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PET tracers for 5-HT$_{1A}$ receptors and uses thereof

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The serotonin 5-HT$_{1A}$ receptor is implicated in the pathophysiology of major neuropsychiatric disorders, including depression, suicidal behavior, panic disorder, epilepsy, bulimia, schizophrenia, Parkinson's disease, and Alzheimer's disease and is, therefore, an important target for drug therapy. 5-HT$_{1A}$ receptors are expressed as somatodendritic autoreceptors in serotonin neurons of the raphé nuclei (presynaptic) and as postsynaptic receptors in cortical and subcortical serotonin terminal fields in the brain. Due to the higher concentration and heterogeneous distribution of this receptor, it is an attractive target for quantification *in vivo* using positron emission tomography (PET) and single photon emission tomography (SPECT). Here, we review the PET radioligands employed for imaging 5-HT$_{1A}$ receptors in living brain.

Serotonin$_{1A}$ (5-HT$_{1A}$) receptors belong to the family of G-protein-coupled receptors (GPCRs) and contribute to serotonin transmission in brain [1]. These receptors are localized presynaptically as somatodendritic autoreceptors in the raphé nuclei and postsynaptically in prefrontal and temporal cortex and other regions [2–5]. 5-HT$_{1A}$ receptors have been implicated in the pathophysiology of mood and anxiety disorders, sexual function, eating disorders, neurodegenerative diseases, and in the mechanism of action of antidepressants [4–11]. *In vitro* and *in vivo* quantification of 5-HT$_{1A}$ receptors reveal high receptor density in the midbrain (somatodendritic autoreceptors in the raphé nuclei), limbic regions (hippocampus, septum), and in the prefrontal and entorhinal cortices. Lower 5-HT$_{1A}$ receptor levels are found in the thalamus and the lowest densities are observed in the striatum, substantia nigra, and adult cerebellum [12–16].

Several 5-HT$_{1A}$ receptor antagonist and agonist PET or SPECT radioligands have been evaluated for imaging purposes [17–20]. Most of these tracers belong to the following structural families: (i) compounds with structural similarity to the 5-HT$_{1A}$ antagonist, *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl)cyclohexane carboxamide (WAY100635); or (ii) derivatives of the 5-HT$_{1A}$ agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT).

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Antagonist radioligands

Currently available successful PET tracers for 5-HT$_{1A}$ receptor binding are all antagonist radioligands and provide the measure of receptor number and affinity, but cannot distinguish the agonist high and low affinity conformations of the receptor (Figure 1).

[*Carbonyl*-^{11}C]WAY100635

N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide (WAY100635) is a potent and selective 5-HT$_{1A}$ antagonist with high affinity for 5-HT$_{1A}$ receptors (K_D = 0.2 nM) [21]. *In vivo* studies in mice and rats with [^{3}H]WAY100635 revealed a specific distribution, consistent with the known distribution of 5-HT$_{1A}$ receptors in human [22,23]. The originally designed [*O-methyl*-^{11}C]WAY100635 had a lipophilic metabolite [*O*-methyl-^{11}C]WAY100634 in primate brain that crosses the blood brain barrier (BBB) and consequently the [*O-methyl*-^{11}C]WAY100635 is not an optimal tracer for the quantification of 5-HT$_{1A}$ receptors [24]. Pike *et al.* proposed labeling of

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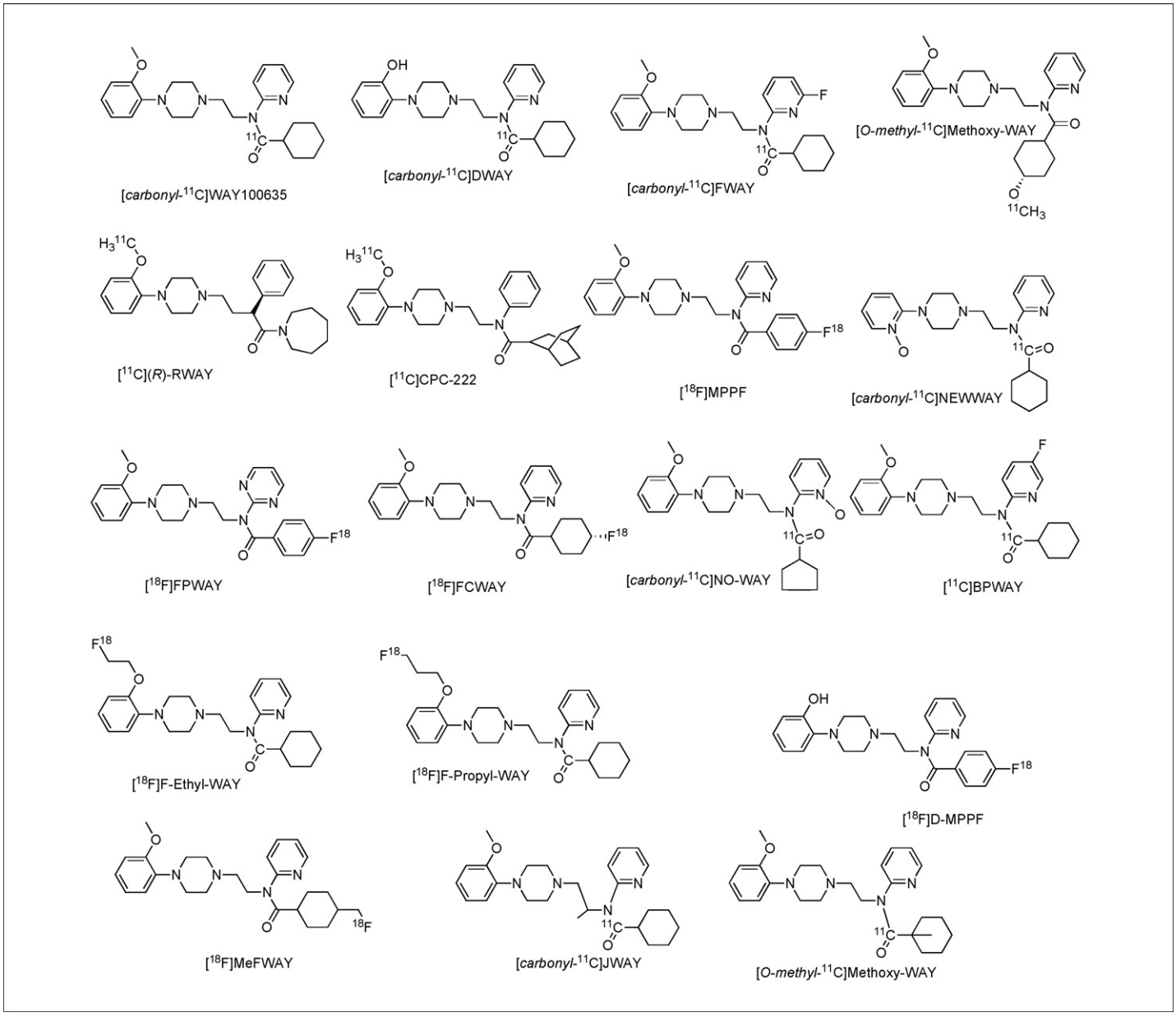

FIGURE 1

Antagonist PET tracers for 5-HT_{1A} receptors with structural skeleton WAY100635.

WAY100635 with carbon-11 in its carbonyl position and this offered a new radioligand, [*carbonyl*-^{11}C]WAY100635 that avoided the formation of [^{11}C]WAY100634 as a radioactive metabolite [25]. Therefore, the authentic compound is the only source of radioactivity measured in the brain and PET scanning following the injection of [*carbonyl*-^{11}C]WAY100635 enables proper quantification of 5-HT_{1A} receptor parameters. As predicted, the signal-to-noise ratio of [*carbonyl*-^{11}C]WAY100635 is enhanced compared to [*O-methyl*-^{11}C]WAY100635 [17–20]. Thus, [*carbonyl*-^{11}C]-WAY100635 is now the most commonly used ligand for *in vivo* patient studies.

Several groups have reported the correlation of regional distribution volumes (V_T, a linear function of free receptor concentration and is the ratio of the tracer concentration in a region to the metabolite corrected plasma concentration at equilibrium) of 5-HT_{1A} receptors derived from PET studies using antagonist radioligand [*carbonyl*-^{11}C]WAY100635 with *in vitro* binding levels from studies on postmortem brain tissue using agonist radioligand [^{3}H]8-OH-DPAT [4,12–15,26]. Overall, the results indicate good correlation except for smaller structures such as the midbrain raphé autoreceptors due to partial volume effects resulting in an under-estimation of binding by PET [27]. The gender specific age effect of 5-HT_{1A} receptor binding with [*carbonyl*-^{11}C]-WAY100635 has been studied by PET. Meltzer *et al.* reported an age-related decline in binding in a group of healthy men, but not women; however, other groups (Rabbiner *et al.*, Tauscher *et al.*, and Bhagwagar *et al.*) reported no age effect in their PET study in healthy males [28–31]. Møller *et al.* recently reported a decrease in BP at the rate of 3 or 4% per decade and a 10% decline of the global mean 5-HT_{1A} receptor BP in elderly relative to young subjects [32]. The above studies were performed without arterial input function measurements and therefore could not definitively rule out the

effects of blood flow or tracer clearance. Parsey *et al.* advocated the derivation of BP for [*carbonyl*-^{11}C]WAY100635 by kinetic modeling, using an arterial plasma input function as the method of choice because of its higher test–retest reproducibility, lower vulnerability, and absence of bias [34] and found a correlation of binding with a functional promotor variant in the gene [15,33]. With this approach Parsey *et al.* found higher 5-HT$_{1A}$ receptor binding potentials in females than in males, and no age effect on 5-HT$_{1A}$ receptors in women [16].

[*Carbonyl*-^{11}C]WAY100635 has been used in a number of clinical experiments to study changes in 5-HT$_{1A}$ receptors. *In vivo* PET studies report lower binding with [*carbonyl*-^{11}C]WAY100635 in major depression. This includes a study by Drevets *et al.* who found a 42% lower binding potential (BP, maximum theoretical ratio between bound and unbound radioligand) in midbrain (raphé) of a group of depressed patients, which is very close to the report of reduced (43%) 8-OH-DPAT agonist binding, determined *postmortem*, in the dorsal raphé nuclei (DRN) of depressed suicide victims [27,4]. Meltzer *et al.* also observed a lower [*carbonyl*-^{11}C]WAY100635 binding in the brainstem region of the DRN in elderly depressed patients [34]. In contrast, *postmortem* studies by Stockmeier *et al.* found higher agonist binding in the DRN of suicide victims with major depressive disorder (MDD) compared to normal controls [26]. A *postmortem* study by Arango *et al.* showed that this effect is confined to the larger, and more rostral, section of the DRN, whereas binding is lower in more caudal sections of the DRN [4]. Dreverts *et al.* and Montgomery *et al.* used [*carbonyl*-^{11}C]-WAY100635 to study the effect of corticosteroid levels in 5-HT$_{1A}$ receptor binding of chronically exposed patients and controls with PET and did not find any alteration in binding [27,35]. Parsey *et al.*, for the first time, demonstrated a negative correlation between 5-HT$_{1A}$ receptor binding and aggression in healthy subjects [15,36]. PET studies with [*carbonyl*-^{11}C]WAY100635 found significantly higher BP in drug naïve MDD subjects during a major depressive episode (MDE) compared to controls and MDD subjects previously treated with antidepressants [36]. Sullivan *et al.* investigated the relationship of anxiety expressed in MDD to regional 5-HT$_{1A}$ binding with [*carbonyl*-^{11}C]WAY100635 and found higher psychic and lower somatic anxiety predicted over 50% of the variance in 5-HT$_{1A}$ receptors BP in multiple cortical regions [6]. More recently, Lanzenberger *et al.* reported a lowering of [*carbonyl*-^{11}C]-WAY100635 binding in the amygdala and mesiofrontal areas of social anxiety disorder (SAD) patients [37]. Higher 5-HT$_{1A}$ receptor binding was detected in mesial temporal cortex, including hippocampus for type 2 subjects relative to controls [38].

5-HT$_{1A}$ receptors are involved in the pathophysiology of epilepsy and a limbic reduction of 5-HT$_{1A}$ receptor binding was observed by Savic *et al.* and Ito *et al.* in their PET study with [*carbonyl*-^{11}C]-WAY100635 in human mesial temporal lobe epilepsy [39–41]. Increased binding of [*carbonyl*-^{11}C]WAY100635 was also found in the cortical areas of patients with bulimia nervosa [42,8].

[*Carbonyl*-^{11}C]WAY100635 binding of 5-HT$_{1A}$ receptors in premenstrual dysphoric disorder (PMDD) women differs from controls across the menstrual cycle [43]. This study provides *in vivo* support for serotonergic dysregulation in women with PMDD. Multiple *postmortem* studies revealed a higher binding of 5-HT$_{1A}$ receptors in the dorsolateral prefrontal cortex, anterior cingulate and motor regions of patients with schizophrenia relative to controls [12,44–47]. Three *in vivo* PET studies have been reported for the involvement of 5-HT$_{1A}$ receptors in schizophrenia. Tauscher *et al.* reported a higher binding in medial temporal cortex in schizophrenia subjects with [*carbonyl*-^{11}C]WAY100635 [48]. However, Yasuno *et al.* found a reduction in 5-HT$_{1A}$ binding in the amygdala [49] and, in a more recent study, Frankle *et al.* reported no difference in [*carbonyl*-^{11}C]WAY100635 binding to 5-HT$_{1A}$ receptors in schizophrenia patients compared to controls [50]. Cleare *et al.* reported a widespread reduction of 5-HT$_{1A}$ receptor bindings in chronic fatigue syndrome (CFS) patients in comparison to control; the highest reduction (23%) was observed in hippocampus [51]. A recent study on the state of 5-HT$_{1A}$ receptors in the *postmortem* neocortex of patients with Alzheimer's disease confirmed the *in vivo* findings of Parsey *et al.*, indicating that 5-HT$_{1A}$ receptor binding in the temporal cortex inversely correlated with aggression and dementia severity [11]. Doder *et al.* found a 27% reduction in 5-HT$_{1A}$ receptor binding in the midbrain raphé in patients with Parkinson's disease (PD) compared to healthy volunteers using [*carbonyl*-^{11}C]WAY100635 [52]. An association between 5-HT$_{1A}$ receptor availability in the raphé and severity of parkinsonian tremor was also found from the above investigation [52]. Turner *et al.* found a marked reduction of [*carbonyl*-^{11}C]WAY100635 binding in global cortical and raphé in amyotrophic lateral sclerosis (ALS) patients compared to control group [53]. PET studies with [*carbonyl*-^{11}C]WAY100635 did not show sufficient 5-HT$_{1A}$ receptor occupancy, even at higher doses of agonist drugs, that would produce unacceptable levels of side effects, though lower doses are sufficient to produce pharmacological effects [54–61]. The binding of [*carbonyl*-^{11}C]WAY-100635 was also found to be insensitive to changes in brain 5-HT levels induced by tryptophan infusion and depletion [29]. An agonist PET radiotracer is likely to increase the sensitivity of detecting agonist binding as they bind preferentially to the high-affinity state (see agonist radioligand section [79,80]).

[*Carbonyl* ^{11}C]DWAY

DWAY is a minor metabolite of WAY-100635, and has been labeled with carbon-11 by reaction of desmethyl-WAY-100634 with [*carbonyl*-^{11}C]cyclohexanecarbonyl chloride [62]. [*Carbonyl*-^{11}C]D-WAY has hippocampus/cerebellum binding ratios of 22 and 6 in rat brain and monkey brain, respectively [62]. Studies with [*carbonyl*-^{11}C]DWAY in human volunteers has a substantially (~75%) greater signal per unit of radioactive dose compared to [*carbonyl*-^{11}C]WAY100635 [63]. Although there are several reports on the successful synthesis of [*carbonyl*-^{11}C]WAY100635 and [*carbonyl*-^{11}C]DWAY, the lack of high yield of the radiotracer and the difficulty in reliable radiolabeling seriously limit its usefulness in clinical research of 5-HT$_{1A}$ receptors [64,65].

[^{18}F]MPPF

4-(2-Methoxyphenyl)-1-[2-(*N*-2-pyridinyl)-*p*-fluorobenzamido)-ethyl]piperazine (MPPF) is a selective 5-HT$_{1A}$ antagonist (K_D = 0.34 nM), and a radiolabeled version ([^{18}F]MPPF) was synthesized by [^{18}F$^-$]fluoride for nitro nucleophilic aromatic substitution [66]. An update of *in vivo* imaging of 5-HT$_{1A}$ receptor in animal and human brain with [^{18}F]MPPF is reviewed by Aznavour *et al.* [67]. In summary, nonhuman primate, rat and human studies show that [^{18}F]MPPF binding to 5-HT$_{1A}$ receptors is reversible, with

low non-specific binding [18,19]. Several studies in rodents, using β-microprobe and microdialysis, show that [^{18}F]MPPF binding is sensitive to pharmacologically induced changes in intra-synaptic serotonin, by the administration of 1–10 mg/kg fenfluramine [68–70]. However, PET studies in awake monkeys did not show sensitivity to intra-synaptic 5-HT levels with [^{18}F]MPPF [71]. Similarly, no significant change in [^{18}F]MPPF binding was found in tryptophan-depleted human subjects and subjects that had suffered from MDD, but at the time of the test they were in remission [72,73]. A [^{18}F]MPPF PET study in anesthetized cats showed a reduction of binding in the DRN after fluoxetine treatment, consistent with higher intra-synaptic serotonin, while it remained unchanged in all other brain regions [74]. The decrease in [^{18}F]MPPF binding may also be associated with the initial internalization of 5-HT$_{1A}$ autoreceptors at the very beginning of SSRI treatment. More recently, Derry *et al*. found significant increase in [^{18}F]MPPF binding in the whole brain, as well as all temporal cortex, mesial temporal region, and cingulate cortex in subjects suffering from narcolepsy–cataplexy [75]. Merlet *et al*. observed that the binding of [^{18}F]MPPF to 5-HT$_{1A}$ receptors in refractory temporal lobe epilepsy (TLE) patients is decreased in the epileptogenic temporal lobe [7]. Kepe *et al*. observed a decrease in medial temporal lobe 5-HT$_{1A}$ receptor density in Alzheimer's disease with the increase of β-amyloid deposits using [^{18}F]MPPF, and [^{18}F]FDDNP as the respective radiotracers [9]. Although [^{18}F]MPPF is a useful radioligand for the quantification of 5-HT$_{1A}$ receptors in human, it is also a substrate for *p*-glycoprotein (*p*-gp) which means the amount of [^{18}F]MPPF reaching the brain is relatively low (0.05% injected dose/gram (ID/g) at 30 min in rats) compared to [^{11}C]WAY100635 (0.46% ID/g at 30 min in rats) [18–20]. However, due to the longer half life of [^{18}F] (109.8 min) compared to [^{11}C] (20 min), [^{18}F]MPPF can be distributed to hospitals without cyclotrons, which is an advantage. In order to improve the brain uptake of [^{18}F]MPPF, a desmethylated analogue, [^{18}F]DMPPF, was synthesized [76]. *In vivo* studies in rats showed that an overall brain uptake of 0.31% ID/g was measured at 15 min after tracer injection with a better brain penetration, better contrast, and a slower clearance than [^{18}F]MPPF [76]. Further studies are warranted to demonstrate the *in vivo* ability of [^{18}F]DMPPF to be a PET tracer for 5-HT$_{1A}$ receptors.

[^{18}F]FCWAY

[^{18}F]3-*cis*-FCWAY is an analogue of FCWAY and had the slowest [^{18}F]defluorination of all FCWAY analogs in rats and human [77]. Lower 5-HT$_{1A}$ receptor binding in the anterior and posterior cingulate cortices of patients with panic disorder was observed in a recent PET study using [^{18}F]FCWAY [78]. A lower 5-HT$_{1A}$ receptor binding and a higher plasma-free fraction of [^{18}F]FCWAY were found in mesial temporal and insular cortex of TLE patients in comparison to control subjects [79,80]. However, no significant changes in 5-HT$_{1A}$ receptor binding was found for antiepileptic drug effects (AEDs) with [^{18}F]FCWAY [79–81]. No significant difference in 5-HT$_{1A}$ receptor binding in PTSD patients with or without current or and past diagnosis of major depression was found with [^{18}F]FCWAY [82]. Nevertheless, the major limitation of [^{18}F]FCWAY is its *in vivo* [^{18}F]defluorination. Treatment with miconazole, a selective inhibitor of CYP450 2EI, reduces the [^{18}F]defluorination of [^{18}F]FCWAY, resulting in improved imaging of brain 5-HT$_{1A}$ receptors in rat [83].

[^{11}C]CPC-222

CPC-222, a structural analogue of WAY100635, in which the cyclohexyl ring has been replaced by a bicyclo[2,2,2]octane (adamantine) ring, designed to overcome the metabolic instability of [*carbonyl*-^{11}C)WAY100635 [84]. Radiosynthesis of [^{11}C]CPC-222 is achieved in high yield by a simple [^{11}C]-methylation of the corresponding desmethyl analogue. Biodistribution studies with [^{11}C]CPC-222 in rats show a hippocampus to cerebellum binding ratio of 10 at 45 min [29]. Pilot study with [^{11}C]CPC-222 in human volunteers indicated that brain uptake was high and target to non-target ratios in the brain reached a maximal value of 4 at 45 min. The metabolism of [^{11}C]CPC-222 in human is also less rapid than that of WAY100635 [85]. Thus, the replacement of the cyclohexane ring by an adamantane ring can, indeed, suppress metabolic deacylation. Although [^{11}C]CPC-222 may be a useful radioligand, no further studies on the development of this tracer have been reported. Similarly, [*O-methyl*-^{11}C]SWAY and [*carbonyl*-^{11}C]JWAY were also designed to overcome the rapid metabolism of [*carbonyl*-^{11}C]WAY100635. PET studies in monkeys show that [*carbonyl*-^{11}C]JWAY gives better signal-to-noise ratio than [*O-methyl*-^{11}C]SWAY. However, the *in vivo* selectivity of [*carbonyl*-^{11}C]JWAY was found to be not superior than [*carbonyl*-^{11}C]-WAY100635 or [*carbonyl*-^{11}C]DWAY [86].

[^{11}C](*R*)-RWAY

[^{11}C](*R*)-RWAY ([^{11}C]2,3,4,5,6,7-hexahydro-1{4-[1[4-(2-methoxyphenyl)piperazinyl]]-2-phenyl-butyry}-1*H*-azepine) is a reverse amide of WAY100635, designed to improve the issues of metabolite stability associated with WAY100635 [87]. [^{11}C](*R*)-RWAY has been shown to be a successful radioligand for 5-HT$_{1A}$ receptor measurements in rodents and monkeys [88]. Despite promising results in rodents and nonhuman primates, interference of radioactive metabolite in brain result slow washout of activity from brain and instability of distribution volume in human brain [89]. Thus, the use of [^{11}C](*R*)-RWAY in human for imaging 5-HT$_{1A}$ receptor is limited. Studies in rats and mouse have shown that [^{11}C](*R*)-RWAY is a *p*-gp substrate, and is rapidly eliminated from the brain [88]. However, [^{11}C](*R*)-RWAY in combination with *p*-gp inhibitors can be useful for imaging 5-HT$_{1A}$ receptors in rodents and nonhuman primates.

[^{18}F]MeFWAY

N-{2-[4-(2-Methoxyphenyl)piperazinyl]ethyl}-*N*-(2-pyridyl)-*N*-(4-^{18}F-fluoromethyl-cyclohexane)carboxamide ([^{18}F]MeFWAY), is an analogue of WAY100635, with comparable binding affinity [90]. The [^{18}F] labeling of MeFWAY is performed on a primary carbon atom which makes the compound more stable to de[^{18}F]-fluorination. PET studies in rats and rhesus monkeys showed [^{18}F]MeFWAY binding in 5-HT$_{1A}$ receptor enriched brain areas with excellent selectivity and has potential as a PET agent for 5-HT$_{1A}$ receptors in human subjects.

A number of other antagonist tracers such as [^{18}F]*p*-MPPCl, [*O-methyl*-^{11}C]methoxy-WAY, [^{18}F]FPWAY, [^{18}F]F-ethyl-WAY, [^{18}F]F-propyl-WAY and other analogues of [*carbonyl*-^{11}C]WAY100635 have been studied as PET tracers for 5-HT$_{1A}$ receptor imaging with limited success [17–20]. A few radiotracers have been developed with structural skeleton different from WAY100635 (Figure 2), but have not been validated as radioligands for PET imaging

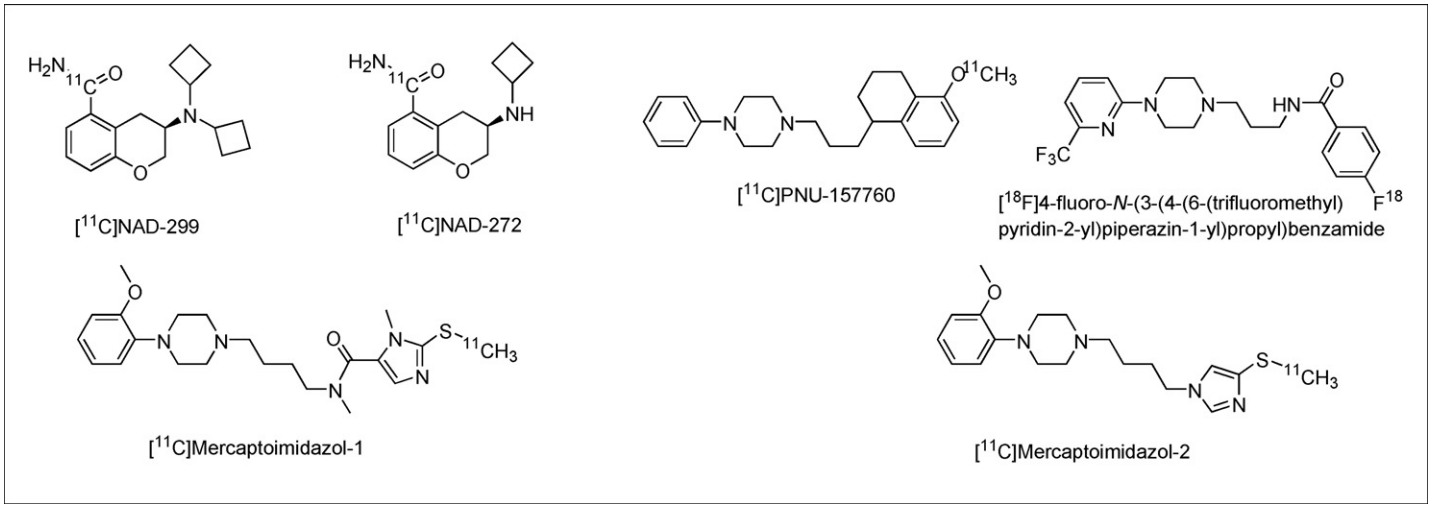

FIGURE 2

Examples of antagonist PET tracers for 5-HT_{1A} receptors with structural skeleton different from WAY100635.

[19,91,92]. Thus, [*carbonyl*-^{11}C]WAY100635, [^{18}F]MPPF, and [^{18}F]FCWAY are the currently available radioligands for imaging 5-HT_{1A} receptors in human and a summary of the clinical imaging data of 5-HT_{1A} receptor antagonist radiotracers with neurologic and psychiatric disorders is summarized in Table 1.

Agonist radioligands

5-HT_{1A} receptors occur in high and low affinity agonist binding states. Antagonists bind to the high affinity (HA) and low affinity (LA) conformations of 5-HT_{1A} receptors with comparable affinity [93]. In contrast, agonists bind preferentially to the HA state of the receptor, which is coupled to G-proteins and therefore agonists provide a measure of functional 5-HT_{1A} receptors [94,95]. Hence, agonist ligands only compete with the binding of antagonist radiotracers to the HA subpopulation of receptors. To date, there is no agonist radiotracer available to study the high affinity binding sites of 5-HT_{1A} receptors *in vivo* in human subjects. An agonist radioligand could provide several potential advantages over antagonist radioligands. It may (1) enable the determination of the HA:LA ratio *in vivo* in human brain; (2) provide a more sensitive

TABLE 1

***In vivo* imaging of 5-HT_{1A} imaging agents in human diseases**

Disease	PET ligand	Effect	Refs
Depression	[*carbonyl*-^{11}C]WAY100635	Lower binding in DRN, limbic and multiple cortical regions	[27,34]
	[*carbonyl*-^{11}C]WAY100635	Higher binding in most brain regions	[6,15,36]
AD	[^{18}F]MPPF	Lower binding in medial temporal lobe	[9]
ALS	[*carbonyl*-^{11}C]WAY100635	Lower binding in cortical and DRN	[53]
TLE	[*carbonyl*-^{11}C]WAY100635	Lower binding in limbic region	[39–41]
	[^{18}F]MPPF	Lower binding in temporal lobe	[7]
	[^{18}F]FCWAY	Lower binding mesial temporal and insular cortex	[79–81]
Bulimia Nervosa	[*carbonyl*-^{11}C]WAY100635	Higher binding in most brain regions	[42,8]
Schizophrenia	[*carbonyl*-^{11}C]WAY100635	Higher binding in mesial temporal cortex	[48]
	[*carbonyl*-^{11}C]WAY100635	Lower binding in amygdala	[49]
	[*carbonyl*-^{11}C]WAY100635	No difference in binding	[50]
Narcolepsy/catalepsy	[^{18}F]MPPF	Higher binding in most brain regions	[74]
PMMD	[*carbonyl*-^{11}C]WAY100635	Lower binding in DRN	[43]
CFS	[*carbonyl*-^{11}C]WAY100635	Lowe binding in hippocampus	[51]
PTSD	[^{18}F]FCWAY	No difference in binding	[82]
Panic disorder	[^{18}F]FCWAY	Lower binding in anterior and posterior cingulate cortices	[71]
SAD	[*carbonyl*-^{11}C]WAY100635	Lower binding in amygdala and mesiofrontal areas	[37]
Diabetics type 2	[*carbonyl*-^{11}C]WAY100635	Higher binding in mesial temporal cortex	[38]
JME	[*carbonyl*-^{11}C]WAY100635	Lower binding in dorsolateral prefrontal cortex, raphé nuclei, and hippocampus	[41]
PD	[*carbonyl*-^{11}C]WAY100635	Lower binding in midbrain raphé	[52]

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; TLE, temporal lobe epilepsy; PMMD, premenstrual dysphoric disorder; CFS, chronic fatigue syndrome; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; JME, Juvenile myoclonic epilepsy; DRN, dorsal raphé nuclei.

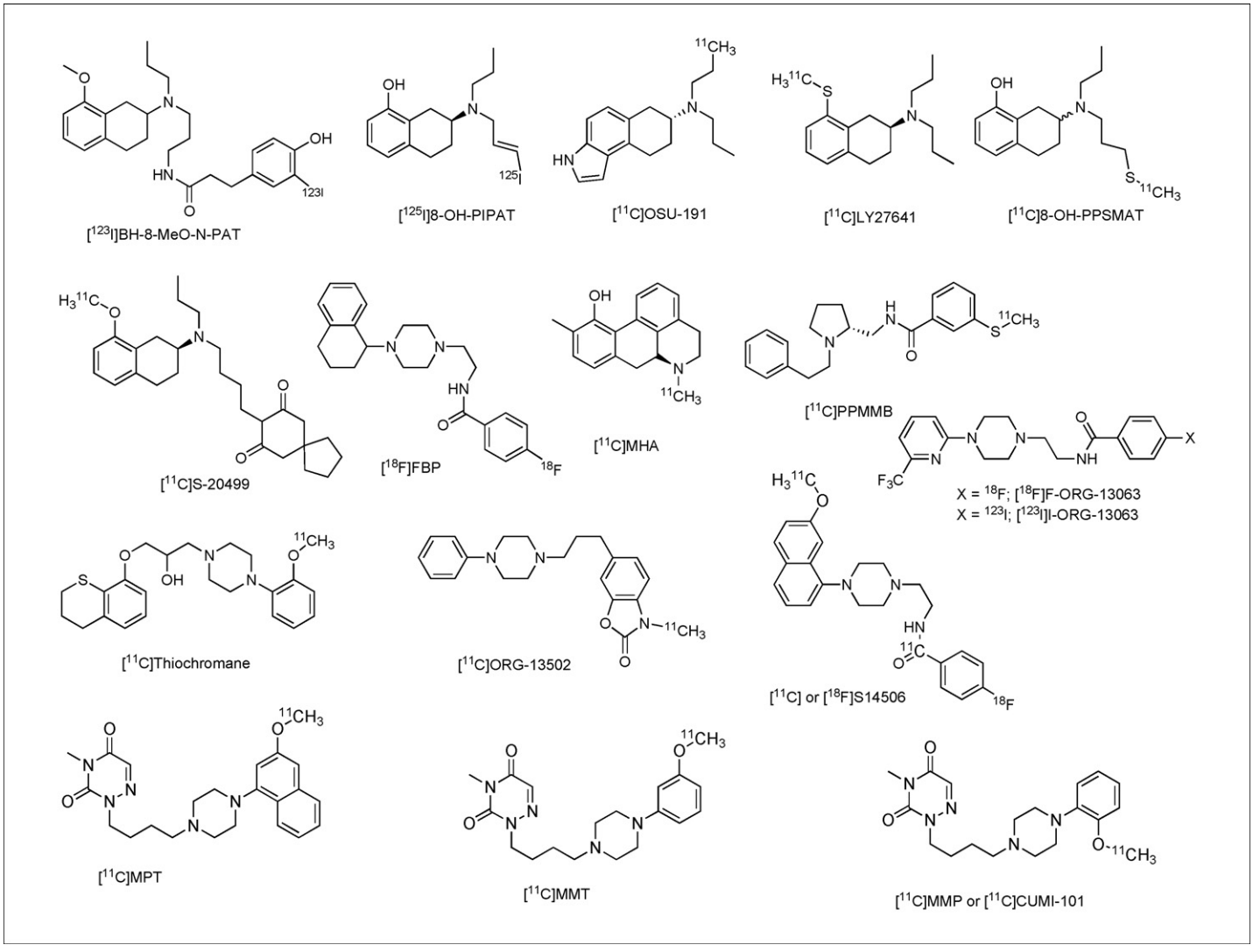

FIGURE 3

Agonist imaging agents for 5-HT_{1A} receptors.

measure of intra-synaptic levels of endogenous neurotransmitters; (3) measure desensitization (down-regulation) or sensitization (up-regulation) of GPCRs; and (4) provide a better estimate of receptor occupancy for agonist therapeutic agents.

Several efforts have been made to develop a 5-HT_{1A} receptor agonist imaging agent with limited success *in vivo* (Figure 3) [96–109]. These include 8-OH-DPAT analogues [^{123}I]-BH-8-MeO-*N*PAT, [^{123}I]-8-OH-PIPAT, [^{11}C]OSU191, [^{11}C]LY-274601, (±)-8-OH-PPSMAT, [^{11}C](+)S-20499 [96–101]; (*R*)-11-hydroxy-10-methylaporphine ([^{11}C]MHA); aryl piperazines, such as [^{11}C]ORG-13502, [^{18}F]FBP, [^{18}F] and [^{123}I] analogues of ORG-13063, and the [^{11}C] analogue of a thiomethane [^{11}C](S)-PPMMB [102–108]. More recently, S14506, a highly selective and potent 5-HT_{1A} agonist, was labeled with [^{11}C]carbon and [^{18}F]fluorine [109], however, *in vivo* data have not yet been reported. [*O*-Methyl-^{11}C]2-{4-[4-(7-methoxynaphthalen-1-yl)-piperazin-1-yl]-butyl}-4-methyl-2*H*-[1,2,4]triazine-3,5-dione ([^{11}C]MPT) has been reported as a promising 5-HT_{1A} receptor agonist radiotracer in baboon [110]. Although [^{11}C]MPT demonstrated specific binding in 5-HT_{1A} receptor-rich regions, the slow washout in baboons made quantification of binding parameters difficult and the free fraction (percentage of parent compound not bound to plasma proteins) could also not be measured [110]. The anticipated slower washout kinetics in human subjects may limit the potential of [^{11}C]MPT as a 5-HT_{1A} agonist tracer in man. The 3-methoxyphenyl analogue (MMT) of MPT, with a superior *in vitro* agonism compared to MPT also did not show specific binding to 5-HT_{1A} receptors [111,112]. However, the 2-methoxyphenyl analogue of MPT [*O*-methyl-^{11}C]2-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5(2*H*,4*H*)dione ([^{11}C]MMP or [^{11}C]CUMI-101) was found to be a superior agonist PET ligand than [^{11}C]MPT in baboon [113]. The percentage free fraction of [^{11}C]MMP in baboon plasma is 59 ± 6% and radioactive metabolites are polar. Preliminary studies with citalopram infusion (1–4 mg/kg, i.v.) showed that [^{11}C]CUMI-101 showed a moderate decrease in binding in nonhuman primates in comparison to untreated baboons. The decrease in radioligand binding may be due to competition from elevated intra-synaptic levels of endogenous 5-HT and further studies are required to determine whether [^{11}C]CUMI-101 is a suitable PET tracer for the reliable quantification of serotonin levels in human.

Conclusion

Although [*carbonyl*-^{11}C]WAY100635, [^{11}C]DWAY, [^{18}F]FCWAY, and [^{18}F]MPPF currently appear to be the most useful antagonist PET ligands for the quantification of 5-HT$_{1A}$ receptors in human, the development of a new antagonist PET tracer that is easier, routinely and reliably, to radiolabel is still required for the facile quantitative measurements of these receptors in clinical studies. The research efforts in the field of antagonist tracers are now aimed at improvement of the metabolic stability in primates for improving the tracer-kinetic modeling and development of radioiodinated or technetium labeled ligands for SPECT. Research is underway for the development of an agonist PET radiotracer that can measure the high affinity state of 5-HT$_{1A}$ receptors, potentially detect endogenous serotonin changes and receptor occupancy by therapeutic agonist drugs in human subjects.

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