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Review

Aspects of PET imaging relevant to the assessment of striatal transplantation in Huntington's disease

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ABSTRACT

Proper assessment of outcome in clinical trials of neural transplantation requires both biochemical and imaging indices of graft survival, and behavioural and physiological indices of graft function. For transplantation in Huntington's disease, a variety of ligands that are selective for striatal degeneration and graft-derived replacement are available, notably ligands of dopaminergic receptors on striatal neurons. However, the validity of such ligands is potentially compromised by adjunctive drug therapies (e.g. neuroleptics) given to patients in the course of normal clinical care. We review the present state of experimental and clinical understanding of the selectivity of available ligands for striatal imaging, their interaction with other drug treatments, and strategies for refining valid assessment protocols in patients.

Key words: Huntington's disease; striatal transplantation; PET imaging.

NEURAL TRANSPLANTATION FOR HUNTINGTON'S DISEASE

Based on the success in initial clinical trials of fetal nigral grafts to alleviate many of the symptoms of Parkinson's disease (Lindvall et al. 1990; Lindvall 1997; Olanow et al. 1997; Wenning et al. 1997), in parallel with an extensive literature on the functional viability of striatal grafts in experimental animals with striatal lesions (Björklund et al. 1994; Sanberg et al. 1998), it has been proposed that fetal striatal transplantation may also provide an effective therapy for Huntington' disease (Lindvall, 1991; Peschanski et al. 1995; Shannon & Kordower 1996; Philpott et al. 1997; Bachoud-Lévy et al. 1998; Kopyov et al. 1998*b*). The first clinical trials have now commenced in several centres world-wide; the surgical procedures as used by the French team have recently been reported in detail (Palfi et al. 1998) and in a preliminary report of outcome from the Los Angeles series of cases, the procedure is reported to be safe up to 1 y following grafting without unexpected complications (Kopyov et al. 1998*a*, *b*).

One of the major outcomes of the pioneering clinical trials of neural transplantation in Parkinson's disease was the recognition of the need for objective and quantifiable assessment tools. This enabled the progress of small numbers of surgical patients to be monitored longitudinally over several years, the time frame that is likely to be required for a graft to integrate and become functional within the host brain, and allowed comparisons to be made between different centres employing variants of surgical technique. The need was resolved by wide adoption of a standardised 'core assessment protocol for intracerebral transplantation' in Parkinson's disease (CAPIT-PD; Langston et al. 1992). The CAPIT protocol combines a standardised set of neurological tests of motor function undertaken at standardised times before and after transplantation, along with positron emission tomography (PET) imaging using ^{18}F-fluorodopa as the ligand to visualise survival of dopamine neurons in the grafts and dopaminergic reinnervation of the host striatum. The availability of objective detection and quantifiable measurement of graft survival and integration has proved fundamental

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in the ability to interpret graft function and develop improved graft methodologies in Parkinson's disease (Olanow et al. 1996; Lindvall 1997; Brownell et al. 1998).

Once it was recognised that Huntington's disease may provide a second suitable neurological target for neural transplantation, it became necessary to develop a comparable assessment tool for identification of graft survival and monitoring of disease progression, resulting in an equivalent core assessment protocol, CAPIT-HD (Quinn et al. 1996). CAPIT-PD and CAPIT-HD share many similarities in their tests of neurological and motor function, but CAPIT-HD also incorporates major sections on neuropsychological and neuropsychiatric function, appropriate for the tripartite—motor, cognitive and behavioural—symptoms of Huntington's disease (Harper, 1996). Moreover, at the outset, it was not clear which were the optimal ligands and parameters for imaging the progression of the disease and integration of striatal grafts in Huntington's disease. This is the primary topic of this review.

IMAGING IN HUNTINGTON'S DISEASE

Magnetic resonance imaging

Magnetic resonance imaging (MRI) provides important information on the structural degeneration in Huntington's disease, and has been used as the basis for quantification of the stage of progress of the disease based on indices of striatal shrinkage and ventricular enlargement (Harper, 1996). Moreover, accurate MRI is an essential component of the most powerful stereotaxic procedures for precise surgical placement of graft tissue (Palfi et al. 1998) and can provide subsequent information on the site of localisation and collateral damage sustained during surgery (Kopyov et al. 1998*b*). Thirdly, when combined with spectroscopy, MRS offers the promise of providing a tool for analysis of cellular metabolism within the grafted striatum (Ross et al. 1997).

Positron emission tomography

Since the development of positron emission tomography (PET), in vivo imaging has become the method of preference to assess a variety of neurodegenerative and neuropsychiatric disorders (Jones, 1996*a*, *b*). In particular, PET has been of proven value in clinical trials of neural transplantation in Parkinson's disease (Sawle & Myers 1993; Kordower et al. 1995; Olanow et al. 1996; Wenning et al. 1997; Brownell et al. 1998).

Clinical assessment of Huntington's disease patients using PET initially focused on the measurement of cerebral metabolism. Patients early in the course of the disease, and even asymptomatic gene carriers, exhibit significantly reduced glucose metabolism, estimated through [^{18}F]fluorodeoxyglucose, in the caudate, putamen and frontal cortex (Grafton et al. 1992; Martin et al. 1992; Antonini et al. 1996). Indeed there is some suggestion that the metabolic changes may precede the neuronal degeneration and that the progression of metabolic change does not match that of striatal atrophy (Kuhl et al. 1984; Hayden et al. 1986; Grafton et al. 1992). More recently, Bartenstein et al. (1997) described, in patients with Huntington's disease, impaired activity of the striatum and motor projection areas in repeated PET cerebral blood flow measurements using $^{15}H_2O$.

The widespread cortical and subcortical metabolic changes and the lack of correlation with neuronal atrophy prompted the investigation of more specific striatal markers such as the D_1 and D_2 dopamine receptors that are located postsynaptically on the vulnerable medium spiny projection neurons. Postmortem studies have demonstrated extreme reductions in D_1 and D_2 receptor densities in the striatum of Huntington's disease patients (Cross & Rossor 1983; Joyce et al. 1988; Filloux et al. 1990; Richfield et al. 1991). Functional PET studies of dopamine D_1 and D_2 receptors in early Huntington's disease revealed a severe and parallel reduction in D_1 and D_2 receptor binding detected in vivo using 2 ligands [^{11}C]SCH-23390 and [^{11}C]raclopride for the D_1 and D_2 receptors, respectively (Turjanski et al. 1995; Antonini et al. 1996, 1998; Ginovart et al. 1997).

The application of PET to extend our knowledge of the rate of disease progression was described by Antonini et al. (1998), who found in Huntington's disease gene carriers a correlation between CAG repeat number and the decrement of [^{11}C]raclopride binding in the striatum. In addition in vivo investigations have demonstrated that reductions in D_1, D_2 and dopamine transporter binding potential accompany strong deficits on a variety of cognitive tasks (Backman et al. 1997). This study highlighted that lesions at multiple sites in the cortico-striato-thalamo-cortical circuitry are related to cognitive impairment. More recently, it was demonstrated that gene-carriers exhibited cognitive changes despite a lack of any motor or/and psychiatric signs (Hahn-Barma et al. 1998). Since Huntington's disease appears as a multifocal disease, follow-up with PET using specific ligands targeted to multiple binding sites could help to pinpoint pathological processes in living

Huntington's disease gene carriers. The need for such ligands is highly relevant to any potential treatment strategy that may involve neuroprotection or neuronal restoration through transplantation where it will be essential to link the clinical progression with actual neuronal changes in frontostriatal regions. Moreover, brain imaging, it may be argued, is needed for the detection of the 'therapeutic window' in order to initiate neuroprotective strategies early in the course of Huntington's disease before extensive overt neurodegeneration has taken place.

IMAGING STRIATAL GRAFTS IN EXPERIMENTAL RATS

A variety of different imaging techniques, and a variety of different ligands, could potentially be used effectively to monitor disease progression in Huntington's disease. However, in designing the CAPIT-HD protocols for neural transplantation it became imperative to determine which of these imaging techniques would be the most sensitive and selective for monitoring the survival and integration of striatal grafts. We therefore initiated a collaboration with Dr Sue Hume and Prof. David Brooks (MRC Cyclotron Unit, Hammersmith Hospital, London) to evaluate striatal lesions and grafts in rodents, comparing different ligands using a small animal PET scanner (Rajeswaran et al. 1992).

The first studies used the D_2 receptor ligand [^{11}C]raclopride. D_2 receptors are a distinctive feature of the intact neostriatum, located predominantly on the major cell population of the striatum, the medium spiny neurons. During the first several minutes after injection, the PET scanner detects unbound raclopride from the whole brain and this outline can be used for unbiased positioning of a mask which is then used to define discrete areas of interest within which specific binding is measured. These are delineated as groups of voxels encompassing the neostriatum bilaterally, and with the midline thalamus and cerebellum as control areas (Fig. 1). After initial washout of the unbound raclopride, the specific binding signal is recorded over the subsequent period 10–40 min after injection and referenced against baseline levels recorded in the thalamic and cerebellar regions within which D_2 receptors are sparse (Hume et al. 1992, 1996).

After establishing the basis for quantitation, the first step was to validate the lesion and graft model. Unilateral ibotenic acid lesions of the striatum in rats result in a total loss of specific binding signal in the striatum ipsilateral to the lesion (Hume et al. 1996). Against this relatively clean background, striatal grafts can be detected by a return of approximately 30% of the normal level of raclopride binding signal observed in the intact brain (Fig. 1; Torres et al. 1995). This was then used to validate the utility of raclopride as a ligand in several distinct ways.

1. The raclopride binding signal derived from individual animals was evaluated against postmortem histology (Torres et al. 1995; Fricker et al. 1997). Not only was the signal found to correlate well with graft survival, but the highest correlations were found specifically with the survival of striatal-like tissues within the grafts (the 'P zones').

2. When different ligands were compared, the highest specific signal and lowest background signal were found using the D_2 antagonist [^{11}C]raclopride. The D_1 antagonist [^{11}C]SCH23390 also correlated with graft survival, but the signal associated with this ligand yielded a higher background from the well lesioned striatum than did raclopride (Fricker et al. 1997). Although widely used in humans, the general marker of cell metabolism [^{18}F]fluorodeoxyglucose was not useful; because of the small size of the rat brain the strength of the signal from the intact cortex completely masked any decline in specific striatal signal.

3. [^{11}C]raclopride was clearly able to distinguish different types of graft tissue. Specifically, control grafts of cortical tissue, which would show as surviving grafts on any scan using a general marker for living tissue (such as MRI or fluorodeoxyglucose in PET), was completely negative (Torres et al. 1995). Moreover, when striatal tissues from donors of different age were used, both the [^{11}C]raclopride and the [^{11}C]SCH23390 signals correlated with the survival and presence of the striatal compartment in the grafts, not total graft volume (Fricker et al. 1997).

4. Behavioural recovery of striatal-grafted animals correlated with an increase in PET binding potentials of both [^{11}C]SCH23390 and [^{11}C]raclopride to D_1 and D_2 receptors, respectively (Fricker et al. 1997). Indeed, the index of striatal graft survival derived from the raclopride signal was found to correlate with the recovery in skilled paw reaching in the individual animals more closely than did any of the postmortem indices based on graft histology. Thus the PET scans appear to incorporate information on graft function over and above a simple index of its survival.

These results confirm that both [^{11}C]SCH23390 and [^{11}C]raclopride are good candidates for monitoring striatal graft survival in clinical transplantation studies. Other things being equal, a somewhat greater sensitivity is offered by the D_2 ligand, raclopride.

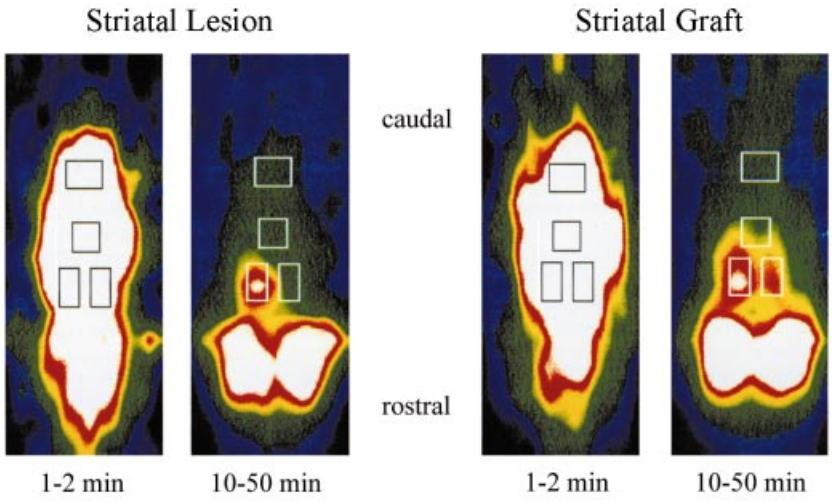

Fig. 1. [^{11}C]Raclopride binding in the intact, lesioned and grafted striatum visualized by PET in vivo. The left panel of each pair indicates the initial unbound signal in the first 1–2 min after injection, which outlines the skull and is used as the basis for unbiased placement of the mask outlining the cerebellum (top box), thalamus (middle box) and bilateral striatum (lower pair of boxes). The right panel of each pair indicates specific binding 10–50 min after injection. The left pair of panels is from a striatal lesion rat; not the strong binding signal in the left striatum but complete loss in the right striatum. The right pair of panels is from a striatal graft rat; note the significant restoration of a partial signal in the right striatum. The very strong diffuse signal at the base of each panel is from the lachrymal glands, outside the skull. (Based on Torres et al. 1995).

Indeed, these experimental studies, along with existing clinical literature, contributed to the adoption of raclopride as the recommended ligand in the proposed CAPIT-HD (Quinn et al. 1996).

IMAGING STRIATAL GRAFTS IN EXPERIMENTAL MONKEYS

The relatively low resolution of PET (with a limit to resolution of 2 point sources at $\sim$2 mm) allows clear definition of a region of interest to cover the rodent neostriatum, but not resolution of striatal subregions, let alone resolution of compartments within a striatal graft. In order to evaluate regional factors, and the extent of graft integration in larger, differentiated basal ganglia, we have undertaken studies of striatal grafts in primates. For these studies we use the common marmoset (*Callithrix jacchus*), not only because this species is small, relatively economic and easy to handle, but also because it breeds readily in captivity, which is necessary to provide a reliable supply of accurately staged embryonic tissues for transplantation. Unilateral quinolinic acid lesions of the putamen produce contralateral impairment in skilled hand use in the marmoset that is alleviated by implants of embryonic striatal tissues grafted into the site of striatal degeneration (Kendall et al. 1998*a*).

In preliminary studies with a new small animal PET scanner (undertaken in collaboration with Drs John Clark, Franklin Aigbirhio and colleagues at the Department of Surgery, Cambridge and with Oxford Positron Systems, Oxford), we have used [^{11}C]raclopride to image the extent of striatal degeneration and graft survival in these animals (Kendall et al. 1998*b*). As shown in Figure 2, the caudate nucleus and the putamen may be clearly resolved on the intact side of the brain of this small primate. Unilateral putamen lesions induce an extensive loss of the more caudal and lateral striatal signal, whereas the more medial binding associated with the unlesioned caudate nucleus remains unaffected. Two of the 3 monkeys with striatal grafts exhibited a partial restoration of raclopride binding. Notably, the 2 monkeys with a positive putaminal binding signal both exhibited significant recovery on the test of skilled reaching whereas the remaining grafted monkey that showed no sign of surviving D_2-positive graft tissue was the one grafted animal that showed no behavioural recovery either. Postmortem investigations of the monkey brains confirmed the link between the PET raclopride ratios and the content of DARPP-32 within the remaining striatum and within the P-zones of the grafts.

These data confirm that raclopride PET provides a sensitive index of graft survival that correlates with functional efficacy in primates with unilateral striatal degeneration akin to that seen bilaterally in Huntington's disease. They open the way for the next stage of experimental studies on the relationship between the time course and topography of graft survival and integration on the one hand and functional recovery on the other.

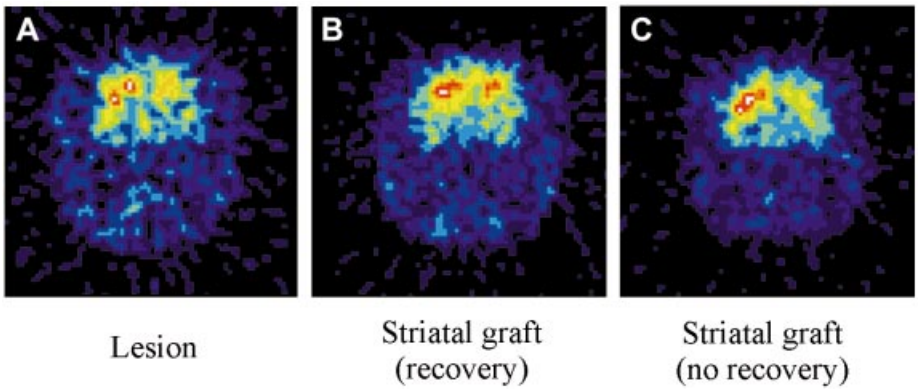

Fig. 2. [^{11}C]Raclopride PET of striatal lesions and grafts in the common marmoset. *A*, Control monkey (#P-43) with a unilateral putamen lesion on right side. Note loss of binding in the posterior and lateral striatum on the lesioned side. *B*, Monkey (#PG(19)-31) with a unilateral lesion and a striatal graft that exhibited good recovery of skilled use of the contralateral hand. Note substantial and significant restoration of signal on the lesioned side. *C*, Monkey (#PG(19)-34) with unilateral lesion and a striatal graft that exhibited poor recovery in the contralateral hand. Note that the raclopride signal is not restored above the levels seen in the animal with lesion alone. (Unpublished observations; abstract in Kendall et al. 1998*b*).

THE PROBLEM OF NEUROLEPTICS

Neuroleptics in Huntington's disease

Many Huntington's disease patients, in the course of disease management, receive medication with a variety of antipsychotic, antidepressant and other psychiatric drugs. Since many of these drugs act at dopamine receptors, they many potentially interfere with the binding of PET ligands at the same sites. Thus concurrent drug therapies given to assist patient management many profoundly compromise the accuracy and validity of assessment protocols based on PET imaging using dopaminergic ligands such as D_1 and D_2 receptor (ant)agonists or blockers of the dopamine transporter. We therefore need to acquire a better understanding of the profiles of interaction between different therapeutic drugs and preferred PET ligands, in the search for combinations that show little interaction. Alternatively, if we can characterise the washout period after cessation of drug treatment that is required for receptor and transporter function to return to 'normal' levels (i.e. reflecting the state of the disease, not of concurrent drug regimes), then it may be possible to establish valid assessment protocols based on temporary discontinuation of neuroleptic administration prior to analysis by PET.

Effects of neuroleptics on PET scans in patients

Neuroleptic drugs induce changes in receptor binding not only in model systems but also as assessed in vivo with PET (Farde et al. 1992). Similarly, receptor upregulation occurs in Huntington's disease patients receiving neuroleptic treatment (Seeman et al. 1987). Thus changes in dopamine receptor density do take place in response to neuroleptic treatment which would confound the interpretation of PET data obtained from the patients, in particular if no washout period is undertaken to restore baseline receptor levels.

Pharmacological profiles, however, differ according to the neuroleptic. Although antipsychotics are well characterised in vitro, it is crucial to demonstrate which receptors are occupied at clinically relevant doses. Human correlation with in vivo receptor binding has been made for most of the antipsychotics used in the clinic (Arnt & Skarsfeldt, 1998). However, to address how neuroleptic therapy may induce dopamine receptor up or downregulation in the basal ganglia, several parameters such as the dose and duration of the medication must be taken into account.

Besides the overt psychotic symptoms, depressive disorders are an additional common feature in Huntington's disease (Harper, 1996). Consequently, antidepressants are administered to many patients. Recent investigations reported an increase in D_2-like binding following fluoxetine and desipramine in nucleus accumbens but not in caudate-putamen after 14 d of treatment in rats (Ainsworth et al. 1998). Previously a decrease in the binding sites of [^{3}H]SCH-23390 was observed following the administration of antidepressant drugs in the rat striatum (Klimek & Nielsen, 1987). Although these data suggest differential regulation, we cannot rule out the possibility that changes in D_2 or D_1 receptor densities would appear different when treatment is longer or at different

doses. On the other hand, although animal experiments are performed in order to achieve plasma levels that are within the therapeutic range, we cannot ascertain that what is observed in rats may also occur in humans, although a recent study employing SPECT concluded that striatal D_2 receptor binding is not changed after antidepressant therapy (Ebert et al. 1996). Moreover, coadministration of antidepressant and antipsychotic drugs could differentially affect postsynaptic dopamine receptor expression; this raises the problem of multimedication in exploring receptor levels in drug-treated Huntington's disease patients.

During the last decade there has been an increase in the development of novel antipsychotics exhibiting fewer extrapyramidal side effects than the classical antipsychotic drugs such as haloperidol or fluphenazine (for review, see Arnt & Skarsfeldt, 1998). To differentiate them from the classical antipsychotics, they were designated 'atypical antipsychotic drugs', although there remains no full consensus on how this distinction should be defined. However, they are distinguished by their higher affinity for serotonergic 5-HT_2 receptors as compared with a preferential action of the classical neuroleptics at dopaminergic D_2 receptors. D_2 occupancy is a condition for antipsychotic response; however, a number of patients (20–50 %) do not respond to treatment at optimal dosing but generally do when medicated with an atypical antipsychotic, such as clozapine (Pilowsky et al. 1992). This clinical observation suggested the necessity of combined 5-HT_2/D_2 antagonism for an optimal response, even though significant antipsychotic activity may be observed with the drugs occupying a minimum of 20–60 % D_2 receptors (Kapur, 1998).

Based on results in neuroleptic-treated patients, PET studies have reported a high D_2 dopamine receptor occupancy in patients treated with conventional doses of neuroleptics such as haloperiodol or sulpiride. In a recent study, Nyberg et al. (1997) followed with PET, central dopamine receptor occupancy for up to 1 y after haloperidol discontinuation. In this experiment, low doses of haloperidol decanoate (30–50 mg every 4 wk) lead to a far from negligible D_2 dopamine receptor occupancy (12–23 %) even 6 mo after the last drug administration. Since higher doses (200 mg) are currently used in patients, an estimation of 70 % D_2 receptor occupancy would be possible as long as 16 wk after discontinuation. These authors suggest a wash-out of at least 6 mo or longer if high doses have been used. Conversely, no D_1 receptor interaction was observed in patients treated with conventional clinical doses of haloperiodol or sulpiride for at least 4 wk suggesting typical antipsychotic drugs are selective for this subtype at clinical doses. PET and/or SPECT studies of risperidone, ziprasidone, sertindole, quietapine and olanzapine indicated moderate to high D_2 occupancies (60–80 %) at therapeutic doses (for review, see Arnt & Skarfeldt 1998).

Experimental studies of washout

In vivo investigations of the more recent compounds are currently underway. However, in vitro investigations showed that clozapine treatment did not affect the binding to D_2 and D_1 receptors in striatum when quantified with [^{3}H]raclopride and [^{3}H]SCH23390, respectively (Florijn et al. 1997). While extended data are now available in the literature for D_2 occupancy, only limited information is available for novel antipsychotic drugs about D_1 receptor occupancy in vivo. To our knowledge, only Farde et al. (1992) have reported such data, and found a D_1 receptor occupancy of 38–52 % i.e., similar to the D_2 occupancy of 38–63 %.

It is clear that we now need an improved in vivo model system within which to establish empirically the dynamic relationship between drug and ligand binding in vivo. The purposes of such a model are to address 2 issues: (1) to determine the degree to which individual therapeutic drug treatments interact with each potential PET ligand, as the basis for selecting ligands that are less confounded by any particular regime of patient pharmacotherapy; (2) to determine the relative washout period of individual drug treatments so that when confounding with a preferred PET ligand is inevitable, a protocol for drug withdrawal and washout can be defined on empirical criteria so as to minimise the confound. This we have sought to establish in the laboratory rat (Besret et al. 2000). It is known that chronic treatment with antipsychotic drugs is associated with an increase in the number of striatal dopamine D_2 receptors (Huang et al. 1997; Tarazi et al. 1997) and variable changes in D_1 receptors (Laruelle et al. 1992; Sasaki et al. 1998) that are relatively long-lasting after drug withdrawal, although the duration of such changes and the washout period necessary to restore baseline receptor levels is poorly understood. We have therefore undertaken a systematic longitudinal study of the washout period, measuring the detailed time course of both behavioural hyperactivity and D_1 and D_2 receptor sensitivity. The receptor changes were measured both by receptor autoradiography to quantify binding of the D_1 and D_2 receptors using the same ligands (SCH-

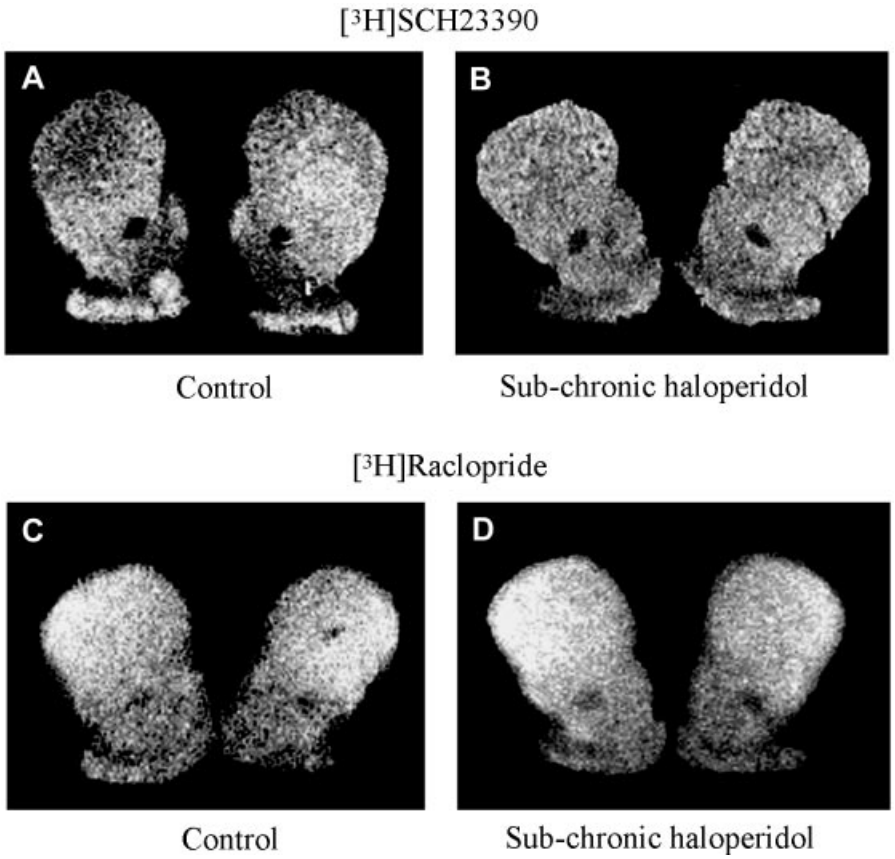

Fig. 3. Receptor autoradiographs of dopamine receptor binding in haloperidol and control treated rats. *A*, *B*, Binding of the D_1 ligand [^{3}H]SCH23390 in the dorsal and ventral striatum of control (*A*) and haloperidol-treated (*B*) rats. *C*, *D*, Binding of the D_2 ligand [^{3}H]raclopride binding in the dorsal and ventral striatum of control (*C*) and haloperidol treated (*D*) rats. (From Besret et al. 2000).

23390 and raclopride, respectively, radiolabelled with ^{3}H; see Fig. 3) as are used in our PET studies, and by in situ hybridisation to measure expression of the receptors (Besret et al. 2000).

Following subchronic (daily for 3 wk) treatment with haloperidol, the animals exhibit behavioural hyperactivity (Fig. 4*A*), and an increase in D_2 receptor binding and expression (Fig. 4*B*) lasting approximately 2 wk after drug withdrawal (Besret et al. 2000). We have gone on to show that longer periods of haloperiodol treatment result in a longer washout period, lasting maximally up to 4 wk after drug withdrawal. Conversely the SCH-23390 D_1 receptor binding was not significantly altered after withdrawal of haloperidol (Fig. 4*C*). These data suggest, first, that if a patient is treated with a classical neuroleptic, with a relatively selective action at the D_2 receptor similar to haloperidol, then the D_1 PET ligand SCH-23390 should be able to provide relatively unconfounded measures of progression of the striatal degeneration and the survival of striatal-like cells within the grafts of a transplanted patient. Secondly, they suggest that the D_2 ligand raclopride, which we had found to be the most sensitive for quantitation of striatal grafts in experimental animals, should also be usable in patients treated with neuroleptics, after an adequate washout period, although of course the pharmacodynamic differences between rodents and humans does not at present allow us to define precisely the minimum acceptable washout period based on these observations alone.

Haloperidol has been used to establish and validate the model system in rats. However, this drug is seldom the clinical neuroleptic of choice, and several more selective compounds are now preferred. Clearly, the next stage for the rodent studies is to use the same experimental design to compare the relative changes in D_1 and D_2 receptor binding, and the duration of those changes during washout, after different durations of acute, subchronic and chronic administration of the range of neuroleptic and antidepressant compounds actually used clinically.

Finally, although systematic quantitative and parametric comparisons can only be properly conducted and controlled in experimental animals, the relative receptor selectivity and washout duration of clinically used compounds established in these experimental studies will need to be validated in man in appropriate

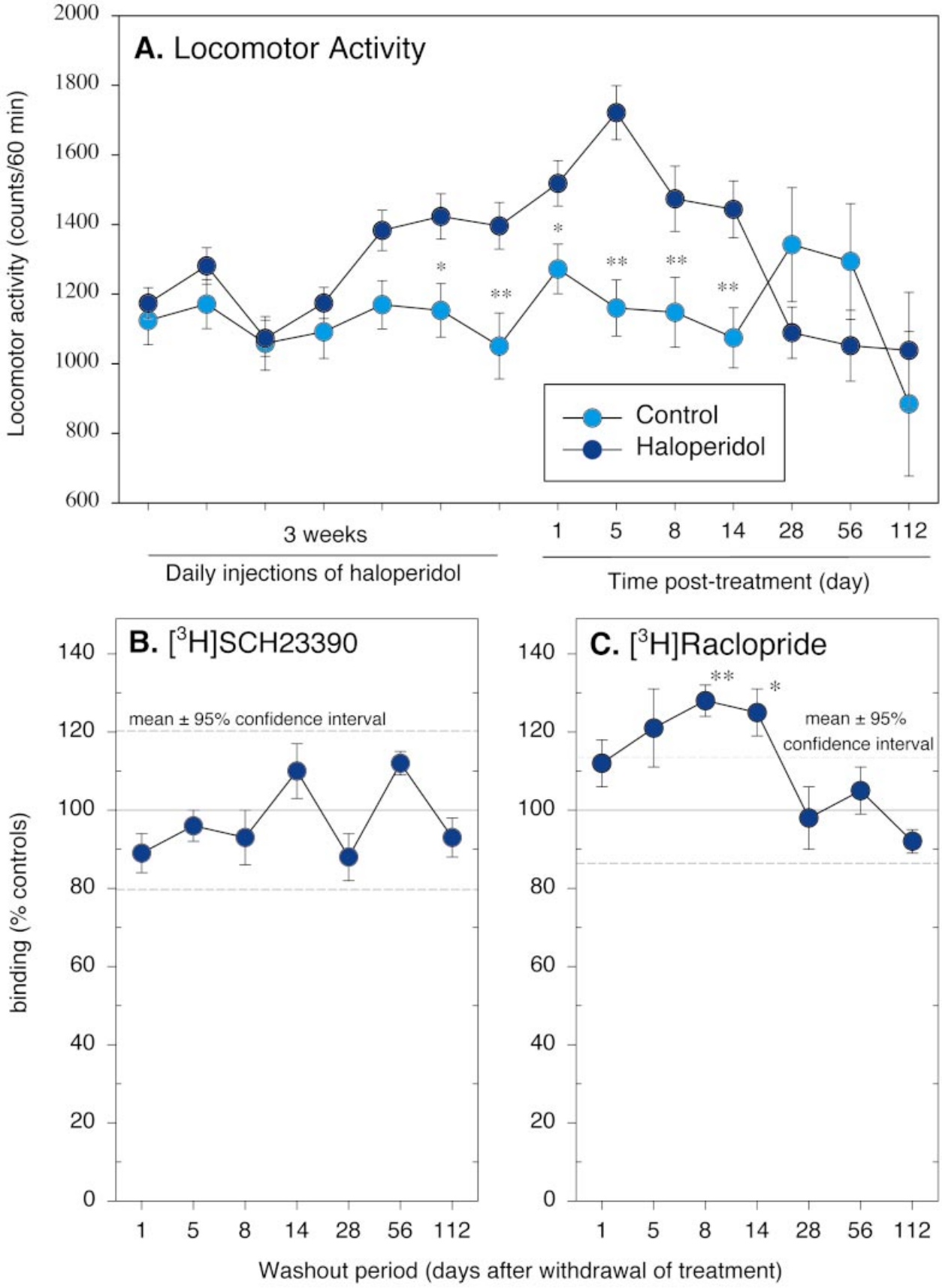

Fig. 4. Time course of changes associated with 3 wk subchronic haloperidol treatment in rats. *A*, Locomotor hyperactivity; *B*, [^{3}H]raclopride binding in the dorsal striatum; *C*, [^{3}H]SCH23390 binding in the dorsal striatum. (Unpublished results by Besret et al.).

clinical studies. Thus, Farde et al. (1990) have used [^{11}C]raclopride as the PET ligand to demonstrate an increase in dopamine receptor binding ratio during clinical treatment with sulpiride. D_2 receptor binding remained 50% higher than in the control group 2 wk after withdrawal from this antipsychotic, and only returned to control levels after a mean duration of 7 wk.

Our knowledge of the in vivo pharmacological profile, both in experimental animals and man, of compounds in clinical psychiatric use is rapidly expanding. In the specific context of neural transplantation in Huntington's disease, several alternatives are now available to overcome the confound posed by concurrent psychiatric drug therapies on valid PET assessment of graft survival, differentiation and integration within the host brain. First, PET ligands should be selected that have minimal interaction with the drugs in use. Secondly, as washout periods become better defined, scanning and dosing protocols can be defined so that substantial interactions are minimised. Thirdly, as the drug-ligand interaction is identified as a potential confound, and the nature of that interaction becomes better defined, it is possible for patients enrolled in a transplant programme to select drugs, when required, that do not confound the imaging assessment, without compromising clinical management.

CONCLUSIONS

Clinical trials of neural transplantation in Huntington's disease have now commenced. Whereas the first reports were somewhat cursory (Madrazo et al. 1995; Sramka et al. 1992), more systematic trials are now under way (Philpott et al. 1997; Kopyov et al. 1998*a*, *b*; M. Peschanski et al. personal communication). Proper evaluation of the outcome of intracerebral allograft transplantation requires the use of quantifiable measures of graft survival and function using alternative methods for in vivo imaging in combination with objective measures of neurological, cognitive and psychiatric dysfunction so as to be able to monitor patients' progress using tools that can distinguish significant effects of the grafts from normal fluctuations in the course of the disease and variability of measures of striatal degeneration and atrophy. Advances in our understanding of the basic neurobiology and neuropharmacology of striatal function contribute to the development of effective assessment tools, as reviewed in the present review, specifically for the in vivo imaging of graft survival, integration and function using PET.

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