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Invited review

Pharmacological imaging as a tool to visualise dopaminergic neurotoxicity

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ABSTRACT

Dopamine abnormalities underlie a wide variety of psychopathologies, including ADHD and schizophrenia. A new imaging technique, pharmacological magnetic resonance imaging (phMRI), is a promising non-invasive technique to visualize the dopaminergic system in the brain. In this review we explore the clinical potential of phMRI in detecting dopamine dysfunction or neurotoxicity, assess its strengths and weaknesses and identify directions for future research. Preclinically, phMRI is able to detect severe dopaminergic abnormalities quite similar to conventional techniques such as PET and SPECT. phMRI benefits from its high spatial resolution and the possibility to visualize both local and downstream effects of dopaminergic neurotransmission. In addition, it allows for repeated measurements and assessments in vulnerable populations. The major challenge is the complex interpretation of phMRI results. Future studies in patients with dopaminergic abnormalities need to confirm the currently reviewed preclinical findings to validate the technique in a clinical setting. Eventually, based on the current review we expect that phMRI can be of use in a clinical setting involving vulnerable populations (such as children and adolescents) for diagnosis and monitoring treatment efficacy.

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1. Introduction

The dopaminergic (DA) neurotransmitter system is widely distributed throughout the brain and involved in a wide variety of CNS functions. The DA system is involved in functions such as for motivation, cognition, movement and reward. The involvement of the DA system has long been recognised in the pathophysiology of neuropsychiatric disorders, such as ADHD and schizophrenia. The current approach to studying these disorders is via targeting the DA system with pharmacological treatment. However, not much is known about the effect of these drugs and how they can alter dopaminergic functioning. For example, it has been shown that long-term use of DA drugs, such as methylphenidate, increases the risk of substance abuse in adults but not in adolescents (Wilens et al., 2003). However, the neurobiological underpinnings for this discrepancy are unknown. Therefore, it is important to investigate both the acute and chronic effects of these drugs on brain function.

At present, there is a rising awareness of the importance of brain imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in the field of psychopharmacology. PET has been successful in identifying receptor densities and levels of circulating enzymes as well as measuring neurotransmitter release after a pharmacological challenge. However, PET is not appropriate for repeated measurements and studies in patients, especially in the paediatric population, due to its invasiveness. As an alternative, a new technique combining fMRI with a pharmacological challenge (phMRI) shows promising results in assessing the integrity of various neurotransmitter systems. This technique is sensitive to changes in blood oxygenation as a result of neuronal activity in response to pharmacological challenges and therefore provides an index of neurotransmitter function. For this reason, as well as its non-invasive nature, it is a very promising method to measure DA imbalances in neuropsychiatric disorders.

This review aims to explore the clinical utility of phMRI in assessing the functional and dysfunctional dopaminergic system. To this end, we will give an overview of conventional neurochemical imaging modalities (PET and SPECT) in visualising DA neurotoxicity, and compare these to phMRI studies. PET/SPECT and phMRI will be compared by means of DA neurotoxicity models in animals and human drug abusers, as they provide good models to study disturbances to neurotransmitter systems in the brain. We will discuss the advantages and shortcomings of phMRI in

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assessing DA dysfunction over conventional PET/SPECT studies. In addition, we will examine whether phMRI is ready to be used in the clinical setting and if not, what advances have to be made to achieve this goal.

2. Models of neurotoxicity

Animal models have been developed to study the intricate workings of the brain. Preclinical work has contributed tremendously to our understanding of neurotransmitter systems. Different types of animal models have been used to study the neurobiological underpinnings of neuropsychiatric disorders. Behavioural models have been used to evaluate the effect of treatment. Yet, this is not particularly informative for understanding about the neuronal basis of these disorders. Therefore, genetic models, in which genes have been modified, have been used in order to induce a certain disease state relevant to particular disorders. However, genes are often responsible for multiple neuronal processes and help to sculpt the brain in development. Interfering with these processes prevents modelling the natural development of neurotransmitter systems and may therefore mask several aspects of development that would otherwise have remained intact. Lesion models are the method of choice to investigate neurotransmitter systems and their development. By means of a physical or pharmacological lesion, neurotransmitter levels, its metabolites and receptors can be manipulated in a predictable fashion. This allows for careful assessment of dose–response relationships, interspecies differences and mechanisms of action. We have chosen the following neurotoxic lesion models because they were best represented in the molecular imaging literature and altogether give the best overview of DA neurotoxicity in both animals and humans. Neurotoxicity in this context refers to the potential of pharmacological agents to produce long-lasting changes in cell bodies and/or nerve terminals that cannot be attributed to an acute or neuroadaptive response to the drug (McCann and Ricaurte, 2004).

Several pharmacological compounds have been used to induce selective DA neurotoxicity and these are frequently used as models for clinical conditions characterized by DA cell loss, such as Parkinson's Disease (PD). In this review we will discuss 6-hydroxidopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), amphetamine (d-AMPH) and methamphetamine (METH). Unlike 6-OHDA, MPTP and d-AMPH, METH damages both the dopaminergic and serotonergic system. Other DA neurotoxins, such as Norsalsolinol and Rotenone will not be discussed, as they have not been extensively studied in this context.

6-OHDA lesions the nigrostriatal pathway and is used as an animal model of PD (Hantraye, 1998). Moreover, it has been shown to be a good model of DA neurotoxicity as its toxicity is selective for monoaminergic neurons. For specific DA neurotoxicity the noradrenaline inhibitor desipramine is often co-administered. 6-OHDA is thought to induce DA neurotoxicity through uptake by dopamine transporters and subsequently free radical formation causing neuronal damage. Although mostly used in rats, it is also a good model for other rodents and non-human primates (Gerlach and Riederer, 1996). This model is only available in an experimental setting and there have been no reports of this drug being (ab)used by humans.

MPTP is a neurotoxin that causes Parkinsonism in humans and is the main animal model for PD (Jakowec and Petzinger, 2004). It damages the DA nigrostriatal pathway and causes cell loss in the substantia nigra. It decreases concentrations of dopamine and its metabolites and reduces enzymatic activity. MPTP readily crosses the blood–brain barrier and is converted into MPP+, a toxic metabolite. MPP+ is taken up by the dopamine transporter (DAT) and subsequently inhibits mitochondrial complex I, depletes adenosine triphosphate (ATP) and consequently causes DA cell death. MPTP is not neurotoxic to the rat brain and has therefore mainly been used as a primate and mouse model of DA lesions. Although originally discovered as a substance misused by heroin addicts, it is no longer used in this way and therefore it is not a neurotoxic dopamine model in humans any more (Gerlach and Riederer, 1996).

Neurotoxic effects of d-AMPH and METH have been demonstrated by biochemical measures in many species, including rodents and primates (Davidson et al., 2001; Ricaurte et al., 1982, 2005). Histological analyses showed long lasting neurochemical deficits in DA nerve terminals after METH administration. This was accompanied by reductions in tyrosine hydroxylase (TH), DA and 3,4-dihydroxyphenylacetic acid (DOPAC). However, d-AMPH and METH administration are thought not to result in neuronal cell death (for review, see (Ricaurte et al., 1982)). METH differs from d-AMPH in that it exerts neurotoxic effects in both the DA and serotonin (5HT) system, although its effects are more pronounced for the DA system in most species (Gouzoulis-Mayfrank and Daumann, 2009). It causes degeneration of both DA and 5HT projections with cell bodies remaining undamaged (Brunswick et al., 1992). This is reflected by reduced DA and 5HT concentrations, reduced metabolite levels and decreased transporter density (Seiden and Sabol, 1996). Research has also shown neurotoxicity of d-AMPH and METH in humans. Both drugs are widely abused and therefore provide important models to study DA neurotoxicity in humans.

6-OHDA and MPTP are best studied in animals because of the extensive and obvious damage they induce in DA neurons, primarily by measuring DAT and D1/D2 receptor densities. However, the relatively mild damage caused by d-AMPH and METH might better reflect dopaminergic abnormalities as observed in neuropsychiatric disorders and are therefore important translational models. Furthermore, abuse of d-AMPH and METH is currently the only possible way to study DA neurotoxicity in humans.

3. Neurochemical imaging methods

The first methods to investigate DA neurotoxicity were conventional 'ex vivo' methods such as autoradiography and immunohistochemistry. These techniques have contributed significantly to the understanding of the DA system. Their strength lies in the high spatial resolution and they can be adapted to reflect neuronal activation, perfusion or metabolism. However, due to the invasive nature of these conventional techniques experimental animals can only be studied once, which does not render them useful for longitudinal designs. Other techniques such as microdialysis and cyclic voltammetry provide 'in vivo' measures of dopamine release and can be used in longitudinal studies, but they cannot be easily translated to human studies. In contrast, neuroimaging techniques such as PET, SPECT and especially MRI allow repeated or longitudinal measurements and can be used in vulnerable populations such as the elderly and paediatric population and patients. Indeed, these imaging techniques are already in use in clinical settings for accurate diagnostic purposes.

PET and SPECT both utilize pharmacologically or biochemically active compounds labelled with radionuclides to produce images of in vivo ligand distribution measured by an external detector. Thus, they can provide an index of number of transporters or extracellular levels of dopamine. PET isotopes have shorter half-lives than those used in SPECT. This results in better spatial and temporal resolution and therefore PET is more sensitive than SPECT. As a consequence, PET can be used for absolute quantification of tracer concentrations in the tissue. However, SPECT radiotracers are less costly and the equipment is more widely available. Nevertheless, both PET and SPECT have a relatively poor spatial resolution reducing the utility