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Current Opinion in Pharmacology

Non-invasive imaging in experimental medicine for drug development

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Clinical imaging offers a range of methods for the support of drug development that are able to address major questions related to target validation and molecule biodistribution, target interactions and pharmacodynamics. Here we review recent innovative applications of positron emission tomography (PET) and magnetic resonance imaging (MRI). New approaches to human target validation exploring MRI or PET biomarker changes related to allelic variation at candidate target loci can contribute to human target validation. PET molecular imaging can define molecule biodistribution directly and, if an appropriate, target-specific radioligand is available, be employed in small experimental medicine studies to provide plasma pharmacokinetic–target occupancy data to guide dose selection. An enlarging range of imaging biomarkers for pharmacodynamic studies is enabling imaging experimental medicine studies to assess the potential efficacy of new therapeutic molecules. Integration of these approaches promises improvements in therapeutic molecule differentiation and may contribute in ways that would improve the value proposition for use of a new drug through patient stratification.

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Current Opinion in Pharmacology 2011, **11**:501–507

This review comes from a themed issue on
New technologies
Edited by David Trist and Ceri Davies

Available online 12th May 2011

1471-4892/$ – see front matter

DOI 10.1016/j.coph.2011.04.009

Introduction

Innovative thinking about the clinical development of new drugs is putting a premium on integration of early biology in the context of 'experimental medicine' (see e.g. the FDA's Critical Path Initiative at www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm). Clinical imaging provides a range of general approaches for the support of drug development able to address major questions related to target validation and a molecule's biodistribution, target interactions and pharmacodynamics. Answers to these questions will have greatest impact early in development. Extensions of the approaches could contribute to improved rationales for a new drug or to stratification of patient populations for its best use.

The clinical imaging tools most generally applicable for drug development are positron emission tomography (PET) for molecular imaging and magnetic resonance imaging (MRI) for structural and functional imaging (see Box 1), although other methods such as X-ray computerised tomography (CT), ultrasound or optical imaging have high utility in specific contexts. Here we review recent innovative applications of PET and MRI.

Multimodal imaging for human target validation

A novel target carries substantial development risks. Preclinical and other information need to be integrated into an evidence base sufficient to justify investments for new drug development. Target validation in preclinical models only provides limited confidence to progress for chronic diseases, diseases determined by the interaction of multiple biological and environmental factors and particularly for diseases with uniquely human phenotypes (notably including most neuropsychiatric disorders). Validation of a target directly in humans thus is ideal.

A new approach to human target validation tests for modulation of disease-related brain structural features or functions as defined by MRI or PET in volunteers or patients showing allelic variation at candidate target loci. The structural or functional features defined by imaging are used as *endophenotypes* (biologically proximate, heritable quantitative traits). For example, to test the hypothesis that GSK3β is relevant to major depression, interactions between differences in localised brain grey volumes associated with GSK3β polymorphism variations or between genetic variations encoding proteins functionally interacting with GSK3β and a diagnosis of depression were demonstrated [1•,2]. Functional imaging methods, based on PET or fMRI, can be used in similar ways [3–5].

Differences in target receptor density can be inferred from PET measures of receptor availability as assessed with a suitably specific radioligand. This can provide evidence for pathological patterns of expression, e.g. pathological expression of dopamine receptors in schizophrenia [6], or targets relevant for serotonergic neurotransmission in depression [7,8]. Serial estimates of

Box 1 Imaging methods.

PET

PET relies on the production of radiolabelled compounds that can be administered to animals or humans at tracer doses. PET involves attaching a positron emitting nuclide either to the drug itself or, alternatively, to a compound that binds selectively to the target or pathway of interest. The short half-lives of PET nuclides (most commonly <2 hours) allow for the administration of radioactive doses high enough to provide sufficient signal-to-noise for precise measurements of signal without substantially increasing long-term health risks associated with the ionising radiation. In addition, the high specific activity achieved means that these signals are achieved at microdoses of compound (typically <10 μg). By measuring the time course of the radiolabelled compound across different tissues, the rates of delivery of the radiotracer and the amount retained can be modelled. Spatial resolution is limited to about ~2–4 mm.

Structural and functional magnetic resonance imaging (fMRI)

MRI imaging conventionally provides an image based on the distribution of hydrogen atoms in the body water and fat. Additional information comes from the intensity of the signal detected, which is determined both by the concentration of hydrogen atoms and their chemical local environment. Together, these give rise to contrast between different tissues. This allows tissue size and shape to be visualised and measured. The MRI signal also often is sensitive to pathological changes, allowing discrimination of diseased and normal tissues. Conventional MRI images have a spatial resolution between 1 and 5 mm^3.

The blood signal can be enhanced selectively by intravenous injection of a contrast agent (usually based on a gadolinium-containing compound). With contrast enhancement, MRI can be used to measure blood volume and flow. Leak of plasma across diseased vascular endothelia (e.g. with a damaged blood–brain barrier or with tumour neovascularisation) can be detected as abnormal, sustained tissue signal enhancement after intravenous contrast administration.

fMRI is an extension of the MRI method for brain studies that provides an indirect measure of brain functions. Increased neuronal activity is associated with a local haemodynamic response involving both increased cerebral blood flow and blood volume in excess of that need for delivery of oxygen and thus leading to a change in relative blood oxygenation [39]. More oxygenated blood gives rise to a higher signal intensity on the MRI image. The underlying *neurovascular coupling* predominantly reflects presynaptic, excitatory neurotransmitter release and thus reflects local information transfer [40].

The signal changes detected by fMRI are small (usually 0.5–5% at 3 T). A typical pharmacological fMRI experiment therefore involves acquisition and subsequent averaging of a large series of brain images during infusion of a drug or over the course of well-controlled, changing cognitive states (e.g. performing a visually presented working memory task versus attending to a simple visual stimulus) before and after drug administration. Regions of significant signal change related to the modulation of brain activity by a drug then are defined by statistical analysis of the averaged signal changes across the brain.

receptor availability after dopamine depletion or pharmacologically stimulated dopamine release allow more detailed characterisation of alterations in neurotransmitter concentrations in patient populations [6,9]. Integrated application of fMRI and PET receptor mapping has the potential to relate system-level brain functions directly with the molecular targets of new drug candidates in ways that enhance target validation for the new molecules faster and more cheaply than conventional clinical designs allow, as has been demonstrated with recent evaluation of a novel μ-opioid receptor antagonist [10].

PET biodistribution: ensuring that a candidate drug reaches the target tissue

The distribution of a drug in a target tissue often cannot be inferred directly from free plasma concentrations because of locally expressed endothelial structural and functional specialisations preventing an equilibrium distribution of the molecule between blood and tissue, e.g. at blood–brain [11•] or blood–tumour barriers [12]. Species differences in biodistribution limit direct translation of measures from many experimental animals (Figure 1), so that there can be substantial uncertainty whether a drug is able to reach the desired target in humans despite pharmacological effects in preclinical models [13].

PET can be used to non-invasively assess molecule biodistribution in humans if the compound of interest can be radiolabelled in a way that does not change its pharmacological properties. Kinetic modelling of the time course of radioactivity in the blood and in the tissue as imaged by PET allows the clearance from plasma to tissue (a function of the blood flow and the tissue extraction of the molecule from the blood) to be estimated. In some instances, tissue free drug concentrations can be estimated [14•]. Although potentially considerably more complex to interpret, there is a considerable potential for these methods to be extended for an understanding of the distribution of biopharmaceuticals as well as small molecules [15].

Defining dose (plasma concentration)–target occupancy relations

Quantification of the relationship between plasma concentration (and thus the administered dose) and the extent of target interaction allows a critical extension of the biodistribution question. Target occupancy studies require availability of radioligand with sufficient affinity and selectivity for the target to provide adequate signal-to-background for measurement of target availability [16]. The development and characterisation of such ligands are non-trivial, although recent advances in approaches to design based on biomathematical modelling approaches promise the potential for a more rational foundation for future efforts [17••]. At present, PET ligand availability is a limiting factor to the application of this approach, although there are many examples of such molecules, particularly for CNS targets (see http://micad.nih.gov). The selected radioligand with appropriate target selectivity then can be used to quantify the free target available before and after the administration of pharmacological doses of the molecule of interest, to