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Challenges for PET Neuroimaging of Depressive Disorders

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1. Introduction

This chapter deals with two major challenges facing PET neuroimaging of depressive disorders: determining the neurobiology of depressive disorders and inventing suitable positron-emitting radioligands for exploring molecular aspects of brain function. Over the years, PET neuroimaging of depressive disorder has focused almost exclusively on monoaminergic neurotransmission, but judging from recent reports, those studies have failed to demonstrate reliable links between either serotonergic or dopaminergic mechanisms and depressive disorders. Today, disturbances in numerous other neurobiological processes are thought to cause depressive disorder, but we lack PET radioligands to test most modern hypotheses in the living human brain. Thus, the future success of PET neuroimaging of depressive disorders depends on advances in neuroscience concerning molecular neurobiology and on advances in radiochemistry for the synthesis of novel positron-emitting molecules to test hypotheses on the neurobiology of depressive disorders. Success in PET neuroimaging of depressive disorders is expected to provide insight toward better prevention and treatment of these disabling conditions.

2. Depressive disorders

Depression is a severe, disabling, and sometime fatal illness. Symptoms of depression include a mental state of hopelessness, sleep disturbance, altered appetite, lack of energy, concentration difficulties, low self-esteem, self-destructive behavior, painful bodily sensations, and suicidal ideation. Needless to say, depressive disorders require prompt attention and appropriate care. A major current issue in psychiatry is the lack effective treatments to relieve the symptoms of depression in many sufferers (Berlim et al. 2008;Rush et al. 2003a;Rush et al. 2009). Hopefully, further studies of neurobiological mechanisms in depressive disorders will eventually lead to more effective antidepressant treatments. That hope has motivated many studies of molecular mechanisms in depression using positron emission tomography (PET).

3. Principles of PET neuroimaging

PET neuroimaging is a challenging technology. It requires rapid synthesis of highly-purified positron-emitting radioligands of high specific activity, intravenous injection of radioactive compound often with arterial blood sampling in partially immobilized subjects, 3-dimensional registration of photon emissions from the target organ over time, and computerized computations of kinetic parameters. The kinetic parameter used most often to describe the outcome of PET neuroimaging, namely the binding potential, is a complex entity composed of three factors: the number of receptors that are available for binding by the PET radioligand, the affinity of the available receptors toward the PET radioligand , and the concentration of molecules other than the PET radioligand that bind to those receptors (Dunlop and Nemeroff 2007;Laruelle 2000;Lammertsma 2002). The binding potential is an estimate that reflects a series of molecular events, and its value depends on the kinetic model selected for the data analysis. The contribution of individual factors to the binding potential cannot be determined by the single-scan design used in most PET studies of depression. Thus, the complexity of both depression and PET sets limits on the interpretation of findings.

Most PET studies of depressive disorders have been based on the monoamine hypothesis (Schildkraut et al. 1968;Schildkraut and Kety 1967), despite the clear-cut need for exploring other strategies (Hindmarch 2002;Berton and Nestler 2006;Pittenger and Duman 2008;Paschos et al. 2009;Covington, III et al. 2010;Wegener and Volke 2010). Here, we first review recent molecular PET reports on depressive disorders in humans. Next, we discuss challenges for PET in studying in humans the molecular basis of depressive disorders. Then, we outline the need for suitable positron-emitting radioligands for testing modern hypotheses on the causes and consequences of depressive disorders. Clearly, there are a number of major challenges facing those who care to know the molecular basis of these disabling and sometimes fatal diseases.

4. Recent PET studies of serotonin in depressive disorders

Serotonergic neurotransmission has received most attention in studies of depression (Nemeroff and Owens 2009;Owens and Nemeroff 1994). We find, however, that PET studies have not provided consistent findings of a causal link between serotonergic dysfunction and the severity of depressive disorders. Ten PET studies published in recent years have used [^{11}C]McNeil 5652 or [^{11}C]DASB to assess the serotonin transporter in depressed subjects and healthy controls. Four of those studies, plus a data re-analysis, noted less binding by the serotonin transporter in brain regions of depressed subjects (Miller et al. 2008;Oquendo et al. 2007;Parsey et al. 2006a;Reimold et al. 2008;Miller et al. 2009b), four studies found more binding by the serotonin transporter in depressed subjects (Reivich et al. 2004;Cannon et al. 2006b;Cannon et al. 2007;Boileau et al. 2008), and two studies found no difference between depressed subjects and healthy controls in binding by serotonin transporters in brain regions (Meyer et al. 2004;Bhagwagar et al. 2007).

Discrepancies are also apparent in the outcome of recent PET studies carried out with [^{11}C]WAY-100635 or [^{18}F]FCWAY to assess serotonin type 1A receptors in depressed subjects and healthy controls. Here, five studies noted less binding by serotonin type 1A receptors in brain regions of depressed subjects (Bhagwagar et al. 2004;Meltzer et al. 2004;Hirvonen et al. 2008;Drevets et al. 2007;Theodore et al. 2007), one study reported no

difference between depressed subjects and healthy controls in binding by serotonin type 1A receptors (Mickey et al. 2008), while more binding by serotonin type 1A receptors was found in three studies of depressed subjects or remitted, depressed subjects compared with healthy controls, with no correlation between receptor binding and depression severity (Parsey et al. 2006b;Miller et al. 2009a;Sullivan et al. 2009). In addition, neither antidepressant treatment including ECT nor induction of depression by depletion of tryptophan affected binding by serotonin type 1A receptors in brain regions (Moses-Kolko et al. 2007;Praschak-Rieder et al. 2004;Saijo et al. 2010). These findings clearly challenge the notion that alterations of serotonergic functions are causally linked with either depressive disorders or antidepressant efficacy.

Serotonin type 2 receptors have also been studied by PET in recent years in relation to depressive disorders. Two closely-related studies used [^{18}F]altanserin for PET and noted less hippocampal binding in depressed subjects than in healthy controls (Mintun et al. 2004;Sheline et al. 2004). In contrast, two other PET studies used either [^{11}C]MDL 100,907 or [^{18}F]setoperone to assess serotonin type 2 receptors and noted more binding in depressive subjects than in healthy controls (Bhagwagar et al. 2006;Meyer et al. 2003). In our view, PET studies with the radioligands that are currently available for assessing serotonergic functions in the living human brain have failed to provide conclusive evidence for aberrant serotonergic mechanisms in depressive disorders. We have noted, however, that receptor occupancy of serotonin transporters can be assessed reliably by PET with [^{11}C]DASB or [^{11}C]McNeil 5652 (Voineskos et al. 2007;Miller et al. 2008). Perhaps studies of receptor occupancy before and during antidepressant therapies can provide a means of determining whether treatment-resistance stems from inadequate receptor blockade.

Monoamine oxidase has also received attention in PET studies of depressive disorders. One study used [^{11}C]harmine, a reversible inhibitor of type A MAO, for PET scanning in order to see whether the activity of that enzyme differs between depressed patients and healthy subjects (Meyer et al. 2006a). More binding of [^{11}C]harmine was noted in brain regions of depressed patients than in healthy controls, but no correlation was found between clinical variables and PET findings in the patients. A lack of correspondence between clinical condition of patients and degree of binding of [^{11}C]harmine in brain regions was also observed in a recent follow-up PET study of type A MAO in depressive disorders; an elevated distribution volume of the PET radioligand persisted in patients despite symptom-reduction during antidepressant drug treatment (Meyer et al. 2009a).

5. Recent PET studies of dopamine in depressive disorders

Dopaminergic neurotransmission is thought to play a role in depression, perhaps via defects in central reward systems (Randrup and Braestrup 1977;Spanagel and Weiss 1999). Several PET radioligands have been used in recent years for probing dopaminergic mechanisms in depressed humans. [^{18}F]Fluoro-L-dopa is used routinely for assessing dopamine synthesis by PET in Parkinson's disease (Takikawa et al. 1994), and it showed reduced striatal uptake in depressed subjects with retarded movement (Bragulat et al. 2007). Certain dopamine receptors have also been examined by PET in recent years in depressed subjects. Dopamine D_1 receptors were assessed by [^{11}C]SCH 23,390 or [^{11}C]NNC-112 in two PET studies of depression (Dougherty et al. 2006;Cannon et al. 2008), and both reports found less binding in striatal regions of depressed subjects than of healthy controls. Dopamine $D_{2/3}$ receptors

have been assessed in five PET studies using either [^{11}C]raclopride or [^{11}C]FLB 457 in depressed subjects and healthy controls; one study noted more striatal binding by dopamine $D_{2/3}$ receptors in depressed subjects (Meyer et al. 2006b), another study found less dopamine $D_{2/3}$ receptor binding in depression (Montgomery et al. 2007), and three studies showed no difference between depressed and healthy subjects in dopamine $D_{2/3}$ receptor binding in brain regions (Kuroda et al. 2006;Montgomery et al. 2007;Busto et al. 2009). The transport of dopamine as well as noradrenaline from the synaptic cleft into presynaptic terminals was assessed by PET using [^{11}C]RTI-32 in 20 Parkinson patients, some of which were depressed (Remy et al. 2005). Less transporter binding was noted in brain regions of depressed Parkinson patients than of non-depressed patients with Parkinson's disease. In our view, a consistent picture of causal relationships between dopaminergic disturbances and depression has failed to appear from PET studies carried out with the positron-emitting radioligands that are currently available for use in humans, except perhaps for movement disorders of depressed subjects.

6. Recent PET neuroimaging of non-serotonergic and non-dopaminergic mechanisms in depressive disorders.

Relatively few PET studies of depressive disorders have been reported recently on molecular mechanisms unrelated to serotonergic and dopaminergic neurotransmission.
In one study, [^{11}C]doxepin was used to see whether human depression depends on histaminergic mechanisms (Kano et al. 2004). The binding potential of the PET radioligand in some brain regions was lower in depressed patients than in healthy subjects and was correlated negatively to the patient's self-rated depression severity. In another PET study, the role of cholinergic processes in major depressive disorder was studied using [^{18}F]FP-TZTP (Cannon et al. 2006a). The depressed patients had a diagnosis of either recurrent major depressive disorder or bipolar disorder. [^{18}F]FP-TZTP binding in cortical brain regions and white matter was lower in bipolar depressed patients than in healthy subjects and was correlated negatively to depression severity. A third PET study used 2-[^{18}F]FA-85380 to look at cholinergic function and self-rated symptoms of depression in patients with Parkinson disease (Meyer et al. 2009b). Although none of the Parkinson patients met standard criteria for major depressive disorder (Schrag et al. 2007;Bech 1984), negative correlations were noted between self-rated depression scores and binding of the PET radiotracer in several cortical regions. Another PET study of subjects with only mild self-rated symptoms of depression used [^{18}F]FDDNP to explore possible correlations with aggregates of amyloid and tau proteins in brain regions (Lavretsky et al. 2009). Subjects with mild cognitive impairment showed a positive correlation between self-rated depression scores and radioligand binding in medial temporal lobe.

7. Challenges for PET neuroimaging of depressive disorders

Molecular tools currently available for PET neuroimaging in humans assess primarily monoaminergic receptors on surface of brain cells. As a result, most PET neuroimaging studies of depressive disorder focus on some aspect of the monoamine hypothesis. In our view, such PET studies have neither proved nor refuted conclusively any aspect of the monoamine hypothesis for depression (Schildkraut and Kety 1967;Asberg et al. 1976;Meltzer

and Lowy 1987). While that monoamine hypothesis has been fruitful in certain ways, advances in neurobiology and neuropsychopharmacology have introduced a variety of additional molecular mechanisms into research on depressive disorders (Figure 1). Today, depression is viewed as the result of multiple neurobiological processes including disturbances of gene expression, intracellular signaling, cytokines and neurotropic agents (Tanis and Duman 2007;Berton and Nestler 2006;Krishnan and Nestler 2008;Maes 2008;Pittenger and Duman 2008). In our view, the success of PET scanning in determining the role of diverse neurobiological processes in depression will depend heavily on the invention of appropriate molecular tools, in the form of positron-emitting radioligands, for testing directly, in the living human brain, ever-changing hypotheses on causal connections between neuromolecular processes and the symptoms and severity of depressive disorders.

PET neuroimaging has been unable to pinpoint neurobiological defects in the brain of humans suffering from depressive disorders. This is perhaps not surprising, given the limited number of suitable positron-emitting radioligands that are currently available for PET studies of neurobiological processes in humans. Despite more than two decades of research, inconsistent findings have been obtained between molecular PET studies of depressive disorders, with few replication attempts. An important challenge facing PET neuroimaging of depressive disorders resides, therefore, in determining which aspects of depressive disorders to study next. We propose that particular attention be given to studying antidepressant non-response by PET, because that condition remains a major challenge for medical and social resources, with 25 – 50% of people suffering from major depressive disorder never recovering fully (Rush et al. 2003b;Rush et al. 2008;Fava 2003;Petersen et al. 2005;Berlim and Turecki 2007). Severe aberrations in molecular mechanisms at multiple cerebral sites may be involved in antidepressant non-response (Krishnan and Nestler 2008;Berton and Nestler 2006;Ressler and Mayberg 2007;Drevets et al. 2008). Success in determining by PET the neurobiological basis of antidepressant non-response can be expected to provide an improved understanding of depressive disorders and point to more effective ways of treating them.

The richness of human emotions, thoughts, and actions along with the complexity of molecular events in the human brain caution, however, against expectations of rapid progress in discovering by PET neuroimaging an improved diagnostic system or a panacea for depression (MacQueen 2009). This brings us to another challenge for PET neuroimaging of depressive disorders, namely that of integrating rapid advances in neuroscience into suitable positron-emitting radioligands and PET research designs. In view of the heterogeneous nature of depressive disorders (Berlim and Turecki 2007;Parker 2000;Pae et al. 2009;Thase 2009), multiple molecular pathways may cause symptoms of the disease. Some of the pathways that may be causally connected to depressive disorders include genes that encode presynaptic vesicular proteins, plasma membrane receptors, intracellular signaling molecules, proteins that regulate the actin cytoskeleton, and the transcriptional regulatory machinery (Covington, III et al. 2010). Additional molecular pathways thought to be either causative or curative of depression include neuroplasticity, neuropeptides, and nitric oxide synthase (Pittenger and Duman 2008;Paschos et al. 2009;Wegener and Volke 2010). Clearly, responding promptly to ever-changing notions on molecular pathways of depressive disorders constitutes a major challenge for PET neuroimaging.

Another challenging issue for PET neuroimaging of depressive disorders concerns financial support of research. Compared with the costs of brain diseases in the US and Europe

(Sobocki et al. 2006;Greenberg et al. 2003;Russell et al. 2004), national funding of molecular brain imaging is miniscule. In Europe, for example, the total annual cost of depression in 2004 was 120 billion Euro, for a population of 466 million with at least 21 million affected residents (Sobocki et al. 2006), making depression the most costly brain disorder. In contrast, recent annual funding for molecular brain imaging of depressive disorders can be estimated at only 0.001 – 0.003 billion Euro, which is 100,000 times less than the annual cost of the disease. Without substantial funding, molecular brain imaging by PET may continue to be severely handicapped in providing reliable findings on molecular causes, consequences, and cures of depressive disorders.

An additional challenge for PET neuroimaging of depressive disorders concerns the invention of appropriate research strategies for testing multiple hypotheses on molecular mechanisms in the living brain. At present, two opposing strategies characterize research in this field. One strategy advocates the use of positron-emitting radioligands with marked selectivity and high affinity for a single, specific neuronal macromolecule such as a monoamine receptor or enzyme. That approach has, in fact, been used in the majority of PET studies on molecular mechanisms in depression and may reflect the assumption that depressive disorders are caused by a dysfunction of a single molecular mechanism. The other strategy advocates the use of positron-emitting radioligands with affinities for several neuronal macromolecules. This approach may rest on the assumption that depressive disorders are caused by disturbances in any number of multiple molecular pathways. Recently, we followed the notion of multiple molecular pathways in a PET study of treatment-resistant depression (Smith et al. 2009). Using [^{11}C]mirtazapine, a positron-emitting radioligand of an antidepressant drug affecting several receptor systems (Millan 2006;Millan 2009;Smith et al. 2007), we studied by PET a group of depressed subjects who had failed to benefit from at least two antidepressant treatments (Smith et al. 2009). All subjects had received no antidepressant medication for at least 2 months before the study. We found that binding potentials of [^{11}C]mirtazapine in cerebral cortical regions were, in general, lower in depressed nonresponders than in healthy controls, while removal rates of [^{11}C]mirtazapine were generally higher in diencephalic regions of depressed nonresponders than in healthy controls. In keeping with the notion that depressive disorders are heterogeneous (Berlim and Turecki 2007;Parker 2000;Pae et al. 2009;Thase 2009), we noted that the binding of [^{11}C]mirtazapine in brain regions of some of the depressed, antidepressant-nonresponders was well-within the normal range, whereas reduced regional binding of [^{11}C]mirtazapine was noted in other depressed subjects. A challenge for additional PET studies with [^{11}C]mirtazapine is to see whether the procedure can provide a neuromolecular-screening devise that can distinguish between neurobiologically-distinct subgroups of depressed, antidepressant-nonresponders.

One of the most formidable challenges for PET neuroimaging of depressive disorders relates to the blood-brain-barrier (BBB). The BBB is a limiting factor for PET studies of neuromolecular processes in the living human brain because it both restricts the passage of endogenous and foreign substances into the brain and expels many substances rapidly from the brain (Beduneau et al. 2008;Gjedde et al. 2000;Halldin et al. 2001;Kreuter 2001;Laruelle et al. 2002;Misra et al. 2003;Tosi et al. 2008). Thus, failure to traverse the BBB in sufficient quantities and/or to remain in brain tissue for a sufficient duration in the course of a PET-scanning session has caused many candidate radioligands to be discarded. PET neuroscientists will need to devise ways of improving the passage of novel positron-

emitting radioligands across the BBB for binding to molecular targets within the central nervous system. One possibility that may deserve close attention in the time ahead concerns the use of nanoparticles in PET neuroimaging. Some nanoparticles have already been shown to markedly enhance the level of certain drugs in the central nervous system (Gelperina et al. 2009;Kreuter 2002;Vergoni et al. 2009), indicating a potential role of nanoparticles as carrier-molecules for ushering novel PET radioligands to their neurobiological targets.

8. Challenges for PET radiochemistry

The synthesis and development of radiopharmaceuticals for PET is a complicated and extremely challenging process. The main challenge of using the short-lived PET radioisotopes carbon-11 ($t_{1/2}$ = 20.4 min), fluorine-18 ($t_{1/2}$ = 110 min), nitrogen-13 ($t_{1/2}$ = 9.97 min) or oxygen-15 ($t_{1/2}$ = 2.04 min) for the synthesis of radiopharmaceuticals is that of time (Fowler and Wolf 1997). The short half-lives of these radioisotopes imposes severe time restrictions when preparing radiolabelled compounds for PET. Such short time periods limit the range of synthetic strategies that are available to obtain target radiolabelled compounds, confining them to chemical reactions and processes that are on the order of seconds and minutes rather than hours. Many PET radiolabelling procedures are therefore limited to only one or two distinct chemical steps with the introduction of the PET radioisotope as late in the radiosynthesis as possible. The radioisotopes ^{13}N and ^{15}O are of limited applicability for imaging receptor-related processes of the CNS because their short half-lives prohibit the synthesis of complex tracer molecules and are generally not commensurate with the time frames required for monitoring ligand-receptor based processes. ^{11}C and ^{18}F are therefore the most commonly used radioisotopes in PET for imaging neuroreceptor processes, having half-lives that are long enough to enable multi-step synthesis of quite complex radioligands in addition to being appropriate for monitoring ligand-receptor processes. The choice of which radioisotope, ^{11}C or ^{18}F, to use depends on a number of decisive factors. Firstly, the structure of the target molecule. For example, does it have fluorine atom and would introducing an ^{18}F adversely affect its biological properties? Secondly, the ease of synthesis. Can the target molecule be synthesised using available chemical techniques and are the appropriate ^{18}F or ^{11}C precursors available for reaction? There may be an obvious advantage in using one radioisotope over the other in terms of radiochemical yield, specific activity or speed of labelling. Thirdly, the time frame of the biological process under investigation; ^{18}F may be a more appropriate isotope for the investigation of longer biological processes such as protein synthesis.

Carbon is present in all natural products and almost every artificially synthesised drug-like compound. The replacement of a naturally abundant ^{12}C atom with that of a positron-emitting ^{11}C isotope results in ^{11}C-labeled molecules that will have essentially identical chemical and biological properties of the parent compound. This is a hugely important feature since it removes any doubts about the effect of introducing an artificial exogenous radioisotope (e.g. ^{18}F) or tag (e.g. [Ga-DOTA] complex) into the parent molecule which may affect its biological behaviour. Although the short 20 min half-life of ^{11}C precludes long multistep syntheses, a wide range of chemical reactions have been developed for synthesising ^{11}C labelled compounds (Miller et al. 2008). In comparison, ^{18}F has a considerably longer half-life of 110 min which permits longer and more complex radiosynthetic strategies in addition to allowing the transportation of doses to scanning sites

several hours away. The key concern, alluded to above, of introducing an ^{18}F radioisotope into a molecule is the unknown effects the fluorine atom may have on the biological properties of the newly labelled compound. Radiosynthesis with ^{18}F may be classified into two areas: (i) direct fluorination, where the ^{18}F isotope is introduced into the target molecule in one chemical step, and (ii) indirect fluorination which requires a multi-step synthesis for the preparation of so-called ^{18}F prosthetic groups that are then further reacted to give the target molecule. Considerable effort has been devoted to the development of these small and reactive ^{18}F prosthetic groups for the rapid labelling of a range of ^{18}F molecules. In recent years the development of rapid 'click chemistry' methods continues to generate much interest in this area (Glaser and Robins 2009).

Some of the challenges within PET radiochemistry are evidently more obvious than others and relate to the technical challenges associated with the fast, efficient and safe handling of short-lived radioactive material. The production of a pharmaceutical-quality radiotracer sample ready for injection requires the synthesis, purification, and analysis to be complete, generally, within three half-lives of the radioisotope in order to provide enough radioactivity for a reliable scan. In the case of a ^{11}C radiosynthesis, this would be within 60 min from the end of bombardment. The need for such fast reactions and processes has lead, not only to new chemical methodologies, but to technological advancements in the development of fully automated and programmable synthesis units for performing and processing radiosynthetic reactions. New technologies such as microwave cavities (Elander et al. 2000), microfluidic reactors (Miller 2009), and solid-phase synthesis methods (Marik et al. 2006) have been adapted to enhance the speed, reproducibility, and efficiency of radiolabelling reactions.

Other challenges are more subtle and include the unusual scale of PET labelling reactions where the cold precursor in the reaction is often in huge excess (>1000 fold) compared with the radiolabelled compound. This can lead to unpredictable reaction kinetics and the formation of unwanted by-products from competing side reactions. There is often a desire to improve radiochemical yields (RCY) and to obtain high specific activities from labelling reactions. Although high RCYs are not always essential, they do provide a very useful measure of the efficiency of the radiolabelling procedure. The requirement of high specific activity, on the other hand, is often essential for the study of neuroreceptors such as those associated with depressive disorders. Specific activities of a radiolabelled compound for a PET study of neuroreceptors are typically required to be in the order of 50–500 GBq μmol^{-1}.

The requirement of high specific activities is most apparent if the radioligand has a high affinity for a receptor. Radiotracers produced with low specific activity will result in poor PET images owing to the rapid saturation of the binding sites by the proportionately higher amount of non-radioactive ligand. The production of radiotracers with high specific activity is therefore highly desirable but can be challenging and depends on the radioisotope selected for the radiosynthesis, choice of synthetic precursor material and radiosynthetic labelling route. Take, for example, the selective 5-HT_{1A} receptor antagonist WAY-100635 which can be radiolabelled using ^{11}C in the carbonyl position to give [*carbonyl*-^{11}C]WAY-100635 (figure 2). This is usually achieved via the two-step reaction of $^{11}CO_2$ with cyclohexylmagnesium chloride sequentially followed by addition of thionyl chloride to give the reactive [*carbonyl*-^{11}C]cyclohexyl acid chloride. Reaction of [*carbonyl*-^{11}C]cyclohexyl acid chloride with the WAY-100634 amine precursor generates the desired [*carbonyl*-^{11}C]WAY-100635 (McCarron et al. 1996). One of the key challenges with the synthesis of [*carbonyl*-

[11C]WAY-100635 is the exclusion of atmospheric $^{12}CO_2$ which poses a significant risk of contaminating the reaction at the initial first step. Without due care, contamination from atmospheric ^{12}C results in an undesirably low specific radioactivity, and consequently poor PET images.

The labelling position of radioisotope on the ligand is also a key consideration, and can pose significant challenges. Two key questions should be asked regarding labelling position, (i) is it viable, synthetically, to radiolabel in the position that we desire? and (ii) will the labelling position be metabolically stable? An understanding of the metabolic fate of a radiotracer can be vitally important in the development of a radiotracer and in determining the best position to radiolabel. There is usually a choice of positions within the molecule for radioisotope labelling, with some positions being more challenging than others. However, labelling a molecule in several different positions can yield important metabolic information about the fate of the molecule *in vivo* and can be useful in determining which labelling position is best for imaging. Metabolism of the labelled compound in the body may result in undesired labelled metabolites which can give two undesired effects: (i) an enhanced unwanted background signal which results in poor quality PET image, and (ii) pharmacologically active metabolites that compete with the parent compound for the biological target and complicate the interpretation of PET data. The importance of the labelling position can be illustrated by past experiences with the ^{11}C labelling of WAY-100635 radioligand. WAY-100635 can be labelled in either the *O*-methyl position on the phenyl ring via a [^{11}C]methylation reaction or on the carbonyl position as previously mentioned above (figure 2). [*O-methyl*-^{11}C]WAY-100635 was however found to have limitations for imaging 5-HT_{1A} receptors in human owing to the formation of the more lipophilic descyclohexanecarbonyl ([*O-methyl*-^{11}C]WAY-100634) metabolite *in vivo.* This metabolite was found to enter the brain much more readily than the parent [*O-methyl*-^{11}C]WAY-100635 (Osman et al. 1996) and thus complicate quantification of the 5-HT_{1A} receptors by competing with [*O-methyl*-^{11}C]WAY-100635 for 5-HT_{1A} binding sites and by contributing to the non-specific binding signal. In contrast, by selecting to label WAY-100635 in the carbonyl position (figure 2) significantly improved PET images with much superior delineation of 5-HT_{1A} receptors in human brain were obtained (Pike et al. 1996). The reason for [*carbonyl*-^{11}C]WAY-100635 giving better images is due to the metabolism of this compound and position of the radioisotope; with the ^{11}C isotope on the carbonyl group adjacent to the cyclohexyl ring, *in vivo* metabolism cleaves the cyclohexyl and ^{11}C carbonyl and generates the labelled metabolite [^{11}C]cyclohexanecarboxylic acid which is hydrophilic and, therefore, does not readily enter the brain to confound the signal from the parent [*carbonyl*-^{11}C]WAY-100635 molecule.

Appropriate pharmacodynamic properties, such as high affinities and selectivities for the target, are central to characterising the success of a PET radioligand (Passchier et al. 2002). The affinity of the probe for the binding site is a key factor that affects the degree of nonspecific binding. Nonspecific binding is a major challenge in the development of radioligands and is often cited for the high failure rate of new radioligands. Nonspecific binding occurs when the radioligand binds or interacts with a molecular target or tissue other than the site of interest. This could include interactions of the radioligand with membrane structures or with receptors which are not under investigation. A high proportion of nonspecific binding signal may result in a severe reduction in the PET signal contrast when investigating a specific receptor with a radioligand. The lipophilicity of the

tracer molecule is frequently quoted as an important factor in discussions of nonspecific binding. Highly lipophilic molecules are known to interact extensively with the fatty residues in membrane bilayers which can prevent penetration of the radioligand into brain tissue and therefore prevent it from reaching the intended molecular target. The challenges in terms of the design and selection of tracer molecules to image the CNS often involve tailoring the lipophilicity of a radioligand. Successful PET CNS radiotracers normally have lipophilicities (logP, logarithm of the octanol/water partition coefficient) within an optimal logP window of 1.5-3 in order to ensure the passage through the BBB. Although logP values are an important indicator in ligand design, they can lead to an oversimplification of ligand selection. A greater understanding of the causes of nonspecific binding at a molecular level may be key to achieving higher success rates for radioligand selection. A recent study has used computation methods to estimate the interaction energy between candidate molecules and phospholipids which can then be used as a predictor for nonspecific binding *in vivo* (Rosso et al. 2008). Results from this study interestingly show that the drug's interaction with the lipid molecule is a better predictor for nonspecific binding than the experimentally measured logP value. Further recent work in this area suggests that alternative transport mechanisms of drug molecules through biological membranes, which result in the chemically activated degradation of the phospholipid membranes, may be related to nonspecific binding (Casey et al. 2008).

Concluding remark

We hope that the challenges described here will inspire scientists to carry out many more studies using PET neuroimaging in order to eventually discover new and better procedures for diagnosing and treating major depressive disorders.

9. Chemical names

Altanserin	3-2-4-4-Fluorobenzoyl-1-piperidinylethyl-2,3-dihydro-2-thioxo-41*H*-quinazolinone
DASB	3-Amino-4-[[2-[dimethylaminomethyl] phenyl]thio] benzonitrile
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
Doxepin	3-dibenzo[*b,e*]oxepin-116*H*-ylidene-*N,N*-dimethylpropan-1-amine
2-FA-85380	2-fluoro-3-(2[S]-2-azetidinylmethoxy)-pyridine
FCWAY	*N*-[2-[4-2-Methoxyphenyl-1-piperazinyl]ethyl]-*N*-2-pyridinyl-*trans*-4-fluorocyclohexylcarboxamide
FDDNP	2-(1-{6-_(2-_fluorine-18_fluoroethyl)(methyl)amino-2-naphthyl}ethylidene) malononitrile
FESP	3-2-Fluoroethyl-8-[4-4-fluorophenyl-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one
FLB 457	5-Bromo-*N*-[[2*S*-1-ethyl-2-pyrrolidinyl]methyl]-2,3-dimethoxybenzamide
Fluoro-L-dopa	2-Fluoro-5-hydroxy-L-tyrosine
FP-TZTP	3-3-3-Flouropropylthio-1,2,5-thiadiazol-4-yl-1,2,5,6-tetrahydro-1-methylpyridine

Harmine	7-Methoxy-1-methyl-9*H*-[3,4-*b*]indole
McNeil 5652	6*S*,10b*R*-1,2,3,5,6,10b-Hexahydro-6-[4-methylthiophenyl]-pyrrolo[2,1-a]isoquinoline
MDL 100,907	*R*-1-[2-4-Fluorophenylethyl]-4-2,3-dimethoxyphenyl-4-piperidinemethano
MPPF	4-Fluoro-*N*-[2-[4-2-methoxyphenyl-1-piperazinyl]ethyl]-*N*-2-pyridinylbenzamide
α-MTrp	α-Methyl-L-tryptophan
NNC-112	+-5-7-benzofuranyl-8-chloro-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazapine
Raclopride	3,5-Dichloro-*N*-[[2*S*-1-ethyl-2-pyrrolidinyl]methyl]-2-hydroxy-6-methoxybenzamide
RTI-32	Methyl-1*R*-2-exo-3-exo-8-methyl-3-4-methylphenyl-8-azabicyclo[3.2.1]octane-2-carboxylate
SCH 23,390	8-Chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol
Setoperone	6-[2-[4-4-Fluorobenzoyl-1-piperidinyl]ethyl]-2,3-dihydro-7-methyl-5*H*-thiazolo[3,2a] pyrimidin-5-one
WAY-100635	*N*-[2-[4-2-Methoxyphenyl-1-piperazinyl]ethyl]-*N*-2-pyridinyl-cyclohexylcarboxamide

10. Conflict of interest

The authors declare that, except for income received from their primary employer, no financial support has been received for their research activity, including the writing of this review.

11. Acknowledgments

We thank everybody at the Center for Psychiatric Research and the PET Center of Aarhus University for providing a positive atmosphere in which to work. DFS thanks the Danish Medical Research Council for research funding, and PWM is grateful to the EPSRC for the award of a Life Sciences Interface fellowship (EP/E039278/1).

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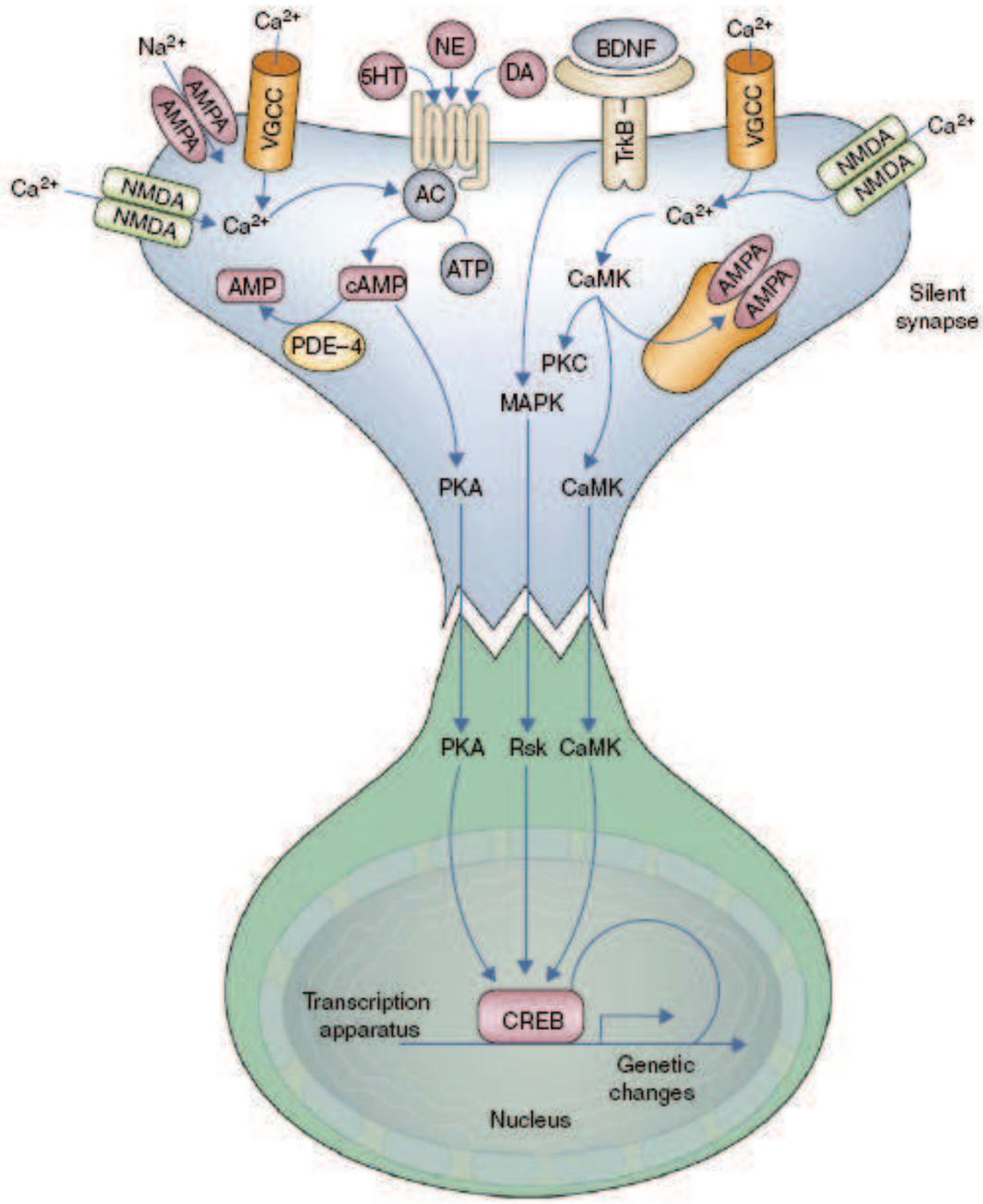
Figure legends

Figure 1. Major molecular pathways involved in neuroplasticity and affected by stress, depression, and antidepressant treatment. Some major molecular pathways involved in both short- and long-term neuroplastic changes are shown. Certain intermediates and other details are left out for clarity. Many of these pathways are influenced in opposite ways by stress and depression. For example, both chronic stress in animals and depression in humans have been associated with reductions in the transcription factor CREB, and antidepressants enhance CREB activity in the hippocampus. Abbreviations: NMDA, N-methyl-D-aspartate glutamate receptor; AMPA, amino-3-hydroxy-5-methyl-isoxozole-4-propionic acid glutamate receptor; VGCC, voltage-gated calcium channel;
5-HT, 5-hydroxytryptamine (serotonin); NE, norepinephrine; DA, dopamine; BDNF, brain-derived neurotropic factor; Trk-B, BDNF receptor; AC, adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; AMP, adenosine monophosphate; PDE, phosphodiesterase, CaMK, calcium-calmodulin-dependent kinase; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; PKA, protein kinase A; Rsk, ribosomal S6 protein kinase; CREB, cAMP response element-binding protein. Reprinted by permission from Macmillan Publishers Ltd: *Neuropsychopharmacology*, Pittinger, C. and Duman, R.S., 33: 88-109, copyright 2008.

Figure 2. The selective 5-HT_{1A} receptor antagonist WAY-100635 which can be labelled on the methyl position to give [*O-methyl*-^{11}C]WAY-100635 or the carbonyl position to give [*carbonyl*-^{11}C]WAY-100635. Labelling positions are indicated with (*).

Figure 1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NMDA
NMDA
Ca2+
AC
ATP
Ca2+
CaMK
AMP
cAMP
PDE–4
AMPA
AMPA
Silent
synapse
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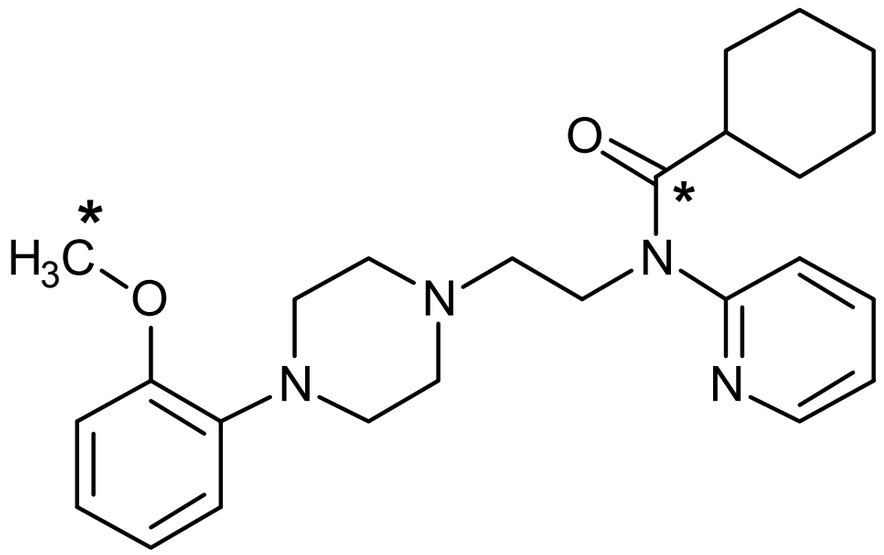
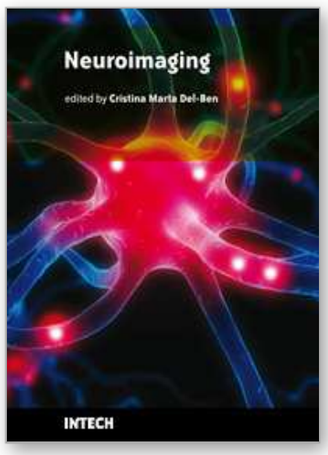
Transcription
apparatus
CREB
Genetic
changes
Nucleus

Figure 2





Neuroimaging

Edited by Cristina Marta Del-Ben

ISBN 978-953-307-127-5
Hard cover, 136 pages
Publisher Sciyo
Published online 17, August, 2010
Published in print edition August, 2010

Neuroimaging has become a crucial technique for Neurosciences. Different structural, functional and neurochemical methods, developed in recent decades, have allowed a systematic investigation on the role of neural substrates involved in functions performed by the central nervous system, whether normal or pathological. This book includes contributions from the general area of the neuroimaging to the understanding of normal functions and abnormalities of the central nervous system.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Donald Smith and Philip W. Miller (2010). Challenges for PET Neuroimaging of Depressive Disorders, Neuroimaging, Cristina Marta Del-Ben (Ed.), ISBN: 978-953-307-127-5, InTech, Available from: http://www.intechopen.com/books/neuroimaging/challenges-for-pet-neuroimaging-of-depressive-disorders

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