We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

PET Imaging of the Serotonergic 5-HT_{1A} System

Amélie Lothe, Sandrine Bouvard and Philippe Ryvlin

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/57122>

1. Introduction

Serotonin (5-hydroxytryptophan, 5-HT) is a modulating neurotransmitter of the central nervous system involved in a large spectrum of emotional and cognitive processes and physiological activities [1, 2], including sleep, locomotion, eating, memory, endocrine modulation, and sexual behaviour. The serotonergic system is modulated in humans by both genetic and environmental factors. Furthermore, the central serotonergic system is altered in multiple diseases such as depression [3, 4], migraine [5, 6], epilepsy [7-9], Alzheimer's disease [10, 11], eating disorders [12], anxiety [13], schizophrenia [14] and autism [15, 16]. Various radioligands are currently available for *in vivo* brain imaging of the serotonergic system in humans, including antagonists for the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT₄ receptors, and for the serotonin transporter (SERT) [17].

5-HT exerts its multiplicity of actions through seven classes of 5-HT receptors (17 subtypes identified to date), involving different signal transduction pathways [18, 19, 2]. The 5-HT_{1A} receptors were the first to be cloned in humans and are probably the best-characterized subtype of 5-HT receptors [20]. These receptors are G protein coupled receptors (GPCRs); 5-HT binding to 5-HT_{1A} receptors causes neuronal hyperpolarization through the G-protein-coupled opening of K⁺ channels [21, 22]. The 5-HT_{1A} receptors are mostly expressed in neurons, either as heteroreceptors when located in target regions of 5-HT neurons with a particularly high concentration in limbic areas, such as cingulate cortex and hippocampus, or as autoreceptors on the soma and dendrites of 5-HT neurons in raphe nuclei, where they exert negative feedback on the serotonergic neuron firing rate and 5-HT release [23, 24]. Thus, serotonergic neurotransmission is strongly modulated by 5-HT_{1A} receptors.

Several PET tracers have been developed for imaging 5-HT_{1A} receptors [25]. The most commonly used radioligands are [¹¹C]WAY-100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazin-

yl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide) and [^{18}F]MPPF (4-(2'-methoxyphenyl)-1-[2'-(N-2-pyridinyl)-p-fluorobenzamido]-ethyl-piperazine) (see figure 1).

Figure 1. Chemical structure of antagonist PET tracers of 5-HT_{1A} receptors

In this chapter, we will start by reviewing the different binding properties of [^{18}F]MPPF versus [^{11}C]WAY-100635. We will then discuss in more detail PET data obtained with [^{18}F]MPPF in comparison with those obtained with [^{11}C]WAY-100635 in various pathological conditions, including major depressive disorder, depressive comorbidity in temporal lobe epilepsy, and schizophrenia.

2. Binding properties of [^{18}F]MPPF versus [^{11}C]WAY-100635

[^{18}F]MPPF and [^{11}C]WAY-100635 are both selective and potent antagonists at 5-HT_{1A} autoreceptors and heteroreceptors, but differ in their binding properties at 5-HT_{1A} receptors.

Firstly, [^{18}F]MPPF is characterized by a lower affinity for 5-HT_{1A} receptors ($K_i=3.3$ nM in rat hippocampal membrane homogenates) than [^{11}C]WAY-100635 ($K_i=0.8$ nM) [26] and [^{18}F]FCWAY ($K_i=0.25$ nM) [27].

The high affinity of [^{11}C]WAY-100635 for 5-HT_{1A} receptors would make it relatively insensitive to changes in endogenous 5-HT concentration. Indeed, the binding of [^{11}C]WAY-100635 remained unchanged after injection of fenfluramine or after depletion of 5-HT by treatment with p-chlorophenylalanine (p-CPA) or with reserpine in rodents [28, 29]. In this regard, a decreased [^{11}C]WAY-100635 binding will be interpreted as reflecting a reduction in the density of 5-HT_{1A} receptors.

Conversely, the affinity of [^{18}F]MPPF is closer to that of endogenous 5-HT for 5-HT_{1A} receptors ($K_i=4.2$ nM in rat frontal cortex homogenates) [30]. Thus, [^{18}F]MPPF appears to be sensitive to the extra-cellular concentration of endogenous 5-HT [31, 32, 33]. Several studies using β -sensitive microprobes and microdialysis in the brain of rats demonstrated decreases in [^{18}F]MPPF binding after pharmacologically or electrical stimulation induced increases in the concentration of extracellular 5-HT [31, 32], while the binding of [^{18}F]MPPF is increased in the hippocampus following a reduction in the extracellular 5-HT concentration in rats treated with p-EPA, an inhibitor of tryptophan hydroxylase [33]. These findings

were confirmed with simulated [¹⁸F]MPPF PET data [34]. Moreover, an original PET study using [¹⁸F]MPPF and alpha-[¹¹C]Methyl-L-Tryptophan (AMT), a precursor of 5-HT, reported a significant negative correlation between 5-HT synthesis and 5-HT_{1A} binding potential (BP) bilaterally in hippocampus and anterior insula and in the left anterior cingulate gyrus in healthy subjects [35].

Accordingly, in contrast to [¹¹C]WAY-100635, a decreased [¹⁸F]MPPF binding could either reflect lower 5-HT_{1A} receptor density or a higher extracellular concentration of 5-HT that could be associated with various changes in the number of 5-HT_{1A} receptors.

Secondly, [¹⁸F]MPPF binds to externalized 5-HT_{1A} receptors only, while [¹¹C]WAY-100635 also binds to internalized receptors [36]. As a result of this property, [¹⁸F]MPPF may allow indirect assessment of the internalization of 5-HT_{1A} autoreceptors [37].

Using β -sensitive microprobes in rats, a significant decrease of [¹⁸F]MPPF binding was observed in the dorsal raphe nucleus (autoreceptors), but not in the hippocampus (heteroreceptors), after acute treatment with 8-OH-DPAT, a 5-HT_{1A} receptor agonist, or with fluoxetine, a selective serotonin reuptake inhibitor (SSRI) [37, 38]. This reduction is associated with the internalization of 5-HT_{1A} autoreceptors of dorsal raphe nucleus observed in parallel using quantitative electron microscopic immunocytochemistry [38]. Similarly, a [¹⁸F]MPPF PET study conducted in cats reported a decreased BP in the dorsal raphe nucleus after acute fluoxetine administration [39]. Finally, an interesting [¹⁸F]MPPF PET study has examined this property by investigating healthy subjects five hours after the randomized, double-blind administration of a single oral dose of fluoxetine [40]. As expected, [¹⁸F]MPPF binding in raphe nuclei is decreased in response to fluoxetine in each healthy subject [40].

Thirdly, the 5-HT_{1A} binding of both ligand was found to be differentially influenced by several factors, including genetic factors, age and gender.

Several genetic factors, including the triallelic 5-HT transporter gene-linked polymorphic region (5-HTTLPR) and 5-HT_{1A} promoter polymorphism, have a significant impact on [¹⁸F]MPPF and [¹¹C]WAY-100635 binding [41-47].

Two [¹¹C]WAY-100635 PET studies showed a significant impact of the 5-HTTLPR polymorphism on the 5-HT_{1A} receptor binding, but in different directions [41-42]. One of the two studies reported lower [¹¹C]WAY-100635 BP in various limbic and neocortical brain regions in healthy subjects (predominantly men) with S/S or S/L genotypes compared to those with L/L genotype [41], whereas the other series found greater BP in the cingulate gyri in healthy women with S/S and S/L genotypes compared to those with L/L genotype [42]. Similarly, we observed a greater [¹⁸F]MPPF non displaceable BP_{ND} ($BP_{ND} = f_{ND} \cdot B_{avail} / K_D$ where f_{ND} is the fraction of radioligands free and non specifically bound, B_{avail} is the total number of available receptors for binding and $1/K_D$ is the affinity of the radioligand) [48] in homozygote women carriers of the S allele of 5-HTTLPR compared with carriers of at least one L_A allele over large brain regions including temporal and parietal lobes as well as the insula, cingulate gyri and left orbitofrontal cortex [43]. In contrast, a recent PET study failed to show a significant effect of the 5-HTTLPR polymorphism on the [¹¹C]WAY-100635 BP in a large population of 54 healthy volunteers, but that included men predominantly [47].

The association of C(-1019)G 5-HT_{1A} promoter polymorphism and 5-HT_{1A} receptor binding has also been evaluated in humans in three [¹¹C]WAY-100635 PET studies and one [¹⁸F]MPPF study [41, 44-46]. One of these [¹¹C]WAY-100635 studies reported no association between C(-1019)G 5-HT_{1A} promoter polymorphism and 5-HT_{1A} receptor BP in a homogenous group of healthy subjects [41]. We also failed to detect a significant relationship between C(-1019)G 5-HT_{1A} promoter polymorphism and [¹⁸F]MPPF binding in healthy subjects. However our data suggest that women homozygote for the G allele have greater [¹⁸F]MPPF BP_{ND} compared to other individuals primarily over the frontal and temporal neocortex. The other two [¹¹C]WAY-100635 PET studies, performed in a mixed population of depressed and healthy individuals, demonstrated greater BP in limbic regions and the raphe nuclei, in carriers with at least one G allele compared to the C/C genotype [45, 46].

5-HT_{1A} receptor binding measured by either [¹⁸F]MPPF and [¹¹C]WAY-100635 significantly declines with age [49-52]. However, this effect was especially observed on [¹⁸F]MPPF binding in women [50] and, conversely, on [¹¹C]WAY-100635 binding in men [52]. Note that one [¹¹C]WAY-100635 PET study failed to show any significant correlation between age and 5-HT_{1A} receptor binding [53].

With regard to the gender factor, greater [¹⁸F]MPPF BP_{ND} values independent of age were demonstrated in women compared to men, in limbic and paralimbic regions, predominantly in the right hemisphere [50]. Furthermore, after controlling for age and 5-HTTLPR polymorphism, a higher [¹⁸F]MPPF BP_{ND} to 5-HT_{1A} receptors was also observed in women than in men over a very restricted set of brain regions, including the left temporal pole and parahippocampal gyrus [43]. Thus, we might speculate that the larger gender difference could partly reflect unbalanced 5-HTTLPR polymorphism between men and women.

A few PET studies have also examined the effects of gender on [¹¹C]WAY-100635 binding to 5-HT_{1A} receptors, reporting contradictory findings. Two previous studies found no effect of gender on [¹¹C]WAY-100635 binding [51, 54], whereas other series reported higher binding in women compared to men [47, 53, 55].

Overall, [¹⁸F]MPPF and [¹¹C]WAY-100635 are likely to yield different and complementary PET findings in different pathological conditions.

3. Major depressive disorder

Depression is a common mental disorder, affecting about 121 million people worldwide. By the year 2020, depression is projected to become the second most important cause of disease burden, as measured by Disability-Adjusted Life Years (DALYs) (World Health Organization). The average lifetime prevalence of Major Depressive Disorder (MDD) is 14.6% in high-income countries [56], with the typically reported rates of 5% to 12% for men and 10% to 26% for women.

According to the Diagnostic Statistical Manual of Mental Disorders [57], Fourth edition, Text revision (DSM-IV-R), a Major Depressive Episode is characterized by a depressed mood and/

or a markedly diminished interest or pleasure in all or almost all activities most of the day during the same 2-week period. In addition, three or more of the following symptoms must be present: gain or loss of weight, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, diminished ability to concentrate, and recurrent thoughts of death or suicidal ideation.

MDD is associated with diminished role functioning, poor health-related quality of life, medical comorbidity, such as cardiovascular disease [58], and increased risk of mortality [59].

Since roughly the 1970s, 5-HT has been involved in the pathophysiology of MDD [60, 61]. Numerous studies reported a reduction of 5-HT plasma concentrations and 5-HT metabolite levels in the cerebro-spinal fluid of patients with MDD [62, 63]. In addition, pharmacological agents that reduce brain 5-HT levels (e.g. reserpine) can induce depressive symptoms in healthy subjects as well as in recovered depressed patients [4, 64-66]. More recently, PET studies using alpha-[¹¹C]Methyl-L-Tryptophan (AMT) showed a reduction of this tracer uptake in the anterior cingulate gyrus and left mesial temporal cortex in MDD patients, supporting the possibility of reduced extracellular 5-HT concentration in depression [67, 68].

The involvement of 5-HT_{1A} receptors in depression is well recognized; however the nature of their modifications is still controversial (see for review [69, 70]). A large number of PET studies have investigated 5-HT_{1A} receptors in patients with MDD using [¹¹C]WAY-100635 [3, 69, 71-81].

Most previous [¹¹C]WAY-100635 PET studies showed a reduction of 5-HT_{1A} receptor BP_{ND} in various limbic and neocortical brain regions, as well as in the raphe nuclei, of untreated, treated, remitted MDD patients as well as in drug-naïve primary-care patients with MDD [3, 71, 73, 74-76, 79]. Interestingly, a [¹⁸F]MPPF PET study performed in a monkey model of depression also reported a reduced BP in limbic regions and raphe nuclei [82]. It is in agreement with the majority of post-mortem data demonstrating decreased 5-HT_{1A} receptor density in depressed suicide victims in different brain regions including the raphe nuclei, the hippocampus, and the frontal cortex [83-89]. The reduction of 5-HT_{1A} receptor binding could be partly the consequence of a possible hypersecretion of endogenous corticosteroids (see for review [69, 90]).

However, other PET studies using [¹¹C]WAY-100635 reported an increased ratio of specifically bound ligand over free ligand (BP_F) in the same regions in MDD patients never or not recently exposed to antidepressants, compared with controls [77-79]. Similarly, an increased 5-HT_{1A} BP_F has been shown in patients with MDD during sustained remission and not having taken antidepressant medications for at least six months, compared with healthy controls [81]. These authors suggest that higher 5-HT_{1A} autoreceptor binding in the raphe nuclei could lead to greater inhibition of 5-HT neuron firing rate and decreased 5-HT release in the target regions of 5-HT neurons, possibly leading to compensatory up-regulation of 5-HT_{1A} receptors in the same regions [78].

These discordant PET findings might partly reflect differences in the modeling methods used to calculate BP (BP_{ND} versus BP_F) [48], the choice of the reference region (e.g. inclusion of cerebellar vermis and gray matter in the reference region or use of white matter) [91], MDD severity, treatment status, and genetic polymorphism status (e.g. for the C-1019G 5-HT_{1A}

receptor and 5-HTTLPR polymorphisms) of the patients selected [79] (see for review [70]). Thus, regarding the choice of the reference region, scans from the same patient population, analysed with SRTM and a cerebellar reference region, could either demonstrate reduced 5-HT_{1A} BP_{ND} when using cerebellar gray matter, or increased or unchanged BP_{ND} when using cerebellar white matter [79, 81]. Indeed, the grey matter of cerebellum contains limited but significant amount of 5-HT_{1A} receptors, while its white matter does not and thus represents a more appropriate reference. Furthermore, as already mentioned, [¹⁸F]MPPF and [¹¹C]WAY-100635 BP_{ND} were reported to be influenced by the triallelic 5-HTTLPR polymorphism, which S allele is associated with depressive disorder [92, 93].

3.1. Effects of antidepressants

A small number of PET studies have examined the potential impact of chronic antidepressant medication on 5-HT_{1A} receptor binding.

Three test-retest [¹¹C]WAY-100635 studies reported no change of BP_{ND} after selective serotonin reuptake inhibitor (SSRI) treatment in MDD patients [75, 94, 95]. Contrary to these findings, a reduction of [¹¹C]WAY-100635 BP_F was found in MDD patients previously treated by antidepressants (most of the antidepressant exposure ended between 21 and 14 days prior to PET scans) when compared with medication naïve MDD patients, but not when compared with healthy controls [77]. In line with this result, a decreased 5-HT_{1A} BP_{ND} was observed following at least 12 weeks of SSRI treatment in patients suffering from social phobia or panic disorder [96]. These data suggest that chronic antidepressant treatment could induce a down-regulation of 5-HT_{1A} receptors.

In a recent test-retest [¹⁸F]MPPF PET study, we explored the potential dynamic changes in [¹⁸F]MPPF BP_{ND} in six patients with untreated MDD, before, and after five and 30 days of SSRI treatment [97]. No change of [¹⁸F]MPPF BP_{ND} after SSRI medication was observed within the raphe nuclei and a significant increase of [¹⁸F]MPPF BP_{ND} from baseline to 30 days of SSRI treatment was reported primarily in the medial orbital region and the anterior cingulate gyrus. These findings are in contradiction with the three previous test-retest [¹¹C]WAY-100635 studies which have addressed this issue [75, 94, 95].

After 30 days of SSRI treatment, no more significant modification of [¹⁸F]MPPF BP_{ND} was found in MDD patients compared with healthy subjects in the medial orbital region and the anterior cingulate gyrus. Thus effective SSRI treatment is associated with a trend toward normalisation of the serotonergic function. In agreement with these human PET imaging data, no change in the in vivo [¹⁸F]MPPF binding was found in the dorsal raphe nucleus, frontal cortex and hippocampus of rats undergoing chronic SSRI treatment, as measured with β -microprobes or with the small animal PET scanner YAP-(S)PET system [98, 99].

Overall these preliminary [¹⁸F]MPPF data suggest the existence of SSRI-mediated serotonergic adaptative mechanisms in patients with MDD. However, due to the small sample size, it is necessary to confirm these findings in a larger population.

Apart from the discrepancy of the used radioligands, several points of difference between our [¹⁸F]MPPF study and the three previous [¹¹C]WAY-100635 studies should be noted [75, 94,

95]. Firstly, one of these [¹¹C]WAY-100635 studies did not evaluate specifically the medial orbital region and the anterior cingulate gyrus [94]. Moreover, the treatment response, the treatment duration, the polymorphism status for serotonergic genes as well as the cortisol plasma levels [69] of the patients selected could partly explain these discrepancies. For instance, in one of the [¹¹C]WAY-100635 studies, only half of the patients studied were responders [75], whereas in our [¹⁸F]MPPF study all patients were responders.

4. Depressive comorbidity in temporal lobe epilepsy

Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures, due to an abnormal, excessive, and synchronous neuronal discharges, affecting about 50 million people worldwide. Depressive disorders are the most frequent psychiatric comorbidity in epilepsy but often remain under-recognized and untreated [100-103]. The lifetime prevalence of major depression ranged from 11 and 60% in patients with recurrent seizures [103] and increased in patients with temporal lobe epilepsy (TLE), particularly in those with left TLE and possibly hippocampal sclerosis (for review see [101, 104-108]). The rate of suicide in patients with epilepsy is about two to five times that of the general population, and this rate rises to six to seven times in the case of TLE [109, 110]. In addition, comorbid depression is a strong predictor of poor quality of life in patients with epilepsy [111]. This higher incidence of depressive disorders in patients with epilepsy, in particular in those with TLE, may reflect the existence of common pathogenic mechanisms between mood disorders and epilepsy [112]. In this paragraph, we are referring to the presence of depressive symptoms in interictal period. Indeed, depressive symptoms may also occur transiently during ictal or post-ictal [103].

A large body of evidence from preclinical studies indicates an anticonvulsant and antiepileptic effect of 5-HT mediated by 5-HT_{1A} receptors [113]. The activation of 5-HT_{1A} receptors retards the development of the kindling process in rats [114] and in cats [115, 116] and inhibits epileptiform activity in various cellular models of epilepsy [117, 118]. In addition, agents that raise endogenous 5-HT levels (e.g. SSRI) have an anticonvulsant effect, mediated by 5-HT_{1A} receptors [119], in genetically epilepsy-prone rats [120], in partial seizures generated by low-frequency electrical stimulation in rats [121], as well as in kindled rats [116]. Finally, given their multiple cellular localizations, the 5-HT_{1A} receptors may mediate inhibition of excitatory neurons, but also of inhibitory neurons, leading to opposite effects on the neural network [122]. Accordingly, a possible mechanism of neuronal hyperexcitability in epilepsy could be an excitatory/inhibitory shift mediated by changes in serotonergic transmission.

Abnormalities of the 5-HT_{1A} receptors were reported in TLE using various radioligands, including [¹¹C]WAY-100635, [¹⁸F]FCWAY and [¹⁸F]MPPF. All showed a BP reduction that predominated over the epileptogenic temporo-limbic structures [123-130] (see figure 2).

This reduction of 5-HT_{1A} binding on the side of the epileptogenic zone support the hypothesis of a decrease in 5-HT_{1A} receptors density in TLE. In line with these imaging studies, a decrease of binding of the agonist [³H]8-OH-DPAT (8-hydroxy-2-(di-n-propylamino) tetralin) to 5-HT_{1A} receptors was reported in the hippocampus of genetically epilepsy-prone rats [131].

Figure 2. Typical pattern of $[^{18}\text{F}]\text{MPPF BP}_{\text{ND}}$ in patients with TLE.

Nevertheless, it should be stressed that the P-glycoprotein (PGP) expression could compromise this interpretation of PET findings. PGP is an ATP-driven transmembrane efflux pump, which is located at the blood-brain barrier and transports a wide variety of substrates from the brain to blood and cerebrospinal fluid. $[^{18}\text{F}]\text{MPPF}$ being a substrate for PGP, its brain uptake is modulated. An overexpression of PGP is reported in epileptic foci, probably leading to drug resistance in epilepsy [132]. Thus, the reduction of $[^{18}\text{F}]\text{MPPF BP}_{\text{ND}}$ observed in patients with TLE could reflect a combination between decreased number of $5\text{-HT}_{1\text{A}}$ receptors and a more active PGP pump.

In epilepsy and depression, PET studies of the serotonergic system focused on $5\text{-HT}_{1\text{A}}$ receptors in patients with TLE. Previous PET investigations of $5\text{-HT}_{1\text{A}}$ receptors using $[^{11}\text{C}]\text{WAY-100635}$ and $[^{18}\text{F}]\text{FC-WAY}$ observed greater BP reduction in the more depressed patients with TLE, suggesting decreased expression of $5\text{-HT}_{1\text{A}}$ receptors [126, 127, 133, 134]. This abnormality was primarily reported ipsilateral to the epileptogenic temporal lobe, and more specifically over the anterior cingulate gyrus [126] and the hippocampus [127, 133]. Recently this finding was confirmed in a larger sample of TLE patients, reporting a significant inverse relation between Beck depression inventory (BDI) scores and $[^{18}\text{F}]\text{FC-WAY } 5\text{HT}_{1\text{A}}$ receptor plasma free-fraction corrected volume of distribution (V/f_1) in the hippocampus ipsilateral to the patient's epileptic focus [134]. In 37 TLE patients with or without hippocampal sclerosis, Hasler et al. [135] also showed lower $[^{18}\text{F}]\text{FCWAY}$ binding in patients with a history of MDD compared with those without such a history, in hippocampus, temporal neocortex, anterior insula, anterior cingulate and raphe nuclei. However, a recent $[^{11}\text{C}]\text{WAY-100635}$ PET study performed in a small population of 13 TLE patients with or without hippocampal sclerosis failed to report any correlation between binding potential and depression [130].

In contrast with these findings, we observed greater BP_{ND} of $[^{18}\text{F}]\text{MPPF}$ in the more depressed TLE patients with hippocampal sclerosis and no previous antidepressant exposure, particularly within the insula contralateral to seizure onset as well as in the raphe nuclei [8]. Interestingly, a different set of brain regions was associated with each of the main dimensions explored by the BDI-2, with the insula and raphe abnormalities being associated with symp-

toms of psychomotor anhedonia and negative cognition, whereas somatic symptoms correlated with [¹⁸F]MPPF BP_{ND} in the anterior cingulate gyrus and hippocampus ipsilateral to seizure onset. Considering the sensitivity of [¹⁸F]MPPF to the extra-cellular concentration of endogenous 5-HT, the greater [¹⁸F]MPPF BP_{ND} observed in the more depressed patients suggests a combination of an underlying depletion in the extra-cellular concentration of 5-HT and a decreased density in 5-HT_{1A} receptors.

As previously mentioned, discordance between PET studies of 5-HT_{1A} receptors in patients with epilepsy and depression might also reflect a difference in the modeling methods used to calculate BP [79], the choice of the reference region, as well as the studied patient samples. Indeed, in our [¹⁸F]MPPF PET study, we have selected a more homogeneous group of patients than those of previous [¹¹C]WAY-100635 studies; all patients were naïve to previous antidepressant exposure and showed MRI signs of hippocampal sclerosis. Conversely, the proportion of patients with hippocampal sclerosis varied in other series [126, 127, 133, 134]. The pathophysiology of epilepsy-related depression might differ between TLE patients with and without hippocampal sclerosis [136, 137]. Furthermore, the brain distribution of 5-HT_{1A} receptors would be influenced by previous antidepressant treatment [77]. Finally, it should be noted that antiepileptic drugs, such as carbamazepine [138], could modify the intracerebral concentration of 5-HT. Thus, differences in the proportion of patients with and without depressive symptoms receiving carbamazepine could also play a role in the discordances observed between [¹⁸F]MPPF and [¹¹C]WAY-100635 PET findings.

5. Schizophrenia

Schizophrenia is a severely disabling and complex psychiatric disorder with a lifetime prevalence of approximately 1% in the general population [139]. The diagnosis of schizophrenia encompasses the presence of positive (delusions, hallucinations, thought disorder) and negative (emotional blunting, paucity of speech, loss of motivation, self neglect, and social withdrawal) symptoms, and cognitive deficits (deficits in attention, executive function, and memory). According to DSM-IV-TR, two or more positive symptoms have occurred for at least one month, unless hallucinations or delusions are especially bizarre, in which case one alone suffices for diagnosis. The onset of symptoms typically occurs during adolescence and young adulthood, with men having an earlier age of onset than women. Medical and psychiatric comorbidities, such as substance abuse, anxiety and depressive disorders, are frequent in patients with schizophrenia [140]. Furthermore patients with schizophrenia have higher rates of mortality in comparison to the general population [141].

Schizophrenia has a multifactorial etiology, involving a combination of genetic and environmental risk factors. Several neurotransmitters systems (dopamine, glutamate, acetylcholine, GABA, serotonin) are altered in schizophrenia. Until recently, the predominant focus of research in the pathophysiology of schizophrenia was the dopaminergic neurotransmission. The current dopamine hypothesis postulates that dopaminergic systems in schizophrenia might be characterized by a cortical/subcortical imbalance. Subcortical mesolimbic dopami-

nergic projections might be hyperactive (underlying positive symptoms), while mesocortical dopaminergic projections to the prefrontal cortex might be hypoactive (underlying negative symptoms and cognitive impairments) [142]. However, despite over 100 years of research, the precise pathophysiologic mechanisms of schizophrenia still remain unclear.

Over the years, there is increasing evidence that the serotonergic 5-HT_{1A} system is involved in the pathophysiology of schizophrenia and its treatment [143]. Abnormalities of 5-HT_{1A} receptors were reported in patients suffering from schizophrenia or schizoaffective disorder. Firstly, most post-mortem studies observed an increased 5-HT_{1A} receptor density (between 17% and 79%) in different brain regions of patients with schizophrenia, including the dorso-lateral prefrontal cortex [144-148]. It should be noted that the majority of patients included in post-mortem studies had generally lengthy histories of psychiatric illness and of antipsychotic chronic treatment and/or other medications that could have an impact on the 5-HT_{1A} receptor distribution.

Only few [¹¹C]WAY-100635 PET studies were performed in patients with schizophrenia or schizoaffective disorder and have reported inconsistent results. The first [¹¹C]WAY-100635 PET study showed an increased BP_{ND} in the left medial temporal cortex in patients with schizophrenia who were untreated and never previously exposed to antipsychotic drug (APD) compared to healthy subjects [149]. However, other PET series demonstrated a decreased [¹¹C]WAY-100635 BP in the amygdala in drug-free and drug-naïve patients with schizophrenia or schizophreniform disorder (predominantly drug-naïve) [150] or failed to show BP alterations in various populations of APD-treated, untreated or never exposed to APDs patients with schizophrenia or schizoaffective disorder [151, 152]. There are several possible explanations for these discrepancies including differences in the brain regional distribution of PET changes, in the modeling methods used to calculate BP, in the selected patient samples as well as in their antipsychotic treatment.

Antipsychotic medications are used to treat schizophrenia. Since mid-1950's, numerous APDs with different pharmacological profiles were developed. In agreement with the dopamine hypothesis of schizophrenia, the first generation antipsychotics, such as haloperidol, are dopamine D₂ antagonists and are effective for reducing positive symptoms of schizophrenia. However, they are ineffective against negative symptoms and have high propensity for induction of extrapyramidal symptoms. The second generation antipsychotics, such as clozapine, olanzapine or risperidone, present enhanced efficacy in treating positive and negative symptoms and lower rates of extrapyramidal side effects [153]. The latter are potent 5-HT_{2A/2C} receptor antagonists and relatively weak dopamine D₂ antagonists.

To date, the development of new APDs focuses on agonist properties at 5-HT_{1A} receptors, pharmacologic profile involved in the treatment of negative symptoms and cognitive deficits of schizophrenia and in the reduction of extrapyramidal side effects [154]. Indeed, preclinical studies reported that 5-HT_{1A} agonists reduced D₂-antagonist-induced catalepsy and increased the outflow of dopamine in the striatum [155] and in the medial prefrontal cortex [156, 157]. Aripiprazole is the first APDs with a unique pharmacologic profile combining a partial agonist activity at dopamine D₂ receptors, an antagonism at 5-HT₂ receptors and a partial agonism at 5-HT_{1A} receptors [158]. In rats, aripiprazole modulates the in-vivo 5-HT and dopamine release

in the medial prefrontal cortex through the activation of 5-HT_{1A} receptors [159]. Furthermore, aripiprazole does not induce extrapyramidal symptoms in patients with schizophrenia or schizoaffective disorder [160].

The effects of different APDs on 5-HT_{1A} receptors have been evaluated using PET and [¹¹C]WAY-100635 or [¹⁸F]MPPF as radioligand, but these series reported conflicting results [151, 161-163]. Two [¹¹C]WAY-100635 PET studies showed contradictory findings in treated schizophrenic patients, reporting either no difference between patients taking clozapine or second generation antipsychotics and age-matched controls [151] or a reduction in BP_{ND} obtained after treatment with aripiprazole in comparison to age-matched controls [163]. In addition a recent test-retest study failed to observe a significant effect of chronic treatment of ziprasidone on the 5-HT_{1A} binding in six schizophrenic patients [162].

To investigate the impact of various APDs on the serotonergic system, we performed a [¹⁸F]MPPF PET study in 19 schizophrenic patients treated with either aripiprazole or second generation antipsychotics [161]. We reported a reduced [¹⁸F]MPPF BP_{ND} mainly in the frontal and orbitofrontal cortex, in treated schizophrenic patients compared to age- and gender-matched healthy subjects. These findings may reflect either the pathophysiology of schizophrenia or medication effects. Furthermore, the schizophrenic patients treated with aripiprazole showed a reduction of global [¹⁸F]MPPF BP_{ND} in comparison to healthy subjects and schizophrenic patients with second generation antipsychotic treatment. In addition, in comparison to matched controls, the reduction of regional [¹⁸F]MPPF BP_{ND} was more marked in the schizophrenic patients treated with aripiprazole in comparison to those receiving second generation antipsychotic treatment. These abnormalities were localized in larger clusters encompassing the right and left frontal and orbitofrontal cortex, precune and cingulate regions, the left temporal region as well as the raphe nuclei. These findings could be due to either occupancy by aripiprazole at 5-HT_{1A} receptors or a decreased 5-HT_{1A} receptor density. These findings may possibly reflect the partial agonist activity of aripiprazole at 5-HT_{1A} receptors. However, no modifications of 5-HT_{1A} receptor density and mRNA expression were found in limbic regions in rats after 12 weeks of aripiprazole treatment [164]. In our opinion, our [¹⁸F]MPPF PET data most likely reflect the partial agonist activity of aripiprazole at 5-HT_{1A} receptors. Importantly, in contrast with previous [¹¹C]WAY-100635 PET studies, we take into account cortical atrophy as a confounding factor, by excluding the affected clusters in the right temporal gyrus and insula from our [¹⁸F]MPPF PET analyses. These contradictory 5-HT_{1A} receptors PET findings could be attributable to differences in the used radioligands, the choice of the reference region, in sample populations, including duration of illness, as well as the in vivo agonist properties at the 5-HT_{1A} receptors of studied APDs.

6. Conclusion

Discordance between [¹⁸F]MPPF and [¹¹C]WAY-100635 PET studies of 5-HT_{1A} receptors might reflect their differential sensitivity to extracellular concentration of endogenous 5-HT and to

the internalization of 5-HT_{1A} autoreceptors, but also differences in the data modeling strategies used to calculate BP, including the choice of the reference region (inclusion of cerebellar vermis and gray matter in the reference region)[79], and the population studied. We should also bear in mind that the genetic background for each subject and the gene-by-environment interaction can have a significant influence in different directions on [¹⁸F]MPPF and [¹¹C]WAY-100635 PET findings, which is difficult to control for in the small samples of patients and healthy subjects included in PET studies [41-46].

In future PET studies of 5-HT_{1A} receptors, a more detailed clinical description of studied patients would improve the understanding of discrepancies between studies. Furthermore, particular attention should be paid to the constitution of a group of healthy subjects matched for confounding factors, such as age and sex. For instance, a PET study reported a lower cortical trapping of the alpha-[¹¹C]Methyl-L-Tryptophan (AMT) in women compared to men [165].

Future studies should aim at disentangling these issues by using a traditional multi-injection [¹⁸F]MPPF protocol that enables a precise quantification of binding parameters (B'MAX; Kd) and the estimation of extracellular 5-HT concentration [166] or by coupling [¹⁸F]MPPF and [¹¹C]WAY-100635 PET studies in the same individuals taking advantage of their different affinities for 5-HT_{1A} receptors. Another future challenge will be to image endogenous 5HT release in humans [167].

Acknowledgements

We thank Didier Le Bars for [¹⁸F]MPPF radiosynthesis and the medical team of the CERMEP – Imagerie du vivant. We are indebted to Nicolas Costes and Jérôme Redouté.

The Article Processing Charge was funded by the Translational and Integrative Group in Epilepsy Research (TIGER) (CRNL).

Author details

Amélie Lothe^{1*}, Sandrine Bouvard¹ and Philippe Ryvlin^{1,2}

*Address all correspondence to: amelie.lothe@cermep.fr

1 INSERM U1028, CNRS UMR5292, and University Claude Bernard Lyon 1, Lyon Neuroscience Research Center, Translational and Integrative Group in Epilepsy Research (TIGER), Lyon, France

2 Department of Functional Neurology and Epileptology and Institute for Children and Adolescents with Epilepsy (IDEE), Hospices Civils de Lyon, Lyon, France

References

- [1] Lucki I. The spectrum of behaviors influenced by serotonin. *Biol. Psychiatry* 1998;44:151-16
- [2] Barnes NM, Sharp T. A review of central 5-HT receptors and their function. *Neuropharmacology* 1999;38(8):1083-1152.
- [3] Drevets WC, Thase ME, Moses-Kolko EL, Price J, Frank E, Kupfer DJ, et al. Serotonin-1A receptor imaging in recurrent depression: replication and literature review. *Nucl. Med. Biol.* 2007;34(7):865-877.
- [4] Maes M, Meltzer H. The serotonin hypothesis of major depression. In: Bloom, FE, Kupfer, DJ (Eds.), *Psychopharmacology. The Fourth Generation of Progress*. Raven Press Ltd, New York, NY 1995:933-944.
- [5] Demarquay G, Lothe A, Royet JP, Costes N, Mick G, Mauguière F, et al. Brainstem changes in 5-HT_{1A} receptor availability during migraine attack. *Cephalalgia* 2011;31(1):84-94.
- [6] Lothe A, Merlet I, Demarquay G, Costes N, Ryvlin P, Mauguière F. Interictal brain 5-HT(1A) receptors binding in migraine without aura: a (18)F-MPPF-PET study. *Cephalalgia* 2008;28(12):1282-1291.
- [7] Didelot A, Ryvlin P, Lothe A, Merlet I, Hammers A, Mauguiere F. PET imaging of brain 5-HT_{1A} receptors in the preoperative evaluation of temporal lobe epilepsy. *Brain* 2008;131(Pt 10):2751-2764.
- [8] Lothe A, Didelot A, Hammers A, Costes N, Saoud M, Gilliam F, et al. Comorbidity between temporal lobe epilepsy and depression: a [¹⁸F]MPPF PET study. *Brain* 2008b; 131(Pt 10):2765-2782.
- [9] Merlet I, Ryvlin P, Costes N, Dufournel D, Isnard J, Faillenot I, et al. Statistical parametric mapping of 5-HT_{1A} receptor binding in temporal lobe epilepsy with hippocampal ictal onset on intracranial EEG. *Neuroimage* 2004;22(2):886-896.
- [10] Truchot L, Costes N, Zimmer L, Laurent B, Le Bars D, Thomas-Antérion C, et al. A distinct [¹⁸F]MPPF PET profile in amnesic mild cognitive impairment compared to mild Alzheimer's disease. *Neuroimage* 2008;40(3):1251-1256.
- [11] Buhot MC, Martin S, Segu L. Role of serotonin in memory impairment. *Ann. Med.* 2000;32(3):210-221.
- [12] Hainer V, Kabrnova K, Aldhoon B, Kunesova M, Wagenknecht M. Serotonin and norepinephrine reuptake inhibition and eating behavior. *Ann. N. Y. Acad. Sci.* 2006;1083:252-269.

- [13] Gross C, Zhuang X, Stark K, Ramboz S, Oosting R, Kirby L, et al. Serotonin 1A receptor acts during development to establish normal anxiety-like behaviour in the adult. *Nature* 2002;416(6879):396-400.
- [14] Iqbal N, van Praag HM. The role of serotonin in schizophrenia. *Eur Neuropsychopharmacol.* 1995;5 Suppl:11-23.
- [15] Burgess NK, Sweeten TL, McMahon WM, Fujinami RS. Hyperserotoninemia and altered immunity in autism. *J. Autism. Dev. Disord.* 2006;36(5):697-704.
- [16] Chugani DC. Serotonin in autism and pediatric epilepsies. *Ment. Retard. Dev. Disabil. Res. Rev.* 2004;10(2):112-116.
- [17] Paterson LM, Kornum BR, Nutt DJ, Pike VW, Knudsen GM. 5-HT radioligands for human brain imaging with PET and SPECT. *Med Res Rev.* 2011;Jun 14.doi: 10.1002/med.20245.
- [18] Hannon J, Hoyer D. Molecular biology of 5-HT receptors. *Behav Brain Res.* 2008;195(1):198-213.
- [19] Bockaert J, Claeysen S, Bécamel C, Dumuis A, Marin P. Neuronal 5-HT metabotropic receptors: fine-tuning of their structure, signaling, and roles in synaptic modulation. *Cell Tissue Res.* 2006;326(2):553-72.
- [20] Fargin A, Raymond JR, Lohse MJ, Kobilka BK, Caron MG, Lefkowitz RJ. The genomic clone G-21 which resembles a betaadrenergic receptor sequence encodes the 5-HT1A receptor. *Nature* 1988;335, 358-360.
- [21] Beck SG, Choi KC. 5-Hydroxytryptamine hyperpolarizes CA3 hippocampal pyramidal cells through an increase in potassium conductance. *Neurosci Lett.* 1991; 133: 93–6.
- [22] Okuhara DY, Beck SG. 5-HT1A receptor linked to inward-rectifying potassium current in hippocampal CA3 pyramidal cells. *J Neurophysiol.* 1994; 71: 2161–7.
- [23] Richer M, Hen R, Blier P. Modification of serotonin neuron properties in mice lacking 5-HT1A receptors. *Eur. J. Pharmacol.* 2002;435(2-3):195-203
- [24] Weissmann-Nanopoulos D, Mach E, Magre S, Demassay Y, Pujol JF. Evidence for the localization of 5HT1-A binding sites on serotonin containing neurons in the raphe dorsalis and raphe centralis nuclei of the rat brain. *Neurochem. Int.* 1985;7:1061-1072.
- [25] Kumar JS, Mann JJ. PET tracers for 5-HT(1A) receptors and uses thereof. *Drug Discov Today* 2007;Sep 12(17-18):748-56.
- [26] Zhuang ZP, Kung MP, Chumpradit S, Mu M, Kung HF. Derivatives of 4-(2'-methoxyphenyl)-1-[2'-(N-2''-pyridinyl-p-iodobenzamido)ethyl]piperazine (p-MPPI) as 5-HT1A ligands. *J. Med. Chem.* 1994;37(26):4572-4575.

- [27] Lang L, Jagoda E, Schmall B, Vuong BK, Adams HR, Nelson DL, et al. Development of fluorine-18-labeled 5-HT_{1A} antagonists. *J Med Chem*. 1999 May 6;42(9):1576-86.
- [28] Rice OV, Gatley SJ, Shen J, Huemmer CL, Rogoz R, DeJesus OT et al., 2001. Effects of endogenous neurotransmitters on the in vivo binding of dopamine and 5-HT radiotracers in mice. *Neuropsychopharmacology*;25(5):679-89.
- [29] Maeda J, Suhara T, Ogawa M, Okauchi T, Kawabe K, Zhang MR et al. In vivo binding properties of [carbonyl-11C]WAY-100635: effect of endogenous serotonin. *Synapse* 2001;40(2):122-9.
- [30] Van Wijngaarden I, Tulp MT, Soudijn W. The concept of selectivity in 5-HT receptor research. *Eur. J. Pharmacol*. 1990;188(6): 301-312.
- [31] Rbah L, Levie V, Zimmer L. Displacement of the PET ligand ¹⁸F-MPPF by the electrically evoked serotonin release in the rat hippocampus. *Synapse* 2003;49(4):239-245.
- [32] Zimmer L, Mauger G, Le Bars D, Bonmarchand G, Luxen A, Pujol JF. Effect of endogenous serotonin on the binding of the 5-HT_{1A} PET ligand ¹⁸F-MPPF in the rat hippocampus: kinetic beta measurements combined with microdialysis. *J. Neurochem*. 2002; 80(2):278-286.
- [33] Zimmer L, Rbah L, Giacomelli F, Le Bars D, Renaud B. A reduced extracellular serotonin level increases the 5-HT_{1A} PET ligand 18FMPPF binding in the rat hippocampus. *Journal of Nuclear Medicine* 2003;44 (9):1495-501.
- [34] Millet P, Moulin M, Bartoli A, Del Guerra A, Ginovart N, Lemoucheux L, et al. In vivo quantification of 5-HT_{1A}-[18F]MPPF interactions in rats using the YAP-(S)PET scanner and a beta-microprobe. *Neuroimage*. 2008 Jul 1;41(3):823-34.
- [35] Frey BN, Rosa-Neto P, Lubarsky S, Diksic M. Correlation between serotonin synthesis and 5-HT_{1A} receptor binding in the living human brain: a combined alpha-[11C]MT and [18F]MPPF positron emission tomography study. *Neuroimage* 2008;42(2):850-7.
- [36] Gozlan H, Thibault S, Laporte AM, Lima L, Hamon M. The selective 5-HT_{1A} antagonist radioligand [³H]WAY 100635 labels both G-protein coupled and free 5-HT_{1A} receptors in rat brain membranes. *Eur J Pharmacol*. 1995;288:173-186.
- [37] Zimmer L, Riad M, Rbah L, Belkacem-Kahlouli A, Le Bars D, Renaud B, et al. Toward brain imaging of serotonin 5-HT_{1A} autoreceptor internalization. *Neuroimage* 2004;22(3):1421-1426.
- [38] Riad M, Zimmer L, Rbah L, Watkins KC, Hamon M, Descarries L. Acute treatment with the antidepressant fluoxetine internalizes 5-HT_{1A} autoreceptors and reduces the in vivo binding of the PET radioligand [18F]MPPF in the nucleus raphe dorsalis of rat. *J Neurosci* 2004;24(23):5420-6.

- [39] Aznavour N, Rbah L, Riad M, Reilhac A, Costes N, Descarries L et al. A PET imaging study of 5-HT(1A) receptors in cat brain after acute and chronic fluoxetine treatment. *Neuroimage* 2006;33(3):834-42.
- [40] Sibon I, Benkelfat C, Gravel P, Aznavour N, Costes N, Mzengeza S et al. Decreased [18F]MPPF binding potential in the dorsal raphe nucleus after a single oral dose of fluoxetine: a positron-emission tomography study in healthy volunteers. *Biol Psychiatry* 2008;63(12):1135-40.
- [41] David SP, Murthy NV, Rabiner EA, Munafó MR, Johnstone EC, Jacob R et al. A functional genetic variation of the serotonin (5-HT) transporter affects 5-HT1A receptor binding in humans. *J Neurosci.* 2005;25(10):2586-90.
- [42] Lee M, Bailer UF, Frank GK, Henry SE, Meltzer CC, Price JC et al. Relationship of a 5-HT transporter functional polymorphism to 5-HT1A receptor binding in healthy women. *Mol Psychiatry* 2005;10(8):715-6.
- [43] Lothe A, Boni C, Costes N, Gorwood P, Bouvard S, Le Bars D et al. Association between triallelic polymorphism of the serotonin transporter and [18F]MPPF binding potential at 5-HT1A receptors in healthy subjects. *Neuroimage* 2009;47(2):482-492.
- [44] Lothe A, Boni C, Costes N, Bouvard S, Gorwood P, Lavenne F, et al. 5-HT_{1A} gene promoter polymorphism and [18F]MPPF binding potential in healthy subjects: a PET study. *Behav Brain Funct.* 2010;Jul 7;6:37.
- [45] Parsey RV, Oquendo MA, Ogden RT, Olvet DM, Simpson N, Huang YY et al. Altered serotonin 1A binding in major depression: a [carbonyl-C-11]WAY100635 positron emission tomography study. *Biol Psychiatry* 2006;59(2):106-13.
- [46] Sullivan GM, Ogden RT, Oquendo MA, Kumar JS, Simpson N, Huang YY, et al. Positron emission tomography quantification of serotonin-1A receptor binding in medication-free bipolar depression. *Biol Psychiatry* 2009;66:223-30.
- [47] Borg J, Henningsson S, Saijo T, Inoue M, Bah J, Westberg L, et al. Serotonin transporter genotype is associated with cognitive performance but not regional 5-HT1A receptor binding in humans. *Int. J. Neuropsychopharmacol.* 2009;1-10.
- [48] Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J. Cereb. Blood Flow Metab.* 2007;27(9):1533-1539.
- [49] Møller M, Jakobsen S, Gjedde A. Parametric and regional maps of free serotonin 5HT1A receptor sites in human brain as function of age in healthy humans. *Neuropsychopharmacology* 2007;32:1707-14.
- [50] Costes N, Merlet I, Ostrowsky K, Faillenot I, Lavenne F, Zimmer L, et al. A 18F-MPPF PET normative database of 5-HT1A receptor binding in men and women over aging. *J Nucl Med* 2005;46:1980-9.

- [51] Tauscher J, Verhoeff NP, Christensen BK, Hussey D, Meyer JH, Kecojevic A, et al. Serotonin 5-HT1A receptor binding potential declines with age as measured by [11C]WAY-100635 and PET. *Neuropsychopharmacology* 2001;24:522-30.
- [52] Cidis Meltzer C, Drevets WC, Price JC, Mathis CA, Lopresti B, Greer PJ, et al. Gender-specific aging effects on the serotonin 1A receptor. *Brain Res* 2001;895:9-17.
- [53] Parsey RV, Oquendo MA, Simpson NR, Ogden RT, Van Heertum R, Arango V et al. Effects of sex, age, and aggressive traits in man on brain serotonin 5-HT1A receptor binding potential measured by PET using [C-11]WAY-100635. *Brain Res.* 2002;954(2): 173-82.
- [54] Stein P, Savli M, Wadsak W, Mitterhauser M, Fink M, Spindelegger C, et al. The serotonin-1A receptor distribution in healthy men and women measured by PET and [carbonyl-11C]WAY-100635. *Eur. J. Nucl. Med. Mol. Imaging* 2008;35, 2159–2168.
- [55] Jovanovic H, Lundberg J, Karlsson P, Cerin A, Saijo T, Varrone A, et al. Sex differences in the serotonin 1A receptor and serotonin transporter binding in the human brain measured by PET. *NeuroImage* 2008;39(3), 1408–1419.
- [56] Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, et al. Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med.* 2011 Jul 26;9:90.
- [57] American Psychiatric Association. *Diagnostic Statistical Manual of Mental Disorders*, Forth edition, Wasghiton, American psy press, 2000
- [58] Fenton WS, Stover ES. Mood disorders: cardiovascular and diabetes comorbidity. *Curr Opin Psychiatry.* 2006 Jul;19(4):421-7.
- [59] Ustün TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ. Global burden of depressive disorders in the year 2000. *Br J Psychiatry.* 2004 May;184:386-92.
- [60] Dhaenen H. Imaging the serotonergic system in depression. *Eur Arch Psychiatry Clin Neurosci.* 2001;251 (Suppl 2): II76–80.
- [61] Jans LA, Riedel WJ, Markus CR, Blokland A. Serotonergic vulnerability and depression: assumptions, experimental evidence and implications. *Mol Psychiatry* 2007 Jun; 12(6):522-43.
- [62] Asberg M, Thoren P, Traskman L, Bertilsson L, Ringberger V. 'Serotonin depression'—a biochemical subgroup within the affective disorders? *Science* 1976; 191: 478–80.
- [63] Meltzer HY. Role of serotonin in depression. *Ann N Y Acad Sci.* 1990; 600:486–99.
- [64] Delgado PL, Charney DS, Price LH, Aghajanian GK, Landis H, Heninger GR. Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. *Arch Gen Psychiatry.* 1990 May;47(5):411-8.

- [65] Smith KA, Fairburn CG, Cowen PJ. Relapse of depression after rapid depletion of tryptophan. *Lancet* 1997 Mar 29;349(9056):915-9.
- [66] Young SN, Smith SE, Pihl RO, Ervin FR. Tryptophan depletion causes a rapid lowering of mood in normal males. *Psychopharmacology* 1985;87(2):173-7.
- [67] Berney A, Nishikawa M, Benkelfat C, Debonnel G, Gobbi G, Diksic M. An index of 5-HT synthesis changes during early antidepressant treatment: alpha-[11C]methyl-L-tryptophan PET study. *Neurochem Int.* 2008;52(4-5):701-8.
- [68] Rosa-Neto P, Diksic M, Okazawa H, Leyton M, Ghadirian N, Mzengeza S et al. Measurement of brain regional alpha-[11C]methyl-L-tryptophan trapping as a measure of serotonin synthesis in medication-free patients with major depression. *Arch Gen Psychiatry* 2004; 61(6):556-63.
- [69] Savitz JB, Drevets WC. Neuroreceptor imaging in depression. *Neurobiol Dis.* 2012 Jun 9. [Epub ahead of print]
- [70] Shrestha S, Hirvonen J, Hines CS, Henter ID, Svenningsson P, Pike VW, et al. Serotonin-1A receptors in major depression quantified using PET: controversies, confounds, and recommendations. *Neuroimage* 2012 Feb 15;59(4):3243-51.
- [71] Saijo T, Takano A, Suhara T, Arakawa R, Okumura M, Ichimiya T, et al. Effect of electroconvulsive therapy on 5-HT1A receptor binding in patients with depression: a PET study with [11C]WAY 100635. *Int J Neuropsychopharmacol.* 2010 Jul;13(6):785-91.
- [72] Mickey BJ, Ducci F, Hodgkinson CA, Langenecker SA, Goldman D, Zubieta JK. Monoamine oxidase A genotype predicts human serotonin 1A receptor availability in vivo. *J Neurosci.* 2008; 28:11354-9.
- [73] Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, et al. PET imaging of serotonin 1A receptor binding in depression. *Biol Psychiatry* 1999;46:1375-1387.
- [74] Drevets WC, Frank E, Price JC, Kupfer DJ, Greer PJ, Mathis C. Serotonin type-1A receptor imaging in depression. *Nucl Med Biol.* 2000;27:499-507.
- [75] Sargent PA, Kjaer KH, Bench CJ, Rabiner EA, Messa C, Meyer J, et al. Brain serotonin 1A receptor binding measured by positron emission tomography with [11C]WAY-100635: effects of depression and antidepressant treatment. *Arch Gen Psychiatry* 2000;57:174-180.
- [76] Bhagwagar Z, Rabiner EA, Sargent PA, Grasby PM, Cowen PJ. Persistent reduction in brain serotonin 1A receptor binding in recovered depressed men measured by positron emission tomography with [11C]WAY-100635. *Mol Psychiatry* 2004;9:386-392.

- [77] Parsey RV, Oquendo MA, Ogden RT, Olvet DM, Simpson N, Huang YY, et al. Altered serotonin 1A binding in major depression: a [carbonyl-C-11]WAY100635 positron emission tomography study. *Biol Psychiatry* 2006a;59:106-113.
- [78] Parsey RV, Olvet DM, Oquendo MA, Huang YY, Ogden RT, Mann JJ. Higher 5-HT_{1A} receptor binding potential during a major depressive episode predicts poor treatment response: preliminary data from a naturalistic study. *Neuropsychopharmacology* 2006b;31:1745-9.
- [79] Parsey RV, Ogden RT, Miller JM, Tin A, Hesselgrave N, Goldstein E, et al. Higher serotonin 1A binding in a second major depression cohort: modeling and reference region considerations. *Biol Psychiatry* 2010;68:170-178.
- [80] Hirvonen J, Karlsson H, Kajander J, Lepola A, Markkula J, Rasi-Hakala H et al. Decreased brain serotonin 5-HT_{1A} receptor availability in medication-naïve patients with major depressive disorder: an in-vivo imaging study using PET and [carbonyl-11C]WAY-100635. *Int J Neuropsychopharmacol.* 2008;11(4):465-76.
- [81] Miller JM, Brennan KG, Ogden TR, Oquendo MA, Sullivan GM, Mann JJ, et al. Elevated serotonin 1A binding in remitted major depressive disorder: evidence for a trait biological abnormality. *Neuropsychopharmacology* 2009;34:2275-2284.
- [82] Shively CA, Friedman DP, Gage HD, Bounds MC, Brown-Proctor C, Blair JB, et al. Behavioral depression and positron emission tomography-determined serotonin 1A receptor binding potential in cynomolgus monkeys. *Archives of General Psychiatry* 2006;63, 396-403.
- [83] Bowen DM, Najlerahim A, Procter AW, Francis PT, Murphy E. Circumscribed changes of the cerebral cortex in neuropsychiatric disorders of later life. *Proc. Natl. Acad. Sci. USA* 1989;86:9504-8.
- [84] Cheetham SC, Crompton MR, Katona CL, Horton RW. Brain 5-HT₁ binding sites in depressed suicides. *Psychopharmacology (Berl)*. 1990;102(4):544-8.
- [85] Francis PT, Pangalos MN, Stephens PH, Bartlett JR, Bridges PK, Malizia AL, et al. Antemortem measurements of neurotransmission: possible implications for pharmacotherapy of Alzheimer's disease and depression. *J Neurol Neurosurg Psychiatry*. 1993 Jan;56(1):80-4.
- [86] Arango V, Underwood MD, Boldrini M, Tamir H, Kassir SA et al. Serotonin 1A receptors, serotonin transporter binding and serotonin transporter mRNA expression in the brainstem of depressed suicide victims. *Neuropsychopharmacology* 2001;25(6):892-903.
- [87] Lopez-Figueroa AL, Norton CS, Lopez-Figueroa MO, Armellini-Dodel D, Burke S, Akil H et al. Serotonin 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A} receptor mRNA expression in subjects with major depression, bipolar disorder, and schizophrenia. *Biol. Psychiatry* 2004;55(3):225-33.

- [88] Boldrini M, Underwood MD, Mann JJ, Arango V. Serotonin-1A autoreceptor binding in the dorsal raphe nucleus of depressed suicides. *J Psychiatr Res.* 2008; 42:433-42.
- [89] Anisman H, Du L, Palkovits M, Faludi G, Kovacs GG, Szontagh-Kishazi P, et al. Serotonin receptor subtype and p11 mRNA expression in stress-relevant brain regions of suicide and control subjects. *J Psychiatry Neurosci.* 2008 Mar;33(2):131-41.
- [90] Lopez JF, Chalmers DT, Little KY, Watson SJ. Regulation of serotonin_{1A}, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression. *Biol. Psychiatry* 1998;43(8):547-73.
- [91] Hirvonen J, Kajander J, Allonen T, Oikonen V, Någren K, Hietala J. Measurement of serotonin 5-HT_{1A} receptor binding using positron emission tomography and [carbonyl-(11)C]WAY-100635-considerations on the validity of cerebellum as a reference region. *J Cereb Blood Flow Metab.* 2007;27(1):185-95.
- [92] Kendler KS, Kuhn JW, Vittum J, Prescott CA, Riley B. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. *Arch Gen Psychiatry* 2005 May;62(5):529-35.
- [93] Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003;301(5631):386-389.
- [94] Moses-Kolko EL, Price JC, Thase ME, Meltzer CC, Kupfer DJ, Mathis CA, et al. Measurement of 5-HT_{1A} receptor binding in depressed adults before and after antidepressant drug treatment using positron emission tomography and [¹¹C]WAY-100635. *Synapse* 2007;61:523-530.
- [95] Karlsson H, Hirvonen J, Kajander J, Markkula J, Rasi-Hakala H, Salminen JK, et al. Research letter: Psychotherapy increases brain serotonin 5-HT_{1A} receptors in patients with major depressive disorder. *Psychological Medicine* 2010;40(3):523-528.
- [96] Spindelegger C, Lanzenberger R, Wadsak W, Mien LK, Stein P, Mitterhauser M, et al. Influence of escitalopram treatment on 5-HT_{1A} receptor binding in limbic regions in patients with anxiety disorders. *Mol Psychiatry* 2009 Nov;14(11):1040-50.
- [97] Lothe A, Saoud M, Bouvard S, Redouté J, Lerond J, Ryvlin P. 5-HT_{1A} receptor binding in patients with major depressive disorder before and after antidepressant treatment : A pilot [¹⁸F]MPPF positron emission tomography study. *Psychiatry Research : Neuroimaging* 2012;Jul 30;203(1):103-4
- [98] Riad M, Rbah L, Verdurand M, Aznavour N, Zimmer L, Descarries L. Unchanged density of 5-HT(1A) autoreceptors on the plasma membrane of nucleus raphe dorsalis neurons in rats chronically treated with fluoxetine. *Neuroscience* 2008;151(3): 692-700.

- [99] Moulin-Sallanon M, Charnay Y, Ginovart N, Perret P, Lanfumey L, Hamon M, et al. Acute and chronic effects of citalopram on 5-HT1A receptor-labeling by [18F]MPPF and -coupling to receptors-G proteins. *Synapse*. 2009 Feb;63(2):106-16.
- [100] Téllez-Zenteno JF, Dhar R, Hernandez-Ronquillo L, Wiebe S. Long-term outcomes in epilepsy surgery: antiepileptic drugs, mortality, cognitive and psychosocial aspects. *Brain* 2007;130(Pt 2):334-45.
- [101] Jones JE, Hermann BP, Barry JJ, Gilliam F, Kanner AM, Meador KJ. Clinical assessment of axis I psychiatric morbidity in chronic epilepsy: a multicenter investigation. *J Neuropsychiatry Clin Neurosci* Spring 2005;17:172-9.
- [102] Jones JE, Bell B, Fine J, Rutecki P, Seidenberg M, Hermann B. A controlled prospective investigation of psychiatric comorbidity in temporal lobe epilepsy. *Epilepsia* 2007;48(12):2357-60.
- [103] Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biol Psychiatry* 2003;54:388-98.
- [104] Hermann B, Seidenberg M, Jones J. The neurobehavioural comorbidities of epilepsy: can a natural history be developed? *Lancet Neurol*. 2008;7(2):151-60.
- [105] Gilliam FG, Santos J, Vahle V, Carter J, Brown K, Hecimovic H. Depression in epilepsy: ignoring clinical expression of neuronal network dysfunction? *Epilepsia*. 2004;45 Suppl 2:28-33.
- [106] Quiske A, Helmstaedter C, Lux S, Elger CE. Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. *Epilepsy Res*. 2000;39:121-5.
- [107] Victoroff JL, Benson F, Grafton ST, Engel J Jr, Mazziotta JC. Depression in complex partial seizures. electroencephalography and cerebral metabolic correlates. *Arch Neurol*. 1994; 51: 155-63.
- [108] Altshuler LL, Devinsky O, Post RM, Theodore W. Depression, anxiety, and temporal lobe epilepsy. Laterality of focus and symptoms. *Arch Neurol*. 1990; 47: 284-8.
- [109] Bell GS, Sander JW. Suicide and epilepsy. *Curr Opin Neurol*. 2009 Apr;22(2):174-8.
- [110] Christensen J, Vestergaard M, Mortensen PB, Sidenius P, Agerbo E. Epilepsy and risk of suicide: a population-based case-control study. *Lancet Neurol*. 2007 Aug;6(8): 693-8.
- [111] Kanner AM. Depression and epilepsy: a review of multiple facets of their close relation. *Neurol Clin*. 2009 Nov;27(4):865-80.
- [112] Kanner AM. Mood disorder and epilepsy: a neurobiologic perspective of their relationship. *Dialogues Clin Neurosci*. 2008;10(1):39-45.
- [113] Bagdy G, Kecskemeti V, Riba P, Jakus R. Serotonin and epilepsy. *J Neurochem*. 2007;100(4):857-73.

- [114] Wada Y, Shiraishi J, Nakamura M, Koshino Y. Role of serotonin receptor subtypes in the development of amygdaloid kindling in rats. *Brain Res.* 1997;747:338-42.
- [115] Wada Y, Nakamura M, Hasegawa H, Yamaguchi N. Role of serotonin receptor subtype in seizures kindled from the feline hippocampus. *Neurosci Lett.* 1992;141:21-4.
- [116] Wada Y, Nakamura M, Hasegawa H, Yamaguchi N. Intra-hippocampal injection of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) inhibits partial and generalized seizures induced by kindling stimulation in cats. *Neurosci Lett.* 1993;159:179-182.
- [117] Salgado-Commissariat D, Alkadhi KA. Serotonin inhibits epileptiform discharge by activation of 5-HT_{1A} receptors in CA1 pyramidal neurons. *Neuropharmacology* 1997; 36: 1705-12.
- [118] Tokarski K, Zahorodna A, Bobula B, Hess G. Comparison of the effects of 5-HT_{1A} and 5-HT₄ receptor activation on field potentials and epileptiform activity in rat hippocampus. *Exp Brain Res.* 2002 Dec;147(4):505-10.
- [119] Lu KT, Gean PW. Endogenous serotonin inhibits epileptiform activity in rat hippocampal CA1 neurons via 5-hydroxytryptamine_{1A} receptor activation. *Neuroscience* 1998;86:729-37.
- [120] Yan QS, Jobe PC, Dailey JW. Further evidence of anticonvulsant role for 5-hydroxytryptamine in genetically epilepsy-prone rats. *Br J Pharmacol.* 1995; 115:1314-8.
- [121] Watanabe K, Minabe Y, Ashby CR, Katsumori H. Effect of acute administration of various 5-HT receptor agonists on focal hippocampal seizures in freely moving rats. *Eur J Pharmacol.* 1998; 350:181-8.
- [122] Levkovitz Y, Segal M. Serotonin 5-HT_{1A} receptors modulate hippocampal reactivity to afferent stimulation. *J Neurosci.* 1997; 17:5591-8.
- [123] Toczek MT, Carson RE, Lang L, Ma Y, Spanaki MV, Der MG, et al. PET imaging of 5-HT_{1A} receptor binding in patients with temporal lobe epilepsy. *Neurology* 2003;60:749-56.
- [124] Merlet I, Ryvlin P, Costes N, Dufournel D, Isnard J, Faillenot I, et al. Statistical parametric mapping of 5-HT_{1A} receptor binding in temporal lobe epilepsy with hippocampal ictal onset on intracranial EEG. *Neuroimage* 2004a;22(2):886-96.
- [125] Merlet I, Ostrowsky K, Costes N, Ryvlin P, Isnard J, Faillenot I et al. 5-HT_{1A} receptor binding and intracerebral activity in temporal lobe epilepsy: an [18F]MPPF-PET study. *Brain* 2004b; 127(Pt 4):900-13.
- [126] Savic I, Lindstrom P, Gulyas B, Halldin C, Andree B, Farde L. Limbic reductions of 5-HT_{1A} receptor binding in human temporal lobe epilepsy. *Neurology* 2004;62:1343-51.

- [127] Giovacchini G, Toczek MT, Bonwetsch R, Bagic A, Lang L, Fraser C et al. 5-HT_{1A} receptors are reduced in temporal lobe epilepsy after partial volume correction. *J Nucl Med*. 2005; 46:1128–35.
- [128] Ito S, Suhara T, Ito H, Yasuno F, Ichimiya T, Takano A et al. Changes in central 5-HT_{1A} receptor binding in mesial temporal epilepsy measured by positron emission tomography with [(11)C]WAY100635. *Epilepsy Res*. 2007;73:111-8.
- [129] Didelot A, Ryvlin P, Lothe A, Merlet I, Hammers A, Mauguière F. PET imaging of brain 5-HT_{1A} receptors in the preoperative evaluation of temporal lobe epilepsy. *Brain* 2008;131(Pt 10):2751-64.
- [130] Assem-Hilger E, Lanzenberger R, Savli M, Wadsak W, Mitterhauser M, Mien LK, et al. Central serotonin 1A receptor binding in temporal lobe epilepsy: a [carbonyl-(11)C]WAY-100635 PET study. *Epilepsy Behav*. 2010 Nov;19(3):467-73.
- [131] Statnick MA, Dailey JW, Jobe PC, Browning RA. Abnormalities in brain serotonin concentration, high-affinity uptake, and tryptophan hydroxylase activity in severe-seizure genetically epilepsy-prone rats. *Epilepsia* 1996;37: 311-21.
- [132] Kwan P, Brodie MJ. Potential role of drug transporters in the pathogenesis of medically intractable epilepsy. *Epilepsia* 2005;46(2):224-35.
- [133] Theodore WH, Hasler G, Giovacchini G, Kelley K, Reeves-Tyer P, Herscovitch P, et al. Reduced hippocampal 5HT_{1A} PET receptor binding and depression in temporal lobe epilepsy. *Epilepsia* 2007;48:1526-1530.
- [134] Theodore WH, Wiggs EA, Martinez AR, Dustin IH, Khan OI, Appel S, et al. Serotonin 1A receptors, depression, and memory in temporal lobe epilepsy. *Epilepsia*. 2012 Jan;53(1):129-33.
- [135] Hasler G, Bonwetsch R, Giovacchini G, Toczek MT, Bagic A, Luckenbaugh DA, et al. 5-HT_{1A} receptor binding in temporal lobe epilepsy patients with and without major depression. *Biol Psychiatry* 2007;62:1258-1264.
- [136] Quiske A, Helmstaedter C, Lux S, Elger CE. Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. *Epilepsy Res*. 2000;39:121-5.
- [137] Hecimovic H, Goldstein JD, Sheline YI, Gilliam FG. Mechanisms of depression in epilepsy from a clinical perspective. *Epilepsy Behav* 2003;4 (Suppl 3): S25–30.
- [138] Ahmad S, Fowler LJ, Whitton PS. Lamotrigine, carbamazepine and phenytoin differentially alter extracellular levels of 5-hydroxytryptamine, dopamine and amino acids. *Epilepsy Res*. 2005;63(2-3):141-9.
- [139] Perala J, Suvisaari J, Saarni S, Kuoppasalmi K, Isomesta E, Pirkola S, et al. Lifetime prevalence of psychotic and bipolar disorders in a general population. *Arch Gen Psychiatry* 2007;1 :19-28.

- [140] Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. *Schizophr Bull.* 2009 Mar;35(2):383-402.
- [141] Saha S, Chant D, McGrath J. Meta-analyses of the incidence and prevalence of schizophrenia: conceptual and methodological issues. *Int J Methods Psychiatr Res.* 2008;17(1):55-61.
- [142] Abi-Dargham A. Do we still believe in the dopamine hypothesis? New data bring new evidence. *Int J Neuropsychopharmacol.* 2004 Mar;7 Suppl 1:S1-5.
- [143] Bantick RA, Deakin JF, Grasby PM. The 5-HT_{1A} receptor in schizophrenia: a promising target for novel atypical neuroleptics? *J Psychopharmacol* 2001;15(1):37-46.
- [144] Hashimoto T, Nishino N, Nakai H and Tanaka C. Increase in serotonin 5-HT_{1A} receptors in prefrontal and temporal cortices of brains from patients with chronic schizophrenia. *Life Sci* 1991;48:355-363.
- [145] Joyce JN, Shane A, Lexow N, Winokur A, Casanova MF and Kleinman JE. Serotonin uptake sites and serotonin receptors are altered in the limbic system of schizophrenics. *Neuropsychopharmacology* 1993;8: 315-336.
- [146] Burnet PW, Eastwood SL, Harrison PJ. 5-HT_{1A} and 5-HT_{2A} receptor mRNAs and binding site densities are differentially altered in schizophrenia. *Neuropsychopharmacology* 1996; 15(5):442-55.
- [147] Simpson MD, Lubman DI, Slater P and Deakin JF. Autoradiography with [³H]8-OH-DPAT reveals increases in 5-HT(1A) receptors in ventral prefrontal cortex in schizophrenia. *Biol Psychiatry* 1996;39: 919-928.
- [148] Sumiyoshi T, Stockmeier CA, Overholser JC, Dilley GE and Meltzer HY. Serotonin_{1A} receptors are increased in postmortem prefrontal cortex in schizophrenia. *Brain Res* 1996;708: 209-214.
- [149] Tauscher J, Kapur S, Verhoeff NP, Hussey DF, Daskalakis ZJ, Tauscher-Wisniewski S, et al. Brain serotonin 5-HT(1A) receptor binding in schizophrenia measured by positron emission tomography and [¹¹C]WAY-100635. *Arch Gen Psychiatry* 2002 Jun;59(6):514-20.
- [150] Yasuno F, Suhara T, Ichimiya T, Takano A, Ando T, Okubo Y. Decreased 5-HT_{1A} receptor binding in amygdala of schizophrenia. *Biol Psychiatry* 2004;55(5):439-44.
- [151] Bantick RA, Montgomery AJ, Bench CJ, Choudhry T, Malek N, McKenna PJ et al. A positron emission tomography study of the 5-HT_{1A} receptor in schizophrenia and during clozapine treatment. *J Psychopharmacol* 2004;18(3):346-354.
- [152] Frankle WG, Lombardo I, Kegeles LS, Slifstein M, Martin JH, Huang Y, et al. Serotonin 1A receptor availability in patients with schizophrenia and schizo-affective disorder: a positron emission tomography imaging study with [¹¹C]WAY 100635. *Psychopharmacology (Berl).* 2006 Dec;189(2):155-64.

- [153] Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry* 2003;60:553–564
- [154] Newman-Tancredi A, Kleven MS. Comparative pharmacology of antipsychotics possessing combined dopamine D₂ and serotonin 5-HT_{1A} receptor properties. *Psychopharmacology (Berl)*. 2011 Aug;216(4):451-73.
- [155] Ichikawa J, Meltzer HY. Valproate and carbamazepine increase prefrontal dopamine release by 5-HT_{1A} receptor activation. *Eur J Pharmacol* 1999;380(1):R1-3.
- [156] Arborelius L, Nomikos GG, Hacksell U, and Svensson TH. (R)-8-OH-DPAT preferentially increases dopamine release in rat medial prefrontal cortex. *Acta Physiol Scand* 1993;148(4):465-466.
- [157] Rollema H, Lu Y, Schmidt AW, and Zorn SH. Clozapine increases dopamine release in prefrontal cortex by 5-HT_{1A} receptor activation. *Eur J Pharmacol* 1997;338(2):R3-5.
- [158] Jordan S, Koprivica V, Chen R, Tottori K, Kikuchi T, Altar CA. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT_{1A} receptor. *Eur J Pharmacol* 2002;441(3):137-140.
- [159] Bortolozzi A, Díaz-Mataix L, Toth M, Celada P, Artigas F. In vivo actions of aripiprazole on serotonergic and dopaminergic systems in rodent brain. *Psychopharmacology (Berl.)*. 2007;191(3):745-758.
- [160] Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry*. 2002 Sep;63(9):763-71.
- [161] Lerond J, Lothe A, Ryvlin P, d'Amato T, Bouvard S, Ciumas C, et al. Effects of aripiprazole, risperidone and olanzapine on 5-HT_{1A} receptors in patients with schizophrenia. *J Clin Psychopharmacol* 2012 (in press).
- [162] Frankle WG, Lombardo I, Kegeles LS, Slifstein M, Martin JH, Huang Y et al. Measurement of the serotonin 1A receptor availability in patients with schizophrenia during treatment with the antipsychotic medication ziprasidone. *J Psychopharmacol*. 2011; 25(6):734-743.
- [163] Mamo D, Graff A, Mizrahi R, Shammi CM, Romeyer F, Kapur S. Differential effects of aripiprazole on D(2), 5-HT(2), and 5-HT(1A) receptor occupancy in patients with schizophrenia: a triple tracer PET study. *Am J Psychiatry* 2007;164(9):1411-1417.
- [164] Han M, Huang XF, du Bois TM, Deng C. The effects of antipsychotic drugs administration on 5-HT_{1A} receptor expression in the limbic system of the rat brain. *Neuroscience* 2009;164(4):1754-1763.
- [165] Sakai Y, Nishikawa M, Leyton M, Benkelfat C, Young SN, Diksic M. Cortical trapping of alpha-[(11)C]methyl-l-tryptophan, an index of serotonin synthesis, is lower in females than males. *Neuroimage*. 2006 Nov 15;33(3):815-24.

- [166] Costes N, Benkelfat C, Zimmer L, Dagher A, Le Bars D. Toward a quantification of extra-cellular brain endogenous serotonin concentration with [^{18}F]MPPF in PET and a multi-injection protocol. *NeuroReceptor Mapping* 08, Pittsburg. *Neuroimage* 2008;T149.
- [167] Paterson LM, Tyacke RJ, Nutt DJ, Knudsen GM. Measuring endogenous 5-HT release by emission tomography: promises and pitfalls. *J Cereb Blood Flow Metab.* 2010;30(10):1682-706.