinergic hyperactivity may underlie the negative symptoms associated with schizophrenic illnesses as well (Tandon and Greden, 1989). The highest levels of choline acetyltransferase and cholinergic receptors in the human CNS are found in the striatum and the majority of cholinergic cells are interneurons (Cortes *et al.*, 1987; Fibiger, 1982). These cholinergic interneurons provide excitatory input to local GABA neurons, which in turn are thought to inhibit the activity of dopaminergic neurons (Bunney and Aghajanian, 1976).

Our initial primate investigations demonstrated the binding of ^{18}F-NMSP was reduced by 13% after the animals received an injection of benztropine (an anticholinergic agent) when compared to control animals receiving no benztropine (Dewey *et al.*, 1990a). This result was confirmed in human subjects where the uptake of ^{18}F-NMSP in the striatum was reduced by an average of 10% after benztropine pretreatment (Dewey *et al.*, 1988)[1]. In a related study, we used ^{11}C-raclopride as the radiotracer and scopolamine as the cholinergic challenge drug, as it has a more selective mechanism of action than benztropine. Human subjects treated with scopolamine demonstrated a decrease in striatal ^{11}C-raclopride binding of 17%, indicating greater increases in endogenous dopamine competition after scopolamine when compared to benztropine (Dewey *et al.*, 1993c).

In sum, decreased brain acetylcholine levels secondary to benztropine or scopolamine treatment appear to increase brain dopamine, indicated by decreased ^{18}F-NMSP binding.

These data are consistent with the aforementioned model of a multisynaptic feedback loop linking cholinergic neurons indirectly to dopaminergic neurons via GABAergic interneurons (Bunney and Aghajanian, 1976). By decreasing cholinergic activity, benztropine inhibits the excitatory input to GABAergic neurons, reducing GABAergic inhibition of dopaminergic neurons. Subsequent disinhibition of dopaminergic neurons produces a higher level of synaptic dopamine release, and increased competition with ^{11}C-raclopride at

postsynaptic D_2 receptors. These studies demonstrate that in some circumstances, acetylcholine regulates brain dopamine release.

Serotonergic modulation of dopamine

Further studies investigating the modulation of dopaminergic systems focused on the possible modulation of dopamine by serotonin, as interactions between these systems have been well documented. Functionally, serotonin has been implicated in sleep, aggression, pain transmission, Alzheimer's disease, normal aging, affective disorders and suicide (Wesemann *et al.*, 1983; Stanley and Mann, 1984; Pucilowski and Kostowski, 1983; Bowen *et al.*, 1983; Crow *et al.*, 1984; Middlemiss *et al.*, 1986; Reynolds *et al.*, 1984). In addition, the greater affinity of several atypical neuroleptics, non-benzodiazepine anxiolitics and new antidepressant agents (e.g., selective serotonin reuptake inhibitors, SSRIs) for cortical serotonin receptors has been linked to their therapeutic efficacy. Electrophysiological, biochemical and behavioral evidence indicates ascending serotonergic pathways from the medial and dorsal raphe modulate the function of mesolimbic and mesostriatal dopamine systems (Joyce *et al.*, 1993; Joyce, 1993; Zazpe *et al.*, 1994); (Kapur and Remington, 1996). Our initial primate studies used the 5-HT_2 receptor antagonist altanserin as a pretreatment drug found that ^{11}C-raclopride binding was reduced by 37% in the striatum (Dewey *et al.*, 1995), indicating diminished 5-HT activity actually stimulated dopamine release. In the same study, increasing 5-HT activity with citalopram (SSRI) decreased synaptic dopamine levels and increased striatal ^{11}C-raclopride binding. These studies were later confirmed by Tsukada *et al.*, who decreased 5-HT with ketanserine (similar to altanserin) and found decreased ^{11}C-raclopride binding in the striatum, consistent with increased dopamine release (Tsukada *et al.*, 1999).

By decreasing serotonergic activity with altanserin, we quantified secondary increases in brain dopamine by measuring decreases in ^{11}C-raclopride binding (indicating increased competition from endogenous dopamine). Next, we increased serotonergic activity with citalopram administration and demonstrated decreases in endogenous dopamine release with increased ^{11}C-raclopride binding.

In an attempt to extend this finding to human subjects, we used fenfluramine, a selective 5-HT reuptake inhibitor and releasing agent, to increase serotonergic activity (Smith *et al.*, 1997). Our results, contrary to our previous findings in baboons, indicated that increasing 5-HT

activity *increased* DA activity, as evidenced by a 13% decrease in ^{11}C-raclopride binding. These results are consistent with more recent studies indicating chronic (Tiihonen *et al.*, 1996) or acute (Vollenweider *et al.*, 1999) increases in serotonergic transmission produced increases in synaptic dopamine concentrations, as evidenced by PET and ^{11}C-raclopride binding. The difference between our primate and human results may be due to the broad serotonergic effect of fenfluramine versus altanserin, the effects of anesthesia on the baboon, or species-specific effects.

Increasing serotonergic activity with fenfluramine produced subsequent increases in serotonergic activity measured by decreased ^{11}C-raclopride binding.

GABAergic modulation of dopamine

We have also used the pharmacological challenge paradigm with PET to study the GABA/dopamine interaction. The finding that GABA functions as the most common inhibitory neurotransmitter in the CNS resulted in its implication, either directly or indirectly, in the pathogenesis of several neurodegenerative conditions. These conditions include Huntington's and Parkinson's Disease, epilepsy, schizophrenia and tardive dyskinesias. In addition, studies have shown that GABAergic activity modulates central neurotransmitter systems targeted by drugs of addiction (DeFeudis, 1984; Koob, 2000; Dewey *et al.*, 1998). Thus, numerous PET studies have been aimed at the study of GABAergic systems and their contributions to disease and addictive states. There are several inherent difficulties in perturbing the GABA receptor complex, including the controversy over the GABA receptor subtypes and their functional role in the striatum. The availability of specific GABA receptor agonists or antagonists that reliably affect central GABA levels without producing profound disruptions in CNS function has also been a concern. The administration of gamma-vinyl GABA (GVG, vigabatrin), a suicide inhibitor of the GABA catabolizing enzyme GABA transaminase, has been used to successfully enhance GABAergic neurotransmission through increased brain GABA levels. This compound is used clinically to treat epilepsy, and it has been shown to reliably elevate endogenous GABA levels after systemic administration without affecting other amino acid transmitters.

According to the multisynaptic feedback loop described, we would expect an inhibitory influence of GABA on the activity of dopaminergic neurons and hence an increase in ^{11}C-raclopride binding. To test this, ^{11}C-raclopride in baboons was imaged prior to and following the

administration of GVG (Dewey *et al.*, 1992a). The result was an average increase of 25% in ^{11}C-raclopride binding, indicating significantly depressed synaptic DA activity. In the second part of the study, lorazepam, a clinically prescribed benzodiazepine administered intravenously prior to the scan, led to an average increase of 22% in striatal ^{11}C-raclopride binding. This PET study provided evidence that dopaminergic neurons of the substantia nigra and the ventral tegmental area are responsive to pharmacological alterations in GABA activity. Interestingly, a similar investigation by Hietala *et al.*, (Hietala *et al.*, 1997) found weeklong pretreatment with lorazepam had no effect on striatal ^{11}C-raclopride binding in human patients, but acute lorazepam increased ^{11}C-raclopride binding in primates.

In sum, increasing whole brain GABA levels with vigabatrin produced subsequent decreases in dopamine release, as measured by increases in ^{11}C-raclopride binding.

GABAergic modulation of dopamine in substance abuse

We have also used ^{11}C-raclopride binding and PET to explore the inhibitory potential of GVG on the brain response to substances of abuse. The rewarding effects of psychostimulants have been associated with their ability to increase striatal dopamine levels (Volkow *et al.*, 1999). The system of primary interest in these conditions involves the mesocorticolimbic dopaminergic projections from the ventral tegmental area (VTA) and substantia nigra into the ventral striatum, medial prefrontal cortex, and amygdala, which participate in the neural processing of motivated behavior (Robbins *et al.*, 1989). Alterations in this system are thus hypothesized to play roles in mediating the euphoria and behavioral reinforcement associated with drugs of abuse (for review, see (McBride *et al.*, 1999)). Specifically, the nucleus accumbens (NAcc) has demonstrated the greatest sensitivity to changes induced by drugs that inhibit dopamine reuptake, stimulate dopamine release, or increase dopamine through neurotransmitter system interactions. This evidence is derived from microdialysis studies in rats showing higher extracellular fluid dopamine concentrations after administration of psychostimulants (Di Chiara *et al.*, 1993; Di Chiara *et al.*, 1992).[2] In our extensive PET studies utilizing the strategy of increasing GABAergic activity with GVG as a mechanism for preventing psychostimulant induced dopamine release, we correlate striatal ^{11}C-raclopride binding in primates with microdialysis investigations of NAcc dopamine release in rodents. This allows us to better relate the neural responses from various drug challenges with the many available rodent models of substance

abuse (craving, reward and reinforcement), as well as assess the temporal window for pretreatment strategies.

Our initial studies in the substance abuse arena demonstrated that GVG restores striatal ^{11}C-raclopride binding to normal levels following acute cocaine administration in baboons (Dewey *et al.*, 1997). In other words, while a cocaine challenge diminished ^{11}C-raclopride binding, pretreatment with GVG before cocaine produced a degree of ^{11}C-raclopride binding undistinguishable from animals given ^{11}C-raclopride alone. In further support of this strategy, GVG effectively modulated basal reward thresholds produced by cocaine administration (Kushner *et al.*, 1997), abolished the conditioned place preference produced by cocaine (Dewey *et al.*, 1998), and reduced self-administration of cocaine (Kushner *et al.*, 1999) and heroin (Xi and Stein, 2000) in rodents. Additionally, we have demonstrated that increasing GABAergic activity with GVG can modulate decreases in ^{11}C-raclopride binding produced by nicotine and heroin (Dewey *et al.*, 1999; Gerasimov *et al.*, 1999), consistent with microdialysis studies (Gerasimov *et al.*, 1999).

To further investigate the specific properties of GVG that contribute to its efficacy as a potential anti-addictive agent, as well as to justify the ability of ^{11}C-raclopride to detect changes induced by multiple pharmacologic manipulations, we administered the pure enantiomers of the racemic compound before an acute nicotine challenge (Schiffer *et al.*, 2000). Our previous investigations demonstrating increases in striatal dopamine concentrations after nicotine administration served as the basis for this investigation. Where nicotine diminished ^{11}C-raclopride binding by ~12%, pretreatment with (R,S)-GVG and active S(+)-GVG increased ^{11}C-raclopride binding 9 and 8%, respectively. Figure 1 presents the radioactivity distribution of ^{11}C-raclopride (red). Here, it is clear that nicotine diminishes D_2 receptor occupancy (a), in that there is visibly diminished ^{11}C-raclopride binding. Pretreatment with S(+)-GVG prevents nicotine-induced dopamine release (b) and restores receptor occupancy to near test/retest values, demonstrated by increased ^{11}C-raclopride binding. Additionally, pretreatment with the inactive R(-)-GVG decreased ^{11}C-raclopride binding after a nicotine challenge by ~13%. These results support studies indicating that, as an anticonvulsant, the active S(+) enantiomer also retains the pharmacologic efficacy of GVG. Our microdialysis data corroborate our PET studies in that S(+)-GVG was as effective as the racemic compound at decreasing the extracellular NAcc dopamine response to cocaine in rodents.

GABAergic modulation of dopamine in schizophrenia

The clinical potential of enhanced GABA transmission described above is most likely attributable to decreases in dopaminergic activity, believed to be a common denominator in many schizophrenic psychoses (Wassef *et al.*, 1999). The effects of enhanced GABA function on dopaminergic pathways in the human brain are of particular interest for studies on biological factors in schizophrenia. These studies have formulated a GABA hypofunction hypothesis of schizophrenia, which postulates a deficient GABAergic inhibition in schizophrenia and subsequent alterations in other neurotransmitter systems, including DA hyperactivity in the brain (Keverne, 1999; Egan and Weinberger, 1997; Weinberger, 1997).

To further explore this latter hypothesis, we administered the NMDA antagonist phencyclidine (PCP) to primates and measured ^{11}C-raclopride binding with PCP alone and in the presence of increased GABAergic activity with GVG. The NMDA antagonist model of schizophrenia has surpassed previous dopaminergic theories in both clinical and basic science investigations (Javitt and Zukin, 1991). Administration of NMDA antagonists produces symptoms in healthy controls that closely mimic those found in schizophrenic patients (Krystal *et al.*, 1994). Further, when stable schizophrenic patients are given ketamine, an NMDA antagonist and PCP analog, their symptoms are exacerbated and they experience similar clinical manifestations to their pre-medicated state (Lahti *et al.*, 1995b; Lahti *et al.*, 1995a). We recently demonstrated the sensitivity of ^{11}C-raclopride binding to changes in human brain activity induced by ketamine (Smith *et al.*, 1998), while simultaneously collecting clinical measures of psychosis. Our results indicated that acute administration of ketamine decreased ^{11}C-raclopride binding, thus increasing synaptic dopamine activity while concurrently producing psychosis. Our investigation, and the strategy of using ^{11}C-raclopride binding to measure glutamatergic induced changes in striatal dopamine, was later supported by Breier *et al.*, who found decreased ^{11}C-raclopride binding in healthy subjects after ketamine administration (Breier *et al.*, 1998).

Figure 2 indicates the time activity of basal receptor occupancy by ^{11}C-raclopride and subsequent receptor occupancy after 1.0 mg/kg PCP in both the striatum and cerebellum. It is clear by the difference in striatal receptor occupancy (circles), that PCP administration diminishes ^{11}C-raclopride binding compared to baseline, indicative of increased competition by synaptic dopamine release secondary to PCP. Additionally, the difference in cerebellar D_2

occupancy between pre- and post challenge is clearly minimal (triangles), justifying its use as a reference region in kinetic models.

We have since taken this strategy one step further and demonstrated that decreased ^{11}C-raclopride binding subsequent to NMDA-antagonist administration can be successfully modulated with GABAergic pretreatment. In other words, increased dopaminergic activity by PCP administration was diminished by pretreatment with GVG, as evidenced by restoration of ^{11}C-raclopride binding to levels similar to the test/retest group (Schiffer *et al.*, submitted). Table 3 provides the change in mean distribution volume ratio (DVR) from the baseline scan (^{11}C-raclopride alone) and the post-challenge scan (^{11}C-raclopride in the presence of treatment paradigms) indicated. Lower numbers indicate less ^{11}C-raclopride binding and higher endogenous dopamine receptor occupancy, while higher numbers indicate more ^{11}C-raclopride binding as a result of less competition from synaptic dopamine. Further, changes in striatal dopamine for one primate given PCP Alone and one given GVG prior to PCP pretreatment are presented in Figure 3. Here, it is clear that there is less ^{11}C-raclopride binding in the primate given PCP, whereas in the animal pretreated with GVG, ^{11}C-raclopride binding in the second scan is very similar to baseline.

This investigation demonstrated that it is possible to modulate glutamate-induced increases in dopamine with increased inhibitory GABA levels, and that this pharmacologic interaction can be measured with ^{11}C-raclopride binding and PET. This study is supported by our dialysis investigations employing a similar paradigm by measuring changes in extracellular dopamine release after GVG pretreatment and a PCP challenge (Schiffer *et al.*, submitted). Together, these investigations support the utility of GVG, in combination with neuroleptics, as a possible therapeutic treatment for schizophrenic psychoses. It has been demonstrated that GVG successfully ameliorates many of the extra-pyramidal side effects secondary to chronic neuroleptic treatment (Korsgaard *et al.*, 1983; Thaker *et al.*, 1983). Additionally, it has been demonstrated that patients receiving long-term neuroleptic therapy are more vulnerable to psychostimulant abuse (Roberts and Vickers, 1984; Roberts and Vickers, 1987; Brady *et al.*, 1990), so the anti-addictive properties of GVG demonstrated here might prove additionally therapeutic in schizophrenic populations. Finally, combining GVG with neuroleptic therapy might enable clinicians to diminish the dose of both drugs necessary for therapeutic efficacy (Wassef *et al.*, 1999).

Modulation of cholinergic activity studied with ^{11}C-benztropine

The function of the cholinergic system and its modulation by other systems may be critical to the pathophysiology of Alzheimer's disease and schizophrenia, and may provide insight into the manifestation of extrapyramidal side effects produced by antipsychotic treatment. An example of a relevant application of this approach is to study Alzheimer's disease. Alzheimer's disease has classically been characterized by a cortical cholinergic deficit (Bartus *et al.*, 1982). The majority of drug trials have used therapeutic agents (e.g., cholinergic agonists and cholinesterase inhibitors) that were designed to directly reverse this deficiency. With few exceptions, these drugs have not been efficacious.

Further, a model for schizophrenia has been proposed that hinges on cholinergic/dopaminergic interactions. In this model, cholinergic hyperactivity is postulated as an adaptive response to presumed dopaminergic hyperactivity and is considered to be responsible for the negative symptoms of schizophrenia (Tandon and Greden, 1989). More recent investigations support the involvement of muscarinic receptors specifically, in the pathogenesis of schizophrenia (Crook *et al.*, 2000). It has been difficult to tease out the contributions of the disease mechanism itself, or of the effects of neuroleptic medications on schizophrenic pathology. Side effects associated with neuroleptic treatment (tardive dyskenesia) are alleviated by treatment with anticholinergic drugs (Lewis, 1998). These investigations provided the clinical impetus for investigating the cholinergic system over other neurotransmitter systems.

Prior to addressing the usefulness of PET for investigating intrinsic interactions between ACh and DA, it was essential to develop a radiotracer specific for the cholinergic receptor. We chose benztropine for several reasons. First, it is a clinically prescribed synthetic anticholinergic drug frequently used in conjunction with neuroleptic medication in humans. Benztropine rapidly alleviates the extrapyramidal side effects commonly associated with dopaminergic D_2 receptor blockade. Secondly, benztropine has a long biological half-life, which suggested it remained intact in the systemic circulation. Thirdly, it could be radiolabeled with carbon-11 in high specific activity (0.75 - 2.0 Ci/μmol). Recently, the ligands ^{11}C-tropanyl benzilate and ^{11}C-N-methyl-4-piperidyl benzilate have been developed as radiotracers for the muscarinic receptor (Mulholland *et al.*, 1992; Koeppe *et al.*, 1992; Lee *et al.*, 1991). The primary advantages of ^{11}C-benztropine over other muscarinic cholinergic ligands is that pharmacologic doses can be

administered to humans, so that the extent of specific binding in the PET data, using the unlabeled compound, can be determined. Additionally, striatal DV values obtained with these other radiotracers (^{11}C-tropanyl benzilate and ^{11}C-N-methyl-4-piperidyl benzilate) are consistent with our ^{11}C-benztropine results. It is important to note that benztropine has been shown to inhibit DA reuptake in the corpus striatum *in vitro* (Coyle and Snyder, 1969). In order to determine which component of the PET image of labeled benztropine was due to binding to the DA transporter, we pretreated animals with nomifensine (2.0 mg/kg), a potent DA transport blocker (Dewey *et al.*, 1990b). Incorporation of labeled benztropine was not altered in any brain structure examined following nomifensine pretreatment. Subsequent studies were performed with ^{11}C-benztropine and GBR-12909 and ^{11}C-benztropine and cocaine in order to examine whether or not labeled benztropine was binding to the DA transporter in the striatum of the baboon brain. GBR-12909 was chosen as we have demonstrated that it decreases the striatal binding of labeled raclopride presumably due to its binding to the DA transporter. Cocaine was chosen for similar reasons. Systemic administration of either GBR-12909 or cocaine did not alter the binding of labeled benztropine in any brain region examined. These studies are consistent with the nomifensine data. Finally, unlabeled benztropine did not alter ^{11}C-cocaine binding. It appears that the binding of ^{11}C-benztropine to the DA transporter does not make a significant contribution to the PET image (Dewey *et al.*, 1990b).

Cholinergic cells in the striatum only represent a small population of striatal neurons, but are able to modulate the excitability in this brain region due to their widespread axonal fields and high sensitivity to related neurotransmitter systems (Kincaid *et al.*, 1998). Studies investigating *in vivo* and in vitro acetylcholine release have demonstrated that dopamine controls cholinergic transmission in a facilitory manner both directly and indirectly (Damsma *et al.*, 1990). For a review of our studies with the cholinergic ligand, ^{11}C-benztropine, please see Table 2.

Dopaminergic modulation of acetylcholine

Our initial studies of the cholinergic system as the outcome measure for choline/dopamine interactions explored the effects of decreased dopaminergic activity on ^{11}C-benztropine binding. We first studied the effect of a dopamine antagonist on the binding of the ^{11}C-benztropine in the baboon (Dewey *et al.*, 1990a). Pretreatment with unlabeled NMSP, a potent dopaminergic antagonist, reduced ^{11}C-benztropine binding in all brain regions, with the

effects in the corpus striatum being greater than the cortex and thalamus, and very little binding found in the cerebellum.

Our data are consistent with a physiology where cholinergic interneurons are disinhibited from blockade of D_2 afferents (Bymaster *et al.*, 1986), producing increased acetylcholine release and subsequently decreased ^{11}C-benztropine binding.

Here, we demonstrated decreasing dopaminergic activity with NMSP produced subsequent increases in acetylcholine levels, indexed by decreases in ^{11}C-benztropine binding (Table 2).

Serotonergic modulation of acetylcholine

The modulatory role of serotonin on acetylcholine activity has been extensively documented (Giovannini *et al.*, 1998)), and more recent theories propose serotonin stimulates acetylcholine release through increased dopaminergic activity in animals, consistent with our primate investigations (Ramirez *et al.*, 1997). The dorsal and median raphe nuclei are the major sources of 5-HT in the CNS. 5-HT_2 receptors have been localized to cortical cholinergic nerve terminals as revealed by the loss of these receptors secondary to lesions of the nucleus basalis of Meynert (Quirion and Richard, 1985). Serotonergic enervation to the striatum is derived from the dorsal and medial raphe nuclei, which project to the striatum, pallidum, and substantia nigra (mainly the pars compacta). Serotonin has been shown to inhibit striatal ACh release (Euvrard *et al.*, 1977); (Guyenet *et al.*, 1977) and depletion of endogenous 5-HT increased the release of striatal ACh (Visi *et al.*, 1981). Gillet and coworkers (Gillet *et al.*, 1985) demonstrated that exogenously administered 5-HT, 5-HT agonists, or fluoxetine, an inhibitor of 5-HT uptake, reduced striatal ACh release, whereas methylsergide, a 5-HT agonist, increased ACh efflux in the caudal striatum (Jackson *et al.*, 1988). However, Robinson (Robinson, 1983) found no effect of 5-HT on striatal ACh levels but instead reported an inhibition of Ach in cortex and hippocampus.

We examined the modulation of acetylcholine by serotonin by measuring the effect of the serotonin antagonist altanserin on the binding of ^{11}C-benztropine in primates (Dewey *et al.*, 1993a). Decreasing serotonin activity with altanserin led to a decrease of striatal benztropine binding of ~30%; which is consistent with profound regional increases in acetylcholine release.

These results confirm data from other studies indicating serotonin exerts a predominantly inhibitory influence on cholinergic interneurons in the rat striatum (Visi *et al.*, 1981).

In sum, decreasing serotonin activity with altanserin produced increases in synaptic acetylcholine levels, measured by decreases in ^{11}C-benztropine binding.

GABAergic modulation of acetylcholine

Due to the large inhibitory capacity of the GABA system, many investigations have focused on the effects of GABAergic agents on acetylcholine release. The ventral pallidum receives direct input from ventral striatal regions that contain a large number of GABAergic interneurons (Heimer and Wilson, 1975). It is unresolved, however, whether this GABAergic input originates from these striatal GABAergic neurons or whether it arises from axons of other projection or GABAergic interneurons. Unlike the findings reported with 5-HT, studies with GABA and GABA mimetic drugs such as muscimol and SL 76 002 have demonstrated the ability to increase striatal ACh content, the largest of which was observed in the rat striatum with smaller effects in the cortex, nucleus accumbens, olfactory tubercle, hippocampus, interpendicular nucleus, hypothalamus and brainstem (Scatton and Bartholini, 1980). GABAergic neuronal terminals make contact not only with cholinergic neurons (DeBoer and Westerink, 1994), but also with glutamatergic (Moratalla and Bowery, 1991) and dopaminergic neurons in the striatum (Bowery *et al.*, 1990). Furthermore, striatal cholinergic neurons are regulated by glutamatergic and dopaminergic neurons, which are thought to form synapses on cholinergic neurons. It is thought that striatal GABAergic inhibition of dopaminergic or glutamatergic activity relieves the tonic inhibition or excitation of cholinergic neurons (Ikarashi *et al.*, 1998; Moratalla and Bowery, 1991). A recent microdialysis study demonstrated that the GABAergic system appears to inhibit tonically the output of striatal acetylcholine via $GABA_A$ receptors, but not via $GABA_B$ receptors (DeBoer and Westerink, 1994). GVG provides an ideal mechanism for measuring the effects of increased endogenous GABA activity on the cholinergic system, as its effects are not mediated through any specific receptor system.

Investigating the effects of GVG on the regional binding of ^{11}C-benztropine in the primate brain produced interesting results that supported the utility of PET as a measure of *in vivo* neurotransmitter activity (Dewey *et al.*, 1993a). GVG produced a regionally specific decrease in ^{11}C-benztropine binding. Striatal binding decreased 47% and cortical binding

decreased 28%, but no changes in either thalamic or cerebellar uptake were observed. These regional and quantitative changes are consistent with the aforementioned excitatory role of GABA in striatal and cortical acetylcholine release (Scatton and Bartholini, 1980).

Taken with our previous work using ^{11}C-raclopride and GVG (Dewey *et al.*, 1992b), this study represents the first demonstration with PET that a single drug (GVG), within the same time frame, can produce opposite effects in different neurotransmitter systems within the same animal. Specifically, GVG administration increased ^{11}C-raclopride binding and decreased ^{11}C-benztropine binding.

Increasing GABA activity with vigabatrin produced subsequent increases in cholinergic activity, measured by decreases in ^{11}C-benztropine binding.

SUMMARY

These data support the use of PET not only to monitor changes in synaptic neurotransmitter concentrations, but also to assessing the multiple mechanisms of action of new and potentially useful centrally acting therapeutic drugs. These findings have implications for the pathophysiology and pharmacotherapy of disease states that have classically been defined as neurotransmitter specific in origin. Specifically, we can use this application of PET as a tool to determine whether the ability of a neurotransmitter to modulate the activity of another functionally linked neurotransmitter is involved in the disease process. By capitalizing on our knowledge concerning neurotransmitter interactions, this would have direct implications for treatment in that therapeutic efficacy could be achieved indirectly, rather than directly, altering neurotransmitter activity. Potential treatments could be developed for cholinergic, dopaminergic and serotonergic defect states. Furthermore, this information may be used to predict the potential side effects of pharmacologic treatment in psychiatric disorders.

Combined with an exhaustive literature supporting the fundamental principle that neurotransmitters interact in both functionally-specific and regionally specific neuroanatomical foci, it is becoming increasingly clear that new treatment strategies for brain disorders (including addictions to cocaine, nicotine, heroin, and methamphetamine) should be developed with a more global awareness of this fundamental and well-documented principle. While changes in individual neurotransmitter concentrations may indeed underlie the etiology of a specific disorder, it is likely that disease progression and symptom development are linked to

compensatory or disease-induced changes in other neurotransmitters functionally linked to the original target. With this knowledge, we have been developing novel treatment strategies specifically designed to alter one or more neurotransmitters by targeting another. Our findings with nicotine, cocaine, methamphetamine, alcohol and GVG represent the potential utility of such a fundamental approach.

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FOOTNOTES

[1] Given a five-fold higher affinity than ^{11}C-raclopride, our laboratory demonstrated *in vivo* sensitivity of ^{18}F-NMSP to dopamine in PET studies performed following *d*-amphetamine administration. These studies demonstrated that *in vivo* pharmacokinetic effects such as tissue clearance play an important role in radioligand sensitivity of high affinity radioligands to endogenous DA concentrations (Dewey *et al.*, 1991; Logan *et al.*, 1991).

[2] In primates, the accumbens cells blend with those of the anteroventral putamen and the ventral caudate, so that a distinct border of the accumbens is not evident (Heimer *et al.*, 1991). Recently, Drevets et al, have demonstrated that any potential bias effects due to resolution of PET cameras was significantly smaller than the magnitude of the observed changes in ^{11}C-raclopride binding after amphetamine administration, supporting the correlation between microdialysis studies of psychostimulant activity in the NAcc and PET studies of psychostimulants in primates (Drevets *et al.*, 1999).

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Table 1. Effects of neurotransmitter-specific pharmacological challenges on dopaminergic activity measured with PET

Neurotransmitter System	Radioligand	Drug Challenge	Challenge Effect	Radioligand Response	Dopamine Activity
Dopamine	^{11}C-raclopride	cocaine, amphetamine	⇧ DA	⇩	⇧
Acetylcholine	^{18}F-NMSP	benztropine, scopolamine	⇧ ACh	⇩	⇧
Serotonin	^{11}C-raclopride	altanserin	⇩ 5-HT	⇩	⇧
		citalopram	⇧ 5-HT	⇧	⇩
GABA	^{11}C-raclopride	vigabatrin	⇧ GABA	⇧	⇩
		lorazepam	⇧ GABA	⇧	⇩
GABA/ dopamine	^{11}C-raclopride	GVG + cocaine	⇧ GABA, ⇧ DA	No change	No change
Glutamate	^{11}C-raclopride	Phencyclidine	⇧ Glu	⇩	⇧
Glutamate/ dopamine	^{11}C-raclopride	GVG + phencyclidine	⇧ GABA, ⇧ Glu	No change	No change

Table 2. Effects of neurotransmitter-specific pharmacological challenges on cholinergic activity measured with PET

Neurotransmitter System	Radioligand	Drug Challenge	Challenge Effect	Radioligand Response	Cholinergic Activity
Dopamine	^{11}C-benztropine	NMSP	⇩ DA	⇩	⇧
Serotonin	^{11}C-benztropine	altanserin	⇩ 5-HT	⇩	⇧
GABA	^{11}C-benztropine	vigabatrin	⇧ GABA	⇩	⇧

Table 3. Change in mean Distribution Volume Ratio (DVR) from baseline scan to post-challenge scan

Group	% Change in Mean DVR
T/RT	7 ± 1.2
GVG Alone	18.8 ± 3.2
PCP Alone	-33 ± 5.31
GVG + PCP	12 ± 8.42

Figure 1. Radioactivity distribution of ^{11}C-raclopride (a) afte nicotine alone (0.3mg/kg) and (b) after S(+)-GV pretreatment (150 mg/kg) prior to the same nicotin challenge.

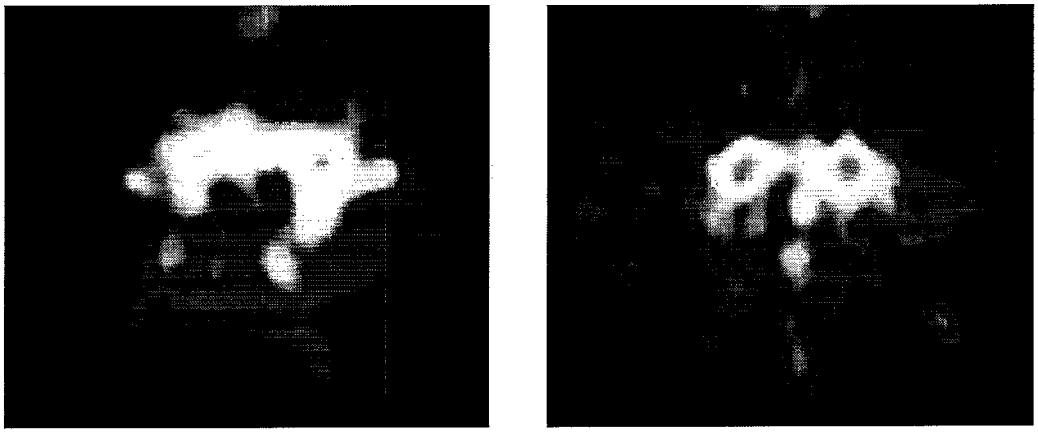

Figure 2. Time activity curve from a baseline ^{11}C-raclopride scan (filled) and after PCP administration (open)

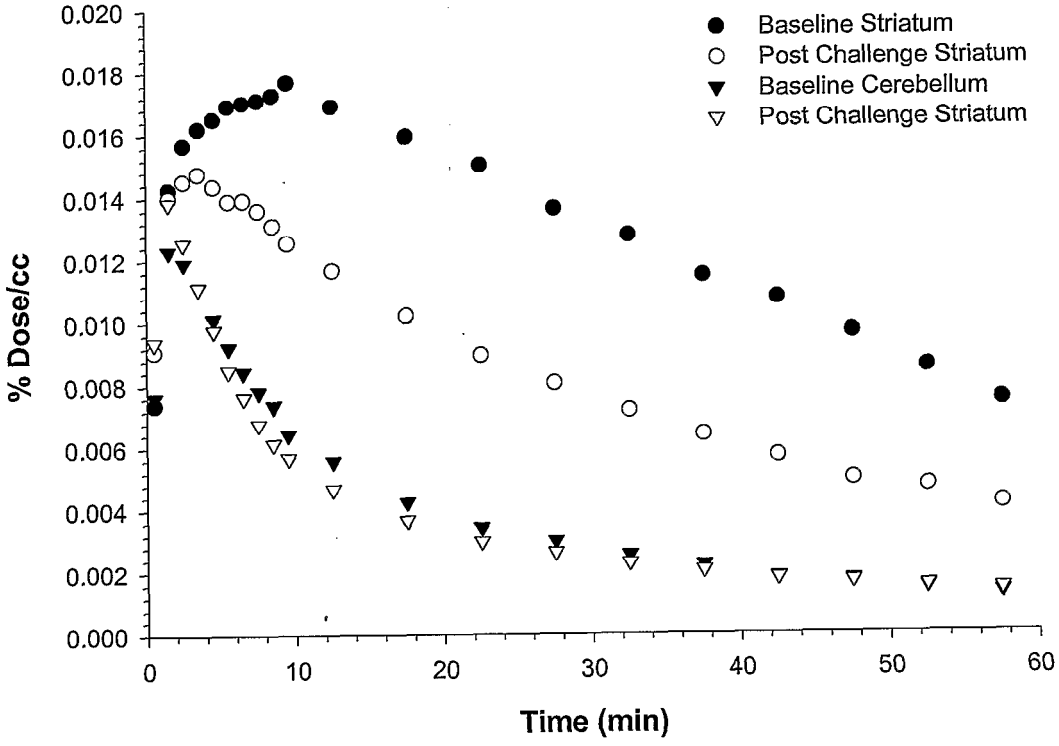

Figure 3. Logan plots of the striatal distribution volume from a non-human primate given PCP Alone (a) or an animal pretreated with GVG and given a PCP Challenge (b).

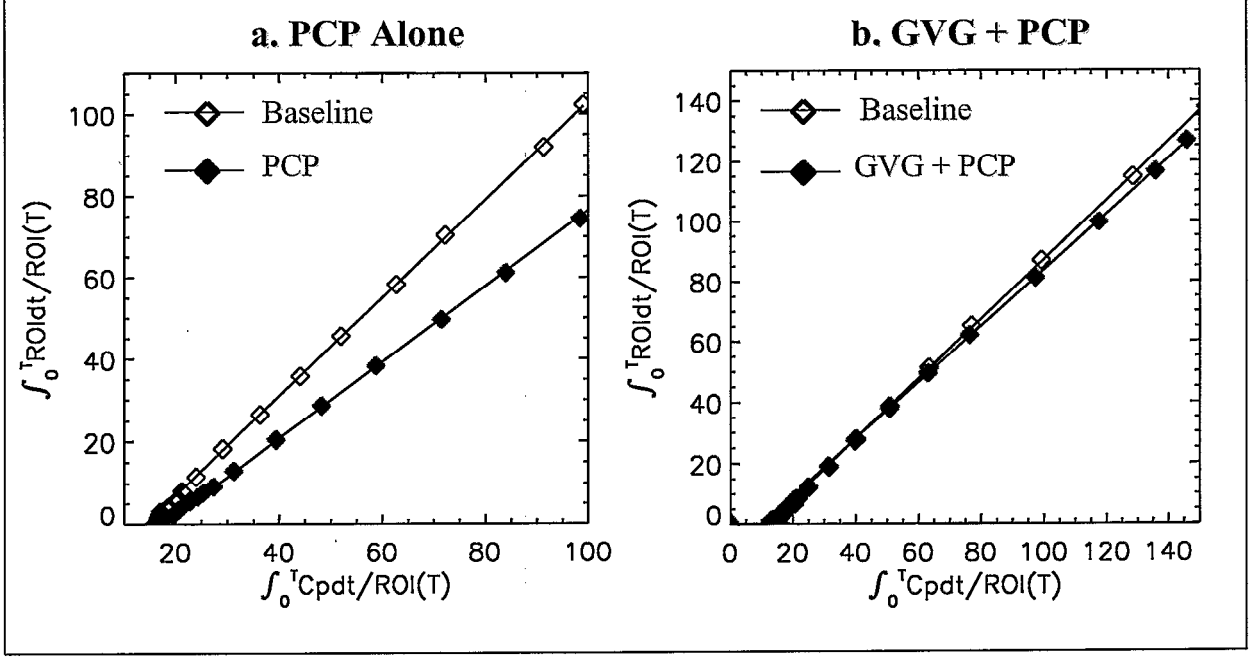

Figure Captions

Figure 1. Radioactivity distribution of ^{11}C-raclopride in the *papio anubis* brain before and after nicotine alone and in the presence of GVG.

Figure 2. Time-activity data from striatum and cerebellum ROIs for *papio anubis* primates given a PCP challenge (1.0 mg/kg) prior to the second ^{11}C-raclopride scan. Points on the graph are calculated for the midpoint of the scan times, represented by T. All points are corrected for the presence of labeled raclopride metabolites.

Figure 3. Graphical analysis of the time activity data from striatal ROIs in (a) one primate given a PCP challenge and (b) a primate pretreated with GVG followed by a PCP challenge. ROI(T) refers to radioactivity in the striatum at time T. $C_p(t)$ is the plasma radioactivity corrected for metabolites.

Keywords

neurotransmitter interactions

dynamic brain scan

dopamine

acetylcholine

serotonin

GABA

schizophrenia

addiction