Imaging of the Antidepressant Drug Response Using SPECT and PET

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Abstract

SPECT and PET imaging has played an important role in the evaluation of pharmaceutical interventions in mood disorders such as depression.

This review highlights the proposed role of monoamines, their precursors and the blood–brain barrier in depression and the antidepressant drug response. Reviewed are trials using SPECT and PET, including levodopa and carbidopa moclobemide and St. John's wort; selegiline; the selective serotonin reuptake inhibitors (SSRIs) citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline; the noradrenaline-dopamine reuptake inhibitor (NDRI) bupropion; the serotonin-noradrenaline reuptake inhibitor (SNRI) venlafaxine; and the tricyclic antidepressants (TCAs) amitriptyline, nortriptyline and desipramine.

So far there is no apparent consensus on SPECT and PET imaging features for depression and its treatment, except that at least 80 % of serotonin transporters have to be occupied by serotonin reuptake inhibitors to achieve a clinically effective antidepressant drug response. The lack of characteristic imaging features may be due to inadequately designed imaging studies with insufficient in- and exclusion criteria, or it may be due to different aetiologies underlying the depressive state. Another possibility is that depression may be a non-regionalised phenomenon with global brain participation, similar to what has been proposed for the generation of the conscious condition.

In the future, it is likely that SPECT and PET imaging will remain an important tool and challenge in individual- and group-based approaches to obtain further information on depression and the antidepressant drug response.

12.1 Introduction

Since the advent of computer-based imaging several decades ago, it has become possible to achieve in vivo quantification of substrates in the brain in conscious and nonconscious patients and in neurological and psychiatric disease. SPECT and PET imaging play an important role in the response evaluation of pharmaceutical interventions in conditions such as mood disorders which are emotional states characterised by feelings and thoughts and mental activities involving consciousness, a continuum of mental states that ranges from full alertness to loss of meaningful communication (Katz et al. 2009). A well-known disorder of mood is depression, a state of low mood that affects a person's feelings, thoughts, behaviour and general health.

In consciousness, oxygen-based amino acids and monoamines are a component of brain function that operates in synapses, sometimes viewed as the main functional unit of the brain in which nerve stimuli are generated with or without external prompting (Liggan and Kay 1999; Südhof 2004; Wasser and Kavalali 2009; Bonansco et al. 2011). It has been proposed that two main networks of oxygen-based neurotransmitter function exist in the brain, namely, the monoamine axes (dopamine, noradrenaline, serotonin) and the amino acid axis (GABA/glutamate) (Clauss 2010, 2011; Nyakale et al. 2010). It has been proposed that mood is driven by monoamines (Schildkraut 1965; Bunney and Davis 1965; Van Praag 1967; Coppen 1969).

Although monoamines act on receptors localised to specific brain regions, they exert their influence globally throughout the brain. This occurs via neuronal circuits and networks which modulate global brain function and metabolism. Hence anomalies and receptor regulation at monoamine input points can have global cerebral effects (Green 2006).

Over the years, three main neurotransmitters are thought to be involved in mood disorders and depression. These are the monoamines dopamine, noradrenaline and serotonin, assumed to regulate emotion, reactions to stress, the drives of sleep, appetite, and sexuality. The monoamine hypothesis of depression is the most prominent chemical imbalance theory of depression today, having led to the development of modern antidepressant drugs, such as the serotonin reuptake inhibitors (SSRIs) (Lieberman 2003).

Monoamines are proposed abnormally high or low in psychiatric disease, for example, high with positive symptoms of schizophrenia and low with its negative ones and with depression. The dopamine theory, for example, attributes the positive symptoms of schizophrenia to an overactive dopaminergic signal transmission, while in depression monoamines are considered low and underactive (Carlsson 1977; Soares and Innis 1999; Abi-Dargham et al. 2000; Schildkraut 1965).

The monoamine hypothesis postulates that deficiencies of certain monoamine neurotransmitters are responsible for features of depression. Dopamine deficiency may be related to lowered attention, motivation, pleasure and reward. Noradrenaline may be related to alertness, energy and anxiety, attention, and interest in life; lack of serotonin may be related to anxiety, obsessions, and compulsions (Nutt 2008).

Some medications that counter depression influence the overall balance of dopamine, noradrenaline and serotonin in the brain. Supporters of the monoamine hypothesis recommend that the choice of antidepressant medication should be based on the possible mechanism of action that impacts most on the symptoms of depression. Anxious and irritable patients should be treated with serotonin or noradrenaline reuptake inhibitors, and those experiencing a loss of energy and enjoyment of life should be treated with noradrenaline and dopamine-enhancing drugs (Nutt 2008).

Cerebral dopamine, noradrenaline and serotonin are brain-produced neurotransmitters that are the end products of a long series of biochemical events that occur within the brain. Dopamine and noradrenaline are sourced from the conditionally essential amino acid tyrosine and the essential amino acid phenylalanine (Fernstrom and Fernstrom 2007). Serotonin is sourced from the essential amino acid tryptophan (Parker and Brotchie 2011). Tyrosine, phenylalanine and tryptophan compete with each other and other amino acids at the large neutral amino acid transporters of the blood–brain barrier to enter the brain (Fernstrom 2013). Once they have entered the brain, they depend on energy, enzymes, oxygen and other raw materials, supplied within the brain to convert them to the desired monoamines. Once the monoamines have been produced, they have to remain at homeostatic levels to be able to generate a normal brain function. It follows that monoamine homeostasis depends on a balance of monoamine production and loss. For adequate monoamine homeostasis, all

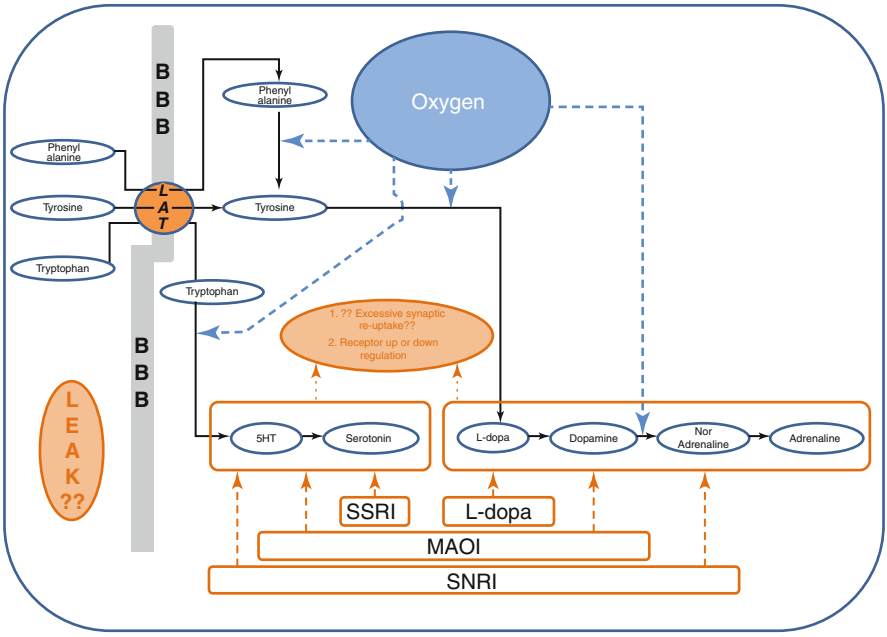

Fig. 12.1 The production pathways of the monoamines dopamine, noradrenaline and serotonin in the brain. The precursors tyrosine, phenylalanine and tryptophan enter the brain through the blood–brain barrier (BBB) after competing for places on the large neutral amino acid transporters (LAT). If sufficient oxygen is available, phenylalanine converts to tyrosine which then converts to L-dopa and dopamine. On oxygenation dopamine converts to noradrenaline and finally adrenaline. With available oxygen, tryptophan converts to 5-hydroxytryptophan (5-HT) which converts to serotonin. Monoamine production has to be maintained to counter metabolic attrition and other causes of depletion, such as leakage through a defective blood–brain barrier. Medications such as serotonin reuptake inhibitors (SSRIs), for example, counter synaptic serotonin reuptake. Other medications are L-dopa and tricyclic antidepressants (TCA) which can be used to supplement deficiencies

elements of production including oxygenation have to function adequately while synaptic removal and losses through metabolic attrition or possible leakage through a defective blood–brain barrier need to be limited.

If depression is caused by monoamine deficiencies, then pharmacological interventions would be a way to redress these, either by replacement or by correcting production anomalies or by stemming loss. For a simplified schematic presentation of the oxygen-reliant intra-cerebral production of the three major mood-associated monoamine neurotransmitters dopamine, noradrenaline and serotonin, please see Fig. 12.1.

In psychiatric disorders such as major depression (MD), potential monoamine deficiencies may benefit from pharmaceutical monoamine supplementation. Supplementation should be considered additional to internally generated monoamines, which depend on adequate precursor supplies, oxygen, cellular and synaptic integrity.

While the monoamine hypothesis explains aspects of biochemical pathology in depression, it does not explain the antidepressant lag time which is the time it takes from first antidepressant application to antidepressant response, often several weeks.

Such lag times may be due to receptor up- or downregulation or binding in adapting neuronal networks and circuits (Malberg and Blendy 2005).

Diurnal neurotransmitter variation may also play a role. For example, noradrenaline and serotonin availability are influenced by sleep when levels transiently decrease in areas such as the pons and amygdala (Shouse et al. 2000).

In a study of mood disorder, six unipolar depressed patients and eight healthy subjects underwent separate (18)F-FDG PET scans during waking and in their first REM sleep period. Compared to healthy controls, the depressed patients showed increased uptake in their tectal regions and in the left sensorimotor cortex, inferior temporal cortex, uncal gyrus-amygdala and subiculum complex during REM sleep (Nofzinger et al. 1999). In a study on sleep deprivation in 14 medicated patients, technetium-99m hexamethylpropyleneamineoxime (99mTc HMPAO) SPECT scans revealed hypoperfusion in the left prefrontal cortex which was reversible upon remission. Before sleep deprivation therapy, the responding patients had a significantly higher anterior cingulate perfusion than nonresponding patients, which normalised after sleep deprivation (Holthoff et al. 1999).

While it is well known that sleep deprivation can temporarily counter depression, it is equally known that repeated REM sleep withdrawal will result in "REM rebound". This "rebound" is associated with symptoms of depression and bipolar disorder. The severity of the rebound is related to the severity of "REM suppression" countered by subsequent increases in REM sleep (Suchecki et al. 2012; Greene and Siegel 2004). In recent drug developments, efforts have been made to explore the effect of sleep influencing medication in depression, for example, by using the melatonergic agonist agomelatine (Kasper et al. 2009).

Hypothyroidism is a well-known cause of depression that can occur due to insufficient thyroid hormone availability in the blood. A prospective cross-sectional study involving 254 patients showed that hypothyroidism increases the risk for critical mood deterioration by sevenfold (Larisch et al. 2004). In a 99mTc HMPAO SPECT study of 24 patients with hypothyroidism, 16 presented with a decreased uptake mostly in the posterior parietal lobes bilaterally and in the occipital lobes, including the cuneus. These areas extended to the bilateral prefrontal cortices when deterioration became more profound. After thyroxine replacement, regional cerebral blood flow improved in 9 of the 16 patients (Nagamachi et al. 2004).

Potential causes of depression are multifaceted with biological, psychological and social factors all playing a role. Its clinical manifestation is often assumed concurrent with anomalies in the monoamine homeostasis of the brain. The term "antidepressant drug" for the purpose of this review encompasses a wide range of substances which relieve aspects of the depressive state.

12.2 SPECT and PET Imaging in Psychiatric Disorders

SPECT and PET imaging of the brain in psychiatric disorders and depression typically comprises two aspects of brain function, namely, brain metabolism and brain neuroreceptor availability.

Brain metabolism can be measured directly by positron emission tomography (PET) using the positron emitting glucose analog [(18)F]-fluorodeoxyglucose ((18) F-FDG) or, indirectly, using the lipophilic cerebral perfusion agent technetium-99m hexamethylpropyleneamineoxime (99mTc HMPAO) that concentrates in neurons and partially in glia (Zerarka et al. 2001). Other tracers include 99mTc ethylcysteinate dimer (99mTc ECD), N-isopropyl-p-[123I]-iodoamphetamine (123I IMP), 133Xe and 195Au (Nikolaus et al. 2000). (18)F-FDG follows the path of glucose into the brain and neuronal tissue where it labels metabolic pathways that reflect the glucose metabolism of the brain (Chételat et al. 2005). The lipophilic amines 99mTc HMPAO, 99mTc ECD and 123I IMP pass through the blood–brain barrier in a blood flow-dependent manner and are trapped within the grey matter of the brain (Colamussi et al. 1999; O'Brien et al. 1999; Weder et al. 1990). (18)F-FDG hence reflects brain metabolism and 99mTc HMPAO, 99mTc ECD and 123I IMP mostly cerebral blood flow.

Neuroreceptor availability can be measured by markers of monoamine receptors. Measurable receptors include D1, D2 and 5-HT receptors and dopamine (DaT) and serotonin transporters (SERT). Multiple tracers can be used for imaging these and other aspects of the antidepressant response. These include amongst others 123 I IBZM, [11C]-raclopride, [123I]beta-CIT, 123 ioflupane (DaT Scan), [(11)C]WAY-100635, alpha-[(11)C]methyl-L-tryptophan, [(123)I]-ADAM, [(11) C]DASB, 123I-FP-CIT, [(18)F]FESP, [11C]verapamil, [(18)F]fluoro-L-dopa, [(11) C]-harmine and [(18)F] MPPF.

12.3 SPECT and PET Imaging in Depression

Early studies investigating depression often made use of brain perfusion tracers to gauge brain metabolism. A finding in these early studies was that of a global cerebral hypoperfusion in depression (Fountoulakis et al. 2004; Kanaya and Yonekawa 1990). This was often more pronounced in temporal, inferior frontal and parietal areas of the brain (Austin et al. 1992; Maes et al. 1993).

In a meta-analysis looking at metabolism and cerebral perfusion in major depression in 337 patients and 321 controls, Nikolaus et al. observed a decreased activity bilaterally in the frontal, parietal and occipital lobes; basal ganglia; and thalamus regions of the brain and right temporally, while the limbic region had a decreased uptake left and an increased uptake right (Nikolaus et al. 2000). In an analysis of major studies looking at the monoamine receptor function in depression until 2012, the same group observed that a complex pattern of dysregulation may exist within and between neurotransmitter systems, possibly linked to the subtype and duration of disease, the predominance of individual symptoms and pharmacological interventions (Nikolaus et al. 2012). Their main observations were that in acute depressive disease:

- Dopamine synthesis increases frontally and pre-frontally, decreasing in remission.
- 5-HT1A binding decreases frontally, pre-frontally and occipitally, expanding to the parietal, temporal and cingulate regions upon remission, while 5-HT2A binding decreases in the cingulate regions, shifting to the parietal regions upon remission.

- SERT binding increases in the insula and decreases in the thalamus and midbrain region, remaining decreased in the midbrain upon remission.

The above studies and others show that anomalies in cerebral blood flow and metabolism occur globally in depressive patients as do anomalies in receptor function. Although regional suppression of fronto-cortical and limbic circuits has been historically considered characteristic of depression, the evidence to date indicates otherwise, namely, that diffuse, rather than regional, abnormalities tend to occur.

12.3.1 SPECT and PET Imaging of Dopamine Receptors

Four major dopaminergic pathways have been identified in the mammalian brain, namely, the nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular pathways. Dopaminergic receptors are metabotropic G protein-coupled receptors classified to two major groups, the D1 (D1, D5) and the D2 group (D2, D3, D4). The D1 type are exclusively postsynaptic, located mostly in the striatum, nucleus accumbens, substantia nigra, olfactory bulb, amygdala, frontal cortex and to a lesser extent in the hippocampus, cerebellum, thalamus and hypothalamus. The D2 type are expressed pre- and postsynaptically mostly in the striatum, nucleus accumbens, olfactory tubercle and to a lesser extent in the substantia nigra, ventral tegmental brain region, hypothalamus, cortical areas, septum, amygdala and hippocampus (for a comprehensive review, see Beaulieu and Gainetdinov 2011). Tracers that can be used to measure D2 density are 123 I IBZM, a SPECT tracer that marks the postsynaptic D2 receptors, and [11C]-raclopride, a PET tracer that measures the D2 receptor binding in the striatum (Laruelle 2000) (Hierholzer et al. 1992). Both IBZM and [11C]-raclopride show increased binding in the striatum when extracellular dopamine is low (Shah et al. 1997) (Laruelle 2000). Results of preclinical and clinical studies implicate that, in addition to serotonin and norepinephrine, dopaminergic mechanisms may play a role in the pathogenesis and treatment of depression (Lemke 2007).

12.3.2 SPECT and PET Imaging of Dopamine Transporters

Dopamine transporters (DaT) are situated in the presynaptic region of the striatal synapses where they pump dopamine from the synaptic cleft into the presynaptic neuronal space. Commonly used tracers to investigate presynaptic dopamine transporter function are the cocaine derivatives [123I]-2-beta-carbomethoxy-3-beta-(4-iodophenyl)-tropane ([123I]beta-CIT) and ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ((123) I]FP-CIT, Ioflupane, DaT Scan) (Brücke et al. 1993; Booij et al. 1998). [123I] beta-CIT imaging can also be used for SERT imaging as it partially binds to these receptors as well (Reneman et al. 2002). Responses to neuroactive drugs can be measured by DaT binding in regions of interest in the brain (Warwick et al. 2012). Decreased DaT availability may occur in affective disorders such as those associated with Parkinson's disease (Weintraub et al. 2005).

12.3.3 SPECT and PET Imaging of Serotonin Receptors

Serotonin receptors are also known as 5-HT receptors, mostly G protein-coupled receptors, of which the 5-HT1A receptors appear to play a key role in depressive disorders (Savitz et al. 2009) and to a lesser extent 5-HT2 receptors (van Heeringen et al. 2003). 5-HT1A receptors have been localised by the piperazine PET tracer [(11)C]WAY-100635 mostly to the cerebral cortices, hippocampus and raphe nucleus (Ito et al. 1999).

In an analysis of eight studies investigating the 5-HT1A receptor in the brains of patients with major depressive disorder, four reported a decreased 5-HT1A receptor density, two no change and two an increased density. These discrepant results were thought to be due to possible methodological research factors, but other options have to be considered. The disparate findings do not reliably answer the question of whether 5-HT1A receptors are altered in major depression or in subgroups of these patients (Shrestha et al. 2012).

12.3.4 SPECT and PET Imaging of Serotonin Transporters

The serotonin transporter (SERT) is a monoamine transporter that transports serotonin from the synaptic space to the presynaptic neuron. It is responsible for the removal of extracellular 5-HT. Increased SERT action will result in decreased 5-HT concentrations. Selective serotonin re-uptake inhibitors (SSRIs) and antidepressants which block serotonin transporters lead to increased synaptic and extracellular 5-HT (Bel and Artigas 1992; Blier and De Montigny 1983). In a study to determine whether patients with major depression have diminished serotonin transporter (SERT) availability in the brainstem, [123I] beta-CIT SPECT showed a statistically significant reduction in brainstem uptake in depressed subjects (Malison et al. 1998).

12.4 SPECT and PET Imaging of the Antidepressant Drug Response

Clinical trials using PET and SPECT imaging have been completed for several antidepressant pharmaceuticals including the selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), noradrenaline-dopamine reuptake inhibitors (NDRIs), monoamine oxidase inhibitors (MAOs) and tricyclic antidepressants (TCAs). For the purpose of this review, references have been sourced through PubMed until October 2012, including keywords such as clinical trial, PET, SPECT and antidepressant.

Some of the more common medications that have been investigated by SPECT and PET in depression are described below. They include the dopamine agonists levodopa and carbidopa; moclobemide and St. John's wort; selegiline; the SSRIs citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline; the NDRI bupropion; the SNRI venlafaxine; and the TCAs amitriptyline, nortriptyline and desipramine.

12.4.1 Levodopa and Selegiline

One of the most investigated diseases involving dopaminergic synapses of the striatum is Parkinson's disease (PD). Depression occurs in around 35 % of PD patients, and antidepressants that have dual serotonergic and noradrenergic effects are the drugs of choice for this disease (Aarsland et al. 2011). In an ioflupane study that correlated striatal DaT uptake with anxiety and depression in PD, affected patients had a lower DaT availability than healthy volunteers (Weintraub et al. 2005). A 99TcHMPAO SPECT study that examined regional cerebral blood flow in 52 PD patients showed a significant decrease in regional cerebral blood flow in PD patients with concurrent major depression. The decrease was less severe on treatment, particularly on a levodopa-selegiline combination therapy, less so with levodopa only therapy (Imamura et al. 2011).

12.4.2 Moclobemide and St. John's Wort

Monoamine oxidase A (MAO-A) inhibitor antidepressants raise the levels of multiple monoamines. MAO-A can be measured using the MAO-A marker [(11) C]-harmine. Brain MAO-A occupancy was measured in 13 depressed patients with a clinically effective dose of the selective MAO-A inhibitor moclobemide and after repeated administrations of St. John's wort, a herb purported to have MAO-A inhibitor properties. [(11)C]-harmine binding decreased significantly throughout all measured regions after moclobemide, but St. John's wort did not significantly alter MAO-A density (Sacher et al. 2011).

12.4.3 The SSRIs

It is generally believed that an 80 % serotonin transporter (SERT) occupancy is the therapeutically useful threshold for SSRI antidepressant therapy (Zipursly et al. 2007).

12.4.3.1 Citalopram

99mTc HMPAO SPECT was used to investigate the response of the brain to the SSRI citalopram in 93 patients with MD. The responder group had a regional cerebral blood flow improvement predominantly in the prefrontal and temporal cortices and in the subgenual cingulate cortex after treatment (Brockmann et al. 2009). In another study, 16 depressed older adults and 13 controls underwent 2 resting (18) F-FDG PET studies after placebo and citalopram infusions. Metabolism decreased in the left superior and middle frontal gyri, while an increase was observed in the left inferior parietal lobule, cuneus and thalamus, and in the right putamen (Smith et al. 2009).

The 5-HT1A receptor antagonist pindolol has been used previously to accelerate the clinical effects of antidepressant therapy by preventing negative feedback. Using alpha-[(11)C]methyl-L-tryptophan PET, a double-blind, randomised study compared the changes in its trapping in patients with unipolar depression treated

with citalopram plus placebo versus citalopram plus pindol. The combination citalopram plus pindol achieved a more rapid and greater increase of 5-HT synthesis in prefrontal cortex (Berney et al. 2008).

In a study examining midbrain SERT availability in patients with major depression, the relation of SERT occupancy by citalopram to treatment response was assessed in 21 non-medicated depressed patients by the SERT marker [(123) I]-ADAM SPECT. There was a rapid clinical improvement after citalopram in 54 % of the investigated patients, but only a variable SERT uptake (Herold et al. 2006). In another study, 12 patients with major depression had a SERT marker [(11)C]DASB PET scan after a minimum of 4 weeks high-dose SNRI venlafaxine treatment or sertraline or citalopram. At high therapeutic dose rates, the mean striatal SERT occupancy for each antidepressant was approximately 85 % (Voineskos et al. 2007).

In another study in patients with MD, interregional balance between SERT binding in the raphe nuclei and key regions of depression including bilateral habenula, amygdala-hippocampus complex and subgenual cingulate cortex before treatment was investigated using [(11)C]DASB PET. Measurements were performed before and after a single oral dose, as well as after 3 weeks (mean 24.73 ± 3.3 days) of continuous oral treatment with either escitalopram (10 mg/day) or citalopram (20 mg/day). Treatment response could be predicted by comparing pretreatment SERT binding in the above regions versus median raphe nucleus binding (Lanzenberger et al. 2012).

12.4.3.2 Escitalopram

Escitalopram is a SSRI approved for the treatment of depression and anxiety disorders. It is the S-enantiomer of citalopram, responsible for serotonin reuptake activity. It has been hypothesised that the therapeutically inactive R-enantiomer competes with the serotonin-enhancing S-enantiomer at low-affinity allosteric SERT sites, reducing the effectiveness of the S-enantiomer at the high-affinity sites. SERT occupancy in citalopram- and escitalopram-treated healthy volunteers was measured after single and multiple doses of these drugs. The single-dose study showed no attenuating effect of R-citalopram, but after multiple dosing, SERT occupancy was significantly reduced in the presence of R-citalopram. A pooled analysis suggests that the R-enantiomer build up after repeated citalopram dosing may lead to increased inhibition of the S-enantiomer occupancy of SERT (Kasper et al. 2009). In another study, 25 healthy subjects received a single dose of escitalopram or citalopram. Midbrain binding was measured with the SERT marker [(123)I]-ADAM on 2 study days, once without dosing and once 6 h after a single dose of escitalopram or citalopram. The midbrain-cerebellum/cerebellum ratio was the outcome measure for specific SERT binding in the midbrain. The SERT occupancies of escitalopram and citalopram give indirect evidence of a fractional blockade of SERT by the inactive R-citalopram enantiomer (Klein et al. 2006).

12.4.3.3 Fluoxetine

In a study using 123 I IBZM, the cerebral dopamine-D2 receptors were characterised in 13 patients with major depression. Dopamine receptor binding was

assessed twice, before and during serotonin reuptake inhibition. An increase in dopamine-D2 receptor binding during serotonin reuptake inhibition was found in the striatum and anterior cingulate gyrus in treatment responders, but not in non-responders (Larisch et al. 1997).

In a study that looked at fluoxetine treatment and psychotherapy, it was found that fluoxetine increased [11C]-raclopride binding in the lateral thalamus but that this increase did not correlate with clinical improvement (Hirvonen et al. 2011). In a study to determine the response of SERT to fluoxetine treatment, 23 patients with major depression underwent SPECT scanning using [123I]beta-CIT. Higher pretreatment SERT availability correlated with a positive treatment response (Kugaya et al. 2004).

In a study in unipolar depressed men, common and unique response effects to administration of placebo or fluoxetine were assessed after a 6-week, double-blind trial. Placebo response was associated with regional metabolic increases involving the prefrontal, anterior cingulate, premotor, parietal, posterior insula, and posterior cingulate and metabolic decreases involving the subgenual cingulate, parahippocampus and thalamus. Regions of change overlapped those seen in responders administered active fluoxetine. Fluoxetine response, however, was associated with additional subcortical and limbic changes in the brainstem, striatum, anterior insula, and hippocampus, sources of efferent input to the response-specific regions identified with both agents (Mayberg et al. 2002).

12.4.3.4 Paroxetine

In 12 medication-free depressed patients who completed a 6-week trial of either paroxetine or citalopram, striatal binding was measured with the SERT marker [(11)C]DASB. PET scans were completed before and after 4 weeks of treatment. A significant decrease in striatal SERT binding potential was found after either treatment. An 80 % occupancy of receptors in multiple regions was reported (Meyer et al. 2001a, b). In a study of drug-free depressed outpatients, SERT occupancy was quantified by 123I-FP-CIT SPECT imaging at baseline and after 6 weeks paroxetine. A significant positive relationship between SERT occupancy and clinical improvement existed only in patients who had certain SERT promoter genotypes, namely, the L(A)/L(A) genotype (Ruhé et al. 2009).

In a study of unipolar MD, 24 subjects underwent resting (18)F-FDG scanning before and after 12 weeks either paroxetine or interpersonal psychotherapy. Subjects with MD had regional brain metabolic abnormalities at baseline compared to controls that tended to normalise with treatment. Regional metabolic changes appeared similar with the two forms of treatment (Brody et al. 2001).

In another study of MD, (18)F-FDG PET scans were performed on 13 male patients before and after 6 weeks of paroxetine therapy. After successful paroxetine therapy, increased glucose metabolism occurred in dorsolateral, ventrolateral, and medial aspects of the prefrontal cortex (left greater than right), parietal cortex, and dorsal anterior cingulate. Areas of decreased metabolism were noted in both anterior and posterior insular regions (left) as well as right hippocampal and parahippocampal regions (Kennedy et al. 2001).

12.4.3.5 Fluvoxamine

The effect of chronic treatment with fluvoxamine, a potent SSRI that attaches to 5-HT2 and D2 receptors, was tested in drug-naive unipolar depressed patients using fluoro-ethyl-spiperone ([(18)F]FESP), a high-affinity 5-HT2 and D2 antagonist receptor marker. Fluvoxamine treatment significantly improved clinical symptoms and increased [(18)F]FESP binding in the frontal and occipital cortex of patients who completed the study. No significant changes were found in the basal ganglia where [(18)F]FESP binds mainly to D2 dopamine receptors (Moresco et al. 2000). In studies looking at receptor occupancy, it was found that in effective antidepressant therapy an approximately 80 % of SERT binding occurs (Suhara et al. 2003).

12.4.4 The NDRIs and SNRIs

12.4.4.1 Bupropion

Bupropion is a norepinephrine-dopamine reuptake inhibitor (NDRI) that appears to have a selective affinity for dopamine transporters. In a study to investigate DaT binding after bupropion in depressive patients, bupropion treatment occupied less than 22 % of DaT sites, which raises the question whether there is another mechanism involved during treatment with bupropion (Meyer et al. 2002). In a study that looked at the effect of bupropion and venlafaxine on brain metabolism, 20 patients with unipolar depression received a baseline (18)F-FDG scan, then at least 6 weeks of bupropion or venlafaxine monotherapy. Pretreatment scans showed a frontal and left temporal hypometabolism in depressed outpatients. Alterations in regional metabolism were linked to positive antidepressant responses on bupropion and venlafaxine monotherapy (Little et al. 2005).

12.4.4.2 Venlafaxine

Venlafaxine is a serotonin norepinephrine reuptake inhibitor (SNRI). In a study of patients with MD, seven subjects underwent a 99mTc HMPAO SPECT scan to assess cerebral blood flow changes after venlafaxine. The subjects showed an increased cerebral blood flow bilaterally in the thalamus and a decreased flow in the temporal cortex bilaterally and in the left occipital lobe and right cerebellum (Davies et al. 2003).

Another study was completed in 24 patients with MD. They received a (18)F-FDG PET scan before randomisation and after 16 weeks of antidepressant treatment with either cognitive behavioural therapy (CBT) or venlafaxine. Response to CBT was associated with a reciprocal modulation of cortical-limbic connectivity, while venlafaxine engaged additional cortical and striatal regions (Kennedy et al. 2007).

In another study involving 28 patients with MD, 13 patients had 1-h weekly sessions of IPT from the same supervised therapist (E.M.). Fifteen patients took 37.5 mg twice daily of venlafaxine hydrochloride. 99mHMPAO brain SPECT scans were completed before and after 6 weeks treatment. Both treatment groups improved substantially, more so with venlafaxine (Martin et al. 2001).

12.4.5 The TCAs

12.4.5.1 Nortriptyline and Sertraline

Twenty elderly outpatients with major depression were treated with either nortriptyline or sertraline. Resting regional cerebral blood flow was assessed by the planar (133)Xenon inhalation technique after medication washout and following 6–9 weeks of antidepressant treatment. At baseline, the depressed patients had a reduced cerebral blood flow in frontal cortical regions when compared with controls. After treatment, responders showed a reduced perfusion in the frontal regions (Nobler et al. 2000).

12.4.5.2 Amitriptyline

Cerebral blood flow was assessed by HMPAO SPECT in 14 depressed patients with primary fibromyalgia before and after amitriptyline treatment. There was an improvement in the visual analog scale and tender point count after treatment, but the Beck Depression Inventory did not change significantly. After treatment, cerebral blood flow increased bilaterally in the hemithalami and basal ganglia, and decreases were seen in the temporal regions bilaterally and in the left tempero-occipital and right occipital regions. Although perfusion deficits improved parallel to clinical recovery, the Beck depression scores did not change significantly (Adigüzel et al. 2004).

12.4.5.3 Desipramine

To assess brain metabolic correlates of the tyrosine hydroxylase inhibitor alpha-methyl-p-tyrosine (AMPT) after receiving desipramine, a randomised, controlled, double-blind trial in 18 patients who had depression in remission was completed, following AMPT and placebo administration. Regional brain metabolism was measured by (18)F-FDG PET in patients with and without AMPT-induced return of depressive symptoms. Depressive symptoms were experienced by 11 of the 18 patients and led to a decreased brain metabolism, mostly in the orbitofrontal and dorsolateral prefrontal cortex, and thalamus (Bremner et al. 2003).

12.5 SPECT and PET Imaging of the Blood–brain Barrier in Depression and the Antidepressant Response

Blood–brain barrier (BBB) integrity, genetic susceptibility and exposure to neurotoxins are currently discussed as possible contributors in depressive disorders. There have been calls to combine anti-inflammatory treatments with antidepressants to enhance the effectiveness of antidepressant therapy (Davis et al. 2010).

Several observations suggest that inflammatory mechanisms play a role in the cause of a major depressive disorder. For example, there are similarities with “sickness behaviour”, a normal response to inflammatory cytokines. Also, elevations in pro-inflammatory cytokines and other inflammation-related proteins are found in the plasma and cerebrospinal fluid of such patients, as well as in post-mortem studies. Pro-inflammatory cytokines persist in remission and can predict the onset of a

depressive episode, while antidepressant treatment can lead to a normalisation of elevated cytokine levels (Raedler 2011).

When the effect of endotoxins on the brain was measured clinically and by (18) F-FDG PET in nine healthy subjects, there was an increased Montgomery-Åsberg Depression Rating, fatigue, reduced social interest, and increased inflammatory cytokines. There was an increased uptake of (18)F-FDG in the insula and a trend to a decreased uptake in the cingulate regions of the brain (Hannestad et al. 2012).

In another study, the effects of interferon-alpha on cerebral glucose metabolism and its correlation to neuropsychiatric symptoms during low-dose IFN-alpha treatment were evaluated in 11 patients treated with low-dose IFN-alpha for chronic hepatitis. Low-dose IFN-alpha therapy was associated with significant prefrontal hypometabolism on (18)F-FDG that covaried with the depression score. However, this was also seen clinically in nondepressed patients (Juengling et al. 2000).

Whole brain radiation therapy (WBRT) is known to result in psychological side effects including loss of memory, loss of concentration and depression (Kondziolka et al. 2005). A possible consideration in radiation therapy is monoamine leakage through the BBB. Twenty patients with metastatic brain tumours underwent (99) mTc-DTPA brain SPECT before and during WBRT and at 2 weeks after the end of irradiation. It was found that irradiation causes direct damage to BBB function and that BBB permeability increased significantly during and within 2 weeks following 20 and 40 Gy WBRT (Jiang et al. 2010).

In end-stage renal disease, the associated depressive mood and cerebral blood flow was measured in the pre-dialytic period and at least 6 months after dialysis initiation. The pre-dialysis 99mTc ECD brain SPECT scan did not show any cerebral blood flow differences between responders to dialysis and non-responders, but follow-up brain SPECT revealed a significantly higher perfusion in left middle temporal gyrus and right parahippocampal gyrus in responder patients. In non-responders, there was a significantly decreased uptake in the left superior frontal gyrus and right orbitofrontal cortex that did not improve after dialysis (Nam et al. 2011).

P-glycoprotein (P-gp) is an efflux transporter that is expressed in high concentration at the blood–brain barrier and regulates the transport of drugs across the BBB. PET was used to measure brain uptake of [11C]verapamil, which is normally expelled from the brain by P-gp transport. In patients with a major depressive episode, a significant decrease of [11C]verapamil was seen in different areas of the brain, particularly in the frontal and temporal regions (de Klerk et al. 2009). In a study using small-animal PET, [(11)C]verapamil imaging showed that P-glycoprotein function at the blood–brain barrier decreases with chronic stress and increases with chronic administration of venlafaxine (de Klerk et al. 2010).

12.6 SPECT and PET Imaging of Monoamine Precursors, LAT Transport and the Antidepressant Response

Large neutral amino acids are transported across the BBB via large neutral amino acid transporters (LAT) also expressed in cerebral tumours, such as gliomas (Langen and Bröer 2004). LAT 1 competitively transports multiple aromatic amino

acid derivatives, including phenylalanine, L-dopa, alpha-methyldopa, melphalan, triiodothyronine, thyroxine, tyrosine and tryptophan (Uchino et al. 2002). The LAT 2 transporter exhibits a similar transport spectrum to LAT 1 (Segawa et al. 1999). The monoamine precursors phenylalanine, tyrosine and tryptophan are competitively sourced from the cerebral circulation through the BBB by these transporters (Boado et al. 1999). The competitive nature of precursor sourcing permits the possibility of interference in precursor provision through the BBB. This can happen in cases where there is a large blood-borne load of neutral amino acids in certain diets and in peripheral and genetic diseases such as maple syrup urine disease and phenylketonuria (PKU). These diseases are associated with neuropsychiatric and mood disorders such as depression (Strauss et al. 2009).

Previous research has suggested that there is an increased risk for individuals with PKU for developing depression and other mood disorders. Significant associations were observed between biochemical markers indicating poorer dietary control and increasing depressive symptoms in adolescents with early and continuously treated PKU (Sharman et al. 2012). In a study of adult patients suffering from PKU, positron emission tomography was used to measure the utilisation of 6-[(18)F] fluoro-l-dopa in the brain compared to healthy controls. The unidirectional clearance of [(18)F]DOPA to brain was impaired in adult patients suffering from PKU, presumably reflecting the competitive inhibition at the large neutral amino acid carriers by phenylalanine (Wasserstein et al. 2006).

Using [(18)F] MPPF PET, 5-HT1A receptor binding was measured after tryptophan depletion (TD) in various brain regions in patients with citalopram-treated depression. Eight remitted patients with major depressive disorder received [(18)F] MPPF PET scans twice: once after TD and once after sham depletion. No effect on regional 5-HT1A binding was observed after TD, despite an 86 % decrease in total plasma tryptophan and a transient depressive relapse in six of eight patients (Praschak-Rieder et al. 2004).

In some patients, short-term depletion of plasma tryptophan results in a relapse in patients who are recovering from major depression. Patients who clinically improved on SSRIs underwent 2 test days tryptophan depletion or placebo, followed 6 h later by (18)F-FDG PET brain scan. Tryptophan depletion resulted in a decreased brain metabolism in the middle frontal gyrus, thalamus and orbitofrontal cortex (Bremner et al. 1997).

MAO-A binding was measured in regions implicated in affective and neurodegenerative disease using [(11)C]-harmine positron emission tomography in healthy volunteers. Monoamine oxidase A V(T), an index of MAO-A density, was decreased following tryptophan depletion in prefrontal cortex and elevated in the striatum following carbidopa-levodopa administration (Sacher et al. 2012).

12.7 Discussion

Monoamine-based medications can produce remarkable improvements in some patients with mood disorders such as depression. However, the exact mode of antidepressant action and location still remains a mystery, not necessarily predictable.

Based on the above, only a few generalisations can be made:

- Specific diseases such as hypothyroidism and Parkinson's disease may be associated with characteristic SPECT and PET imaging features as may their antidepressant drug response. In depressed hypothyroid patients, thyroxine improves the clinical state and cerebral metabolism in parts of the brain in a proportion of the patients. In Parkinson's disease, application of dopamine agonists improves the symptoms of depression and improves the regional cerebral hypometabolism that is associated with this disease.
- Application of SSRIs results in clinical improvements in depressed patients, particularly when 80 % or more of the serotonin transporter receptor sites are occupied.

SPECT and PET imaging after antidepressant drug intervention has shown varied changes in cerebral blood flow and metabolism throughout the brain bilaterally in the prefrontal, frontal, temporal, cingulate and thalamus regions and in the left occipital region and right cerebellum. Additionally, changes in receptor binding have been observed at D2 and 5-HT receptors and at DaT and SERT transporters.

Similar to the highly complex metabolism and receptor binding that is seen in acute depressive disorders, there is a highly complex response and binding to antidepressant drugs. The question must be asked if there is such a thing as a regional centre for mood disorders and depression and if there is such a thing as a regionalised antidepressant drug response. Although the monoamines can be localised to specific brain regions, it appears that abnormal brain function associated with mood disorders such as depression or activity changes associated with a response to antidepressant medication may not necessarily be predictably localised. Either that or patients investigated for this condition need more restrictive in- and exclusion criteria that control for type of depression, diet and nutrition, REM sleep, thyroid and renal function, infection, inflammation, radiation, and more.

We wish to draw attention to the possibility that mood is associated with the subconscious and conscious condition which possibly involves a non-regionalised global participation of the brain (Edelman et al. 2011). Although monoamine input occurs at certain common points such as the striatum or midbrain regions and although there may be common pathways and common intersections of neurotransmission, the resultant output may differ from situation to situation and from person to person.

Conclusion

SPECT and PET imaging can document changes in brain metabolism and receptor binding after antidepressant action. However, due to the complex and varied presentation of depression and the antidepressant drug response on imaging, so far there is a lack of consensus and guidelines for SPECT and PET scans in this condition. While responses can often be demonstrated in individual patients, there is no overall "group-based" characteristic picture of depression and the antidepressant response. Clinical studies that image individual responses to antidepressant drugs are likely to grow in the future as imaging techniques become more and more refined and further investigation into possible imaging features for this condition are also likely to continue.

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