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REVIEW ARTICLE

Serotonin and molecular neuroimaging in humans using PET

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Abstract The serotonergic system is one of the most important modulatory neurotransmitter systems in the human brain. It plays a central role in major physiological processes and is implicated in a number of psychiatric disorders. Along with the dopaminergic system, it is also one of the phylogenetically oldest human neurotransmitter systems and one of the most diverse, with 14 different receptors identified up to this day, many of whose function remains to be understood. The system's functioning is even more diverse than the number of its receptors, since each is implicated in a number of different processes. This review aims at illustrating the distribution and summarizing the main functions of the serotonin (5-hydroxytryptamin, 5-HT) receptors as well as the serotonin transporter (SERT, 5-HTT), the vesicular monoamine transporter 2, monoamine oxidase type A and 5-HT synthesis in the human brain. Recent advances in in vivo quantification of these different receptors and enzymes that are part of the serotonergic system using positron emission tomography are described.

Keywords Serotonin · PET · In vivo · Radioligand · Human brain · Neuroimaging · Molecular imaging

Introduction

Researchers have now studied the serotonergic system for many decades since its discovery in the gastrointestinal tract in the 1930s (Erspamer and Asero 1952) and later in the central nervous system (CNS) in 1953 (Twarog and Page 1953). It is, along with the dopaminergic system, one of the phylogenetically oldest neurotransmitter systems in the human brain and it is also one of the most diverse. Up to this day, 14 different receptors are suggested to belong to the serotonergic (5-hydroxytryptamin, 5-HT) system, some of whose function is still poorly understood.

In the CNS, 5-HT is synthesized in the raphe nuclei of the human midbrain and brainstem as well as their projection sites. From the raphe nuclei, projections run to the forebrain, reaching nearly all parts of the brain thus strongly modulating glutamatergic and GABAergic neurons in the entire brain. Here, we summarize the functioning, distribution and in vivo quantification with positron emission tomography (PET) of the serotonergic system including the serotonin receptors, 5-HT synthesis, 5-HT release as well as 5-HT reuptake by the serotonin transporter (5-HTT, SERT) and degradation of 5-HT in the brain.

The 5-HT system's functions is even more diverse than the number of its receptors since most 5-HT receptor subtypes are highly versatile and part of numerous different processes in the brain.

The 5-HT_1 receptor group consists of the inhibitory serotonin receptors 1A, 1B, 1D, 1E and 1F, with 5-HT_{1A} being of special interest. The 5-HT_{1A} receptor is the pivotal inhibitory 5-HT receptor due to its dense distribution in the CNS (up to 600 fmol/mg protein, Pazos et al. 1987a). It strongly modulates tonic serotonergic firing, mediates neuroplasticity, human reward circuitry (Kranz et al. 2010) and is further implicated in numerous psychiatric disorders such as depression (e.g., Hirvonen et al. 2008; Drevets et al. 2007; Parsey et al. 2010) and panic disorder (e.g., Nash et al. 2008; Neumeister et al. 2004). 5-HT_2 receptors

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(2A–2C) are all excitatory. Again, the type A receptor is most important because it is the main excitatory 5-HT receptor and densely distributed in the human brain (up to 490 fmol/mg protein, Pazos et al. 1987b). It has been linked to changes in sleep patterns (Popa et al. 2005) and neuropsychiatric disorders, e.g., schizophrenia (e.g., Burnet et al. 1996; Erritzoe et al. 2008). Another excitatory receptor is the 5-HT_4 receptor which has been implicated in limbic and visuo-motor functions, as well as memory and learning (Segu et al. 2010). The function of the 5-ht_{5A} receptor still remains unclear, accounting for why it is spelt in lower case. The 5-HT_6 receptor is an excitatory receptor that has been found to play an important role in memory and learning and has been suggested as a target for cognitive enhancers (Gravius et al. 2011; Holenz et al. 2006). The last receptor is the 5-HT_7 receptor which is also excitatory and has been linked to, among other things, the circadian rhythms, thermoregulation and migraine (for review, see Leopoldo et al. 2011). In contrast to the other receptors, which are all metabotropic, the 5-HT_3 receptor family is a group of ligand-gated ion channels comprising five subunits (3A–3E).

The reuptake of serotonin from the extracellular space including the synaptic cleft is carried out by the SERT which is central for the treatment with selective serotonin reuptake inhibitors (SSRIs) of psychiatric disorders such as depression, anxiety disorder and obsessive–compulsive disorder (OCD), (for review, see e.g., Daws and Gould 2011). A non-serotonin specific transporter is the vesicular monoamine transporter type 2 (VMAT2), which is a protein also transporting other neurotransmitters such as dopamine, norepinephrine and histamine. In this review, both transporters will be discussed.

In the synthesis of serotonin, tryptophan hydroxylase (TPH) plays an important role. It synthesizes L-tryptophan to 5-hydroxy-L-tryptophan which in turn is synthesized by amino acid decarboxylase to serotonin. In the chapters below, their role in the quantification of 5-HT synthesis and their measurement with PET will be outlined.

The enzyme monoamine oxidase A (MAO-A) is in charge of degrading serotonin. The resulting aldehyde is then oxidated by aldehyde dehydrogenase to 5-hydroxy-indoleacetic acid (5-HIAA).

Apart from highlighting distribution and functioning, this review summarizes the quantification of each part of the serotonergic system in the living human brain using PET.

Molecular imaging can be used to visualize, characterize and quantify biological processes at the cellular and subcellular levels within an intact living organism (e.g., Massoud and Gambhir 2003).

Positron emission tomography as one successful molecular imaging technique is based on the principle of labeling the ligand of interest with a positron-emitting isotope that after annihilation with an electron produces two γ-rays which can then be detected. The most commonly used isotopes are ^{15}O, ^{13}N, ^{11}C and ^{18}F. For visualizing the serotonergic system with PET, ^{11}C and ^{18}F are predominantly in use (Table 1). An advantage of PET over single-photon emission computed tomography (SPECT), another molecular imaging technique, is its significantly higher sensitivity and resolution, making PET an interesting and promising technique to study molecular processes in the human brain. Further, multimodal imaging combining functional magnetic resonance imaging (fMRI) measures and PET data can provide meaningful information about molecular features and neuronal activity (Gerstl et al. 2008).

Measurement with PET also offers a number of advantages over MRI, such as the possibility to quantify specific cellular and molecular processes in the nanomolar range and to follow trafficking of cells in a living (human) organism. It can be used to monitor pathological processes and environmental factors influencing brain diseases (e.g., Lanzenberger et al. 2010). Also drug effects on receptor up- and down-regulation under pathological conditions can be detected using PET (e.g., Spindelegger et al. 2009). In this review, we will focus on its ability to (1) show the distribution of receptor proteins in different brain regions and (2) quantify these proteins with receptor function to visualize alterations in psychiatric and neurological disorders. Here, whole brain distributions of the human serotonergic system as measured in vivo using PET are comprehensively illustrated. To our knowledge, this is the first publication to give an overview of the human serotonergic system as measured with PET on a systems level.

The serotonin (5-HT) receptors

5-HT_1 receptors

The 5-HT_1 receptor class comprises five receptor subtypes: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1E} and 5-HT_{1F}. It is predominantly coupled to $G_{i/o}$, which in turn is negatively linked to adenylate cyclase leading to a membrane depolarization and inhibiting neuronal firing.

5-HT_{1A}

The 5-HT_{1A} receptor has been described first among the 5-HT receptor family and it is also the receptor which has been characterized in most detail (Hannon and Hoyer 2008). It is further the main inhibitory receptor of the serotonergic system and thus of special interest to research

Table 1 Overview of frequently used PET radioligands for measurement of the serotonergic system in the human brain, as well as recent promising radioligands from animal and human PET studies

Receptor/transporter/ enzyme	Frequently used PET ligands in humans	Recent promising PET ligands (animal, humans)	References
5-HT_{1A}	[*Carbonyl*-^{11}C]-WAY	[^{18}F]MefWAY (primate)	Wooten et al. (2011b)
	[^{11}C]WAY100635	[^{11}C]CUMI-101 (baboon, *Papio anubis*, human)	Milak et al. (2008, 2010, 2011)
5-HT_{1B}	[^{11}C]AZ10419369	–	Varnäs et al. (2011a)
	[^{11}C]P943		Murrough et al. (2011)
5-HT_{1C}	–	–	–
5-ht_{1E}	–	–	–
5-HT_{1F}	–	–	–
5-HT_{2A}	[^{18}F]altanserin	[^{11}C]CIMBI-36 (pig)	Ettrup et al. (2011)
	[^{11}C]MDL100,907	(R)-[^{18}F]MH.MZ (rodent)	Debus et al. (2010)
5-HT_{2B}	–	–	–
5-HT_{2C}	–	–	–
5-HT_3	–	–	–
5-HT_4	[^{11}C]SB207145	[^{11}C]**13** (guinea-pig)	Xu et al. (2010)
5-ht_5	–	–	–
5-HT_6	–	[^{11}C]GSK210583 (pig, human)	Martarello et al. (2005)
			Parker et al. (2008)
5-HT_7	–	–	–
SERT	[^{11}C]DASB	[^{18}F]FPBM (rat)	Wang et al. (2010a)
	[^{11}C]MADAM	[^{18}F]ADAM (rat, monkey)	Huang et al. (2010)
VMAT2	[^{11}C]DTBZ	[^{18}F]AV133 (mouse, human)	Zhu et al. (2010)
	[^{11}C]MTBZ		Okamura et al. (2010)
MAO-A	[^{11}C]harmine	[^{11}C]RS 2360 (mouse)	Soliman et al. (2011)
	[^{11}C]clorgyline		Fowler et al. (2005a)
	[^{11}C]befloxatone		Bottlaender et al. (2003)
			De Bruyne et al. (2010)
5-HT synthesis	[^{11}C]AMT	–	Visser et al. (2011)
	[^{11}C]5-HTP		
Endogenous 5-HT	[^{18}F]MPPF	–	Derry et al. (2006)
			Yatham et al. (2001)
			Varnäs et al. (2011b)

in psychiatry, given the important role of the serotonergic system in psychiatric disorders as a whole.

Distribution studies of the 5-HT_{1A} receptor have shown highest density of binding sites in the cortical areas, especially cingulate and entorhinal cortices, limbic areas, such as the hippocampus and the lateral septum, in the amygdala as well as in the midbrain raphe nuclei (dorsal raphe nucleus, DRN and median raphe nucleus, MRN), (see Fig. 1, for anatomical labeling see Fig. 5). Especially low densities of 5-HT_{1A} receptor binding sites were found in the basal ganglia and the cerebellum, thus offering reference sites in PET analyses based on reference tissue models. In the forebrain this receptor is found mainly on postsynaptic sites, but in the raphe nuclei (midbrain and medullary raphe nuclei) it also acts as an autoreceptor, inhibiting neuronal activity of the raphe nuclei.

5-HT_{1A} antagonists facilitate long-term memory, whereas short-term memory seems to not be affected (Meneses 2007; Meneses and Perez-Garcia 2007). In mice lacking the 5-HT_{1A} receptor, administration of agonists evoked a flattened hypothermic response that is potentially mediated by 5-HT_{1A} receptors located in the hypothalamus (Blier et al. 2002). In healthy human volunteers, 5-HT_{1A} binding potentials in the prefrontal cortex (PFC) and anterior cingulate cortices were positively correlated with aggression (Witte et al. 2009).

In the clinical population, the 5-HT_{1A} receptor has most often been linked to depression, in which nearly all regions of the brain exhibit reduced 5-HT_{1A} binding potentials (Hirvonen et al. 2008; Kennett et al. 1987; but see Miller et al. 2009; Parsey et al. 2010 for different findings). In

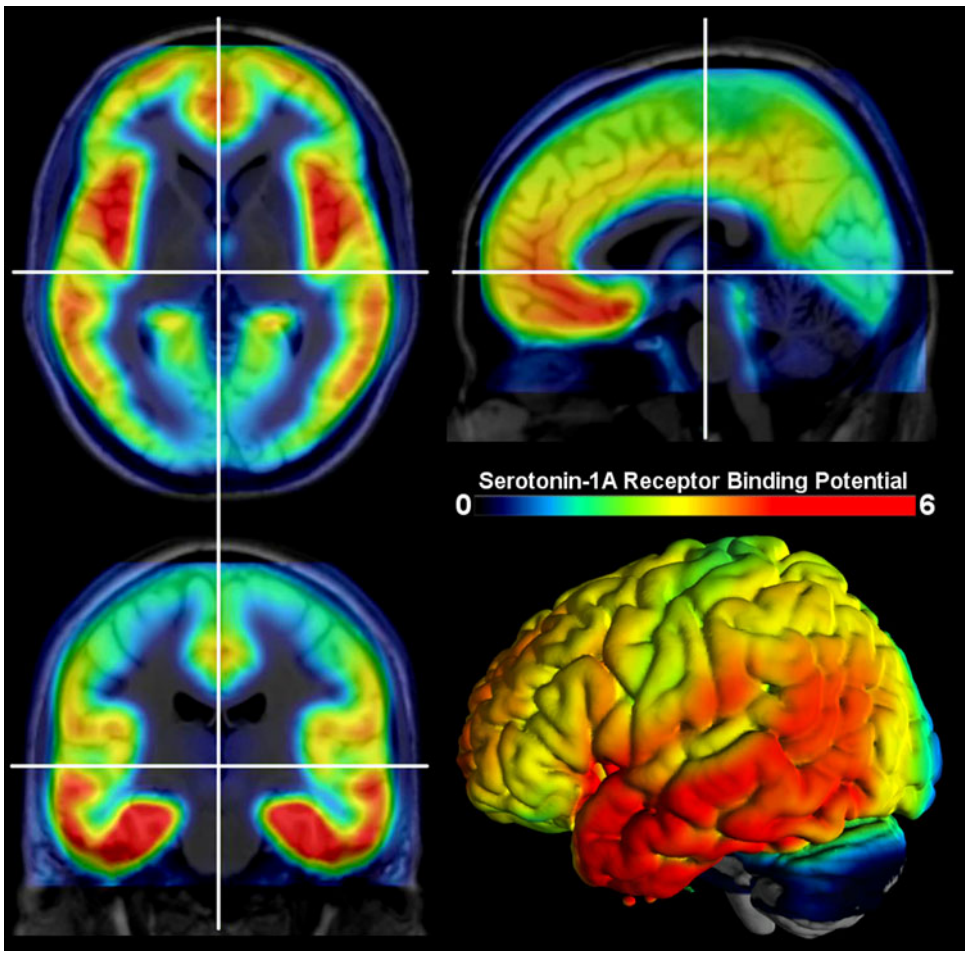

Fig. 1 Distribution of the serotonin 1A (5-HT_{1A}) receptor in the human brain as measured with PET, using the highly specific radioligand [*Carbonyl*-^{11}C]-WAY100635 based on 36 healthy subjects. Highest densities can be observed in the cortical areas in frontal and temporal cortices, especially cingulate and enthorinal cortices as well as the hippocampus and the raphe region. Lowest densities as reflected by low binding potentials can be detected in the occipital cortex. *Color table* indicates receptor binding potentials. For anatomical labeling of the same brain sections and brain surface image see Fig. 5. To compare the protein distribution of the 5-HT_{1A} receptor in the brain with the distributions of the 5-HT_{1B}, 5-HT_{2A}, and 5-HTT see Figs. 2–4

patients suffering from panic disorder, 5-HT_{1A} receptor binding potentials were found to be reduced in orbitofrontal cortex, temporal cortex and amygdala (Choi et al. 2010; Nash et al. 2008; Neumeister et al. 2004). Lower 5-HT_{1A} binding potential was also found in the amygdala, anterior cingulate cortex, insular cortex, raphe nuclei and medial orbitofrontal cortex in (social) anxiety disorder (Akimova et al. 2009; Lanzenberger et al. 2007). Epilepsy was associated with a lateralized reduction of binding potential in the hippocampus, parahippocampal gyrus and amygdala (Assem-Hilger et al. 2010; Didelot et al. 2008). The 5-HT_{1A} receptor has further been implicated in schizophrenia and Parkinson's disease (Ohno 2011), migraine (Demarquay et al. 2011) and anorexia nervosa (Bailer et al. 2005).

Seeing its importance for the serotonergic system, it is not surprising that it was the 5-HT_{1A} receptor for which scientists first found a selective ligand (8-OH-DPAT), (Hannon and Hoyer 2008). [*Carbonyl*-^{11}C]-WAY100635 or [^{11}C]-Way100635 and [^{18}F]-MPPF are the antagonist-based PET radioligands currently most frequently in use. Another two promising PET tracers have been tested in animals, one of which remains to be validated by studies in human subjects: the agonist-derived [^{11}C]CUMI-101 ([^{11}C]MMP) has been tested in baboons (Milak et al. 2008), *Papio anubis* (Milak et al. 2011) and recently in healthy human volunteers (Milak et al. 2010) enabling quantification of receptor distribution, as well as [^{18}F]MefWAY which has also produced promising results in primates (Wooten et al. 2011a, b).

5-HT_{1B}/5-HT_{1D}

When talking about the 5-HT_{1B} and 5-HT_{1D} receptor, the former 5-$HT_{1D\beta}$ and 5-$HT_{1D\alpha}$ receptor, often confusion arises due to the long-lasting ambiguity of its presence in the human brain and its place in the 5-HT nomenclature (for review, see Bockaert et al. 2010).

5-HT_{1B} receptor density is highest in the pituitary gland (hypophysis), basal ganglia, especially the globus pallidum and occipital cortex, while it is only moderately densely distributed in the thalamus (see Fig. 2). Lowest densities are found in the cerebellum, again making the cerebellum a preferred reference region in 5-HT_{1B} receptor PET studies. The density of 5-HT_{1D} receptors has also been found to be high in the basal ganglia, particularly globus pallidus and substantia nigra, but, unlike the 5-HT_{1B} receptor, density of 5-HT_{1D} receptor is also high in the spinal cord and some

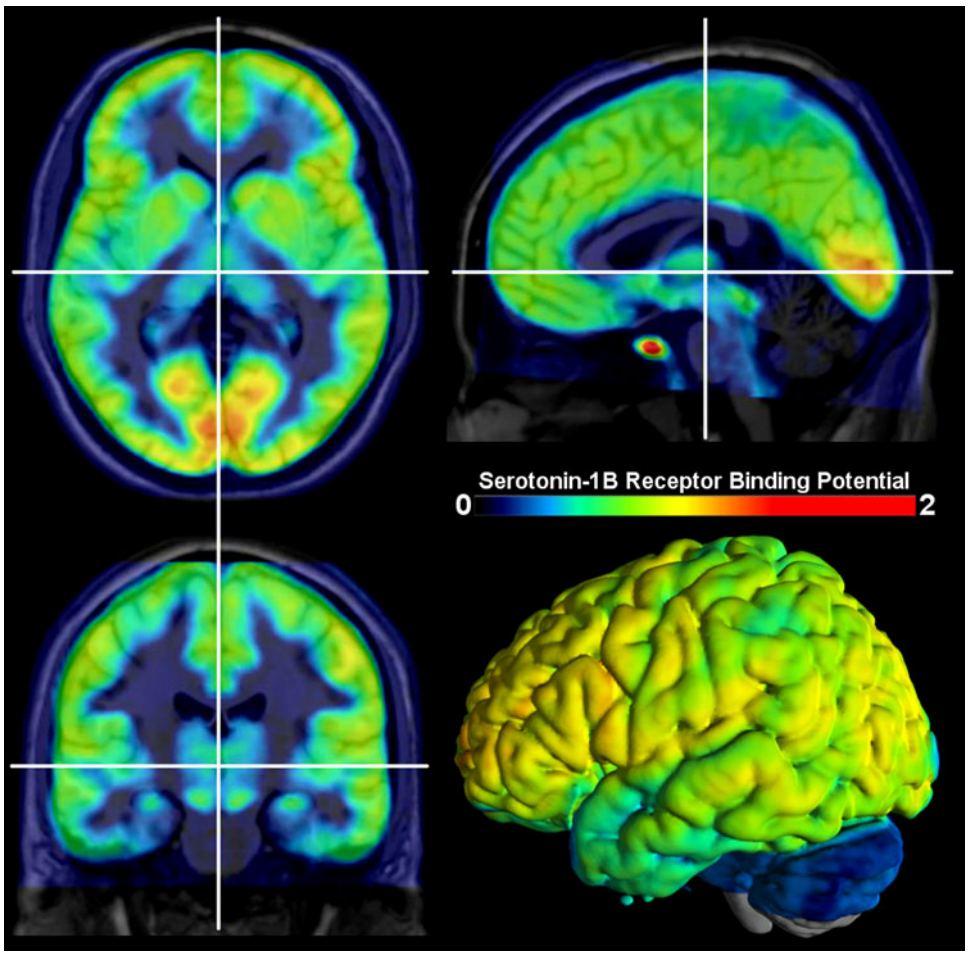

Fig. 2 Distribution of the serotonin 1B (5-HT_{1B}) receptor in the human brain as measured with PET, using the 5-HT_{1B}-specific radioligand [^{11}C]P943 based on 10 healthy subjects. Compared with the 5-HT_{1A} receptor, lower overall densities can be observed, and, complementary to the 5-HT_{1A} receptor, high binding potentials are detected in the occipital cortex. High densities are also found in the pituitary gland (hypophysis, see Fig. 5 for anatomical labels), while moderate densities are seen in the prefrontal cortex. Analogue to the 5-HT_{1A} receptor, the cerebellum is devoid of 5-HT_{1B} receptors. *Color table* indicates receptor binding potentials. For anatomical labeling of the same brain sections and brain surface image see Fig. 5

areas of the midbrain, especially periaqueductal gray (Castro et al. 1997).

Both, 5-HT_{1B} and 5-HT_{1D}, receptors are suggested to play an important role in migraine and the effect of anti-migraine drugs. 5-HT_{1B} antagonists positively affected short-term as well as long-term memory, whereas 5-HT_{1D} antagonists did not show any effects on memory (Meneses 2007). In 5-HT_{1B} knockout mice, an increase in impulsive behavior and defective regulation of impulsivity was observed (Meneses 2007; Meneses and Perez-Garcia 2007).

The 5-HT_{1B} receptor has been implicated in various psychiatric disorders. Studies have found it to be involved in alcoholism (Hu et al. 2010; Soyka et al. 2004) and substance abuse (Huang et al. 2003; Neumaier et al. 2002) (but see Cigler et al. 2001 for different finding), where 5-HT_{1B} receptor levels are increased in the ventral striatal areas and nucleus accumbens, respectively. It has also been suggested to play a role in disorders such as attention deficit hyperactivity disorder (ADHD) (Quist et al. 2003) and aggression (Olivier and van Oorschot 2005; Saudou et al. 1994) In patients suffering from major depression reduced binding of the 5-HT_{1B} receptor has been demonstrated in the ventral striatum/ventral pallidum including the nucleus accumbens (Ruf and Bhagwagar 2009; Murrough et al. 2011). The 5-HT_{1D} receptor has been suggested to be associated with anorexia nervosa (Bergen et al. 2003).

Since there is still a lack of 5-HT_{1D} selective PET ligands, only 5-HT_{1B} PET ligands can be discussed here. The most recent PET ligand, [^{11}C]AZ10419369, has been successfully tested in the human brain by Varnäs et al. (2011a) and might soon join the more validated [^{11}C]P943. The latter had been studied in rhesus monkey (Nabulsi et al. 2010) and a modeling approach for the human brain had deemed it promising (Gallezot et al. 2010). Very recently, in vivo application of [^{11}C]P943 in patients suffering from major depression has been published (Murrough et al. 2011) and even more potential PET ligands have been synthesized and tested in monkeys (Andersson et al. 2011).

5-ht_{1E}/5-HT_{1F}

The true nature of the 5-ht_{1E} receptor is still putative, which is the reason for its spelling in lower case. It appeared when binding sites with low affinity to [^{3}H]5-CT but high affinity to [^{3}H]5-HT were found. These non-5-$HT_{1A,1B,1D,2C}$ [^{3}H]5-HT binding sites are suspected to be a

new 5-HT receptor, the 5-ht_{1E} receptor. Its functional role in the serotonergic system remains unclear, though, and lack of selective radioligands makes the characterization of the 5-ht_{1E} receptor even harder.

Non-5-$HT_{1A,1B,1D,2C}$ [^{3}H]5-HT binding sites, i.e., possible 5-ht_{1E} binding sites, have been found in the cortex, particularly entorhinal cortex, claustrum, caudate and putamen. Lower densities were seen in hippocampus in the subiculum. Autoradiographic studies of the 5-HT_{1F} receptor revealed high density of this receptor's binding sites in the frontal cortex, especially layer V, and substantia gelatinosa. Lower densities were found in the periaqueductal grey and globus pallidus (Castro et al. 1997).

Studies in guinea-pigs (Johnson et al. 1997), rats (Phebus et al. 1997) and humans (Ferrari et al. 2010; Goldstein et al. 2001) strongly support the 5-HT_{1F} receptor to play a major role in the treatment of migraine, introducing its agonist as antimigraine drug (for review, see Neeb et al. 2010).

For the inhibitory 5-HT_{1F} receptor there exists a selective radioligand, [^{3}H]LY334370, which has been used in autoradiographic studies; however, no PET radioligand has yet been developed.

5-HT_2 receptors

The three 5-HT_2 receptor types, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}, preferentially couple to $Gq/_{11}$ increasing inositol phosphates and cytosolic [Ca^{2+}]. 5-HT_2 receptors might also be linked to $G_{12/13}$ which is associated with a number of cellular functions such as migration or structural changes of the cell (Suzuki et al. 2009).

5-HT_{2A}

The 5-HT_{2A} receptor is the most important excitatory receptor in the serotonergic system. It is widely distributed in the human brain with high densities in the cerebral cortex, piriform and entorhinal cortex, claustrum, olfactory bulb as well as in the anterior olfactory nucleus and certain brainstem nuclei, such as the trigeminal, facial, motor, pontine and hypoglossal nuclei. Only moderate levels of binding sites can be found in the limbic system and the amygdala, in particular caudate nucleus and nucleus accumbens, while 5-HT_{2A} receptor densities in the hippocampus are very low (see Fig. 3).

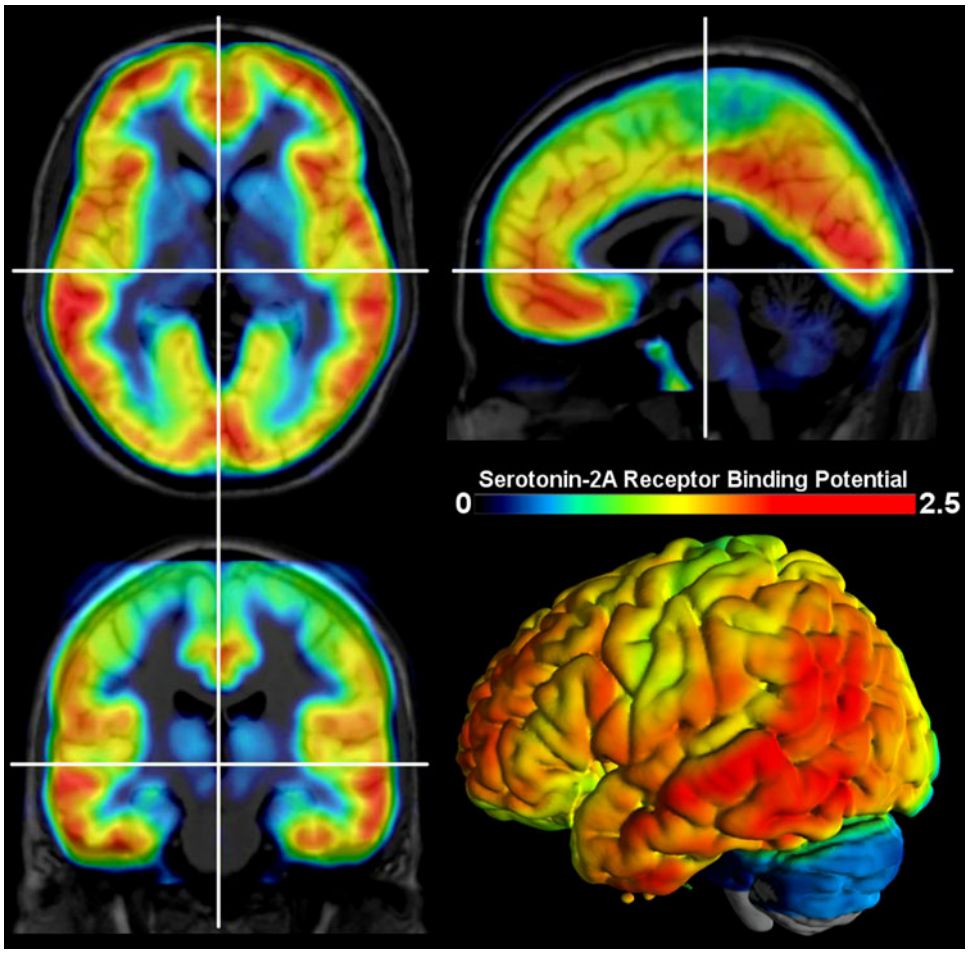

Fig. 3 Distribution of the serotonin 2A (5-HT_{2A}) receptor in the human brain as measured with PET, using the 5-HT_{2A}-specific radioligand [^{18}F]altanserin based on 17 healthy subjects. Highest densities of this receptor are detected in cortical areas, especially medial frontal cortex, temporo-occipital cortex, as well as piriform and entorhinal cortex. Moderate levels are found in the limbic system and the amygdala. Very low levels of 5-HT_{2A} receptor density can be observed in the hippocampus as well as the cerebellum. *Color table* indicates receptor binding potentials. For anatomical labeling of the same brain sections and brain surface image see Fig. 5

5-HT_{2A} antagonists have not been found to have an impact on either short term or long term memory, while the 5-HT_2 agonist 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI) negatively affects both types of memory. Mice lacking the 5-HT_{2A} receptor exhibit changes of sleep patterns (Popa et al. 2005) as well as behavioral sensitization to amphetamine (Salomon et al. 2007). Further, treatment with 5-HT_{2A} antagonists was shown to negatively modulate effects of hallucinogenic drugs such as MDMA (3,4-methylenedioxymethamphetamine, "Ecstasy") (Liechti et al. 2000; Geyer and Vollenweider 2008).

5-HT_{2A} specific radioligands have seen successful application in clinical studies shedding light on the 5-HT_{2A} receptor's function in neuropsychiatric disorders such as Alzheimer's disease (Holmes et al. 1998). In these patients, binding potential in the anterior cingulate measured with PET has been found to be decreased when compared to healthy controls (Santhosh et al. 2009). Reduced 5-HT_{2A} binding in frontal, occipital, temporal and cingulate cortices was found in patients suffering from depression (Gunning and Smith 2011; Messa et al. 2003), while after recovery from anorexia nervosa a reduction was observed in the mesial temporal cortex and cingulate cortex (Frank et al. 2002). In studies by G. Knudsen and co-workers, OCD has been linked to elevated levels of 5-HT_{2A} binding in the caudate nucleus (Adams et al. 2005), as well as to Tourette's syndrome which was associated with increased binding in orbitofrontal cortex, anterior cingulate, frontal cortex and other regions of the brain (Haugbol et al. 2007). In schizophrenia, increased binding was observed in the caudate nucleus (Erritzoe et al. 2008), but decreased levels were found in the dorso lateral prefrontal cortex (dlPFC) and the parahippocampal gyrus (Burnet et al. 1996). Moreover, the 5-HT_{2A} polymorphism −1438G/A has been suggested to play role in OCD (Enoch et al. 1998).

Different PET ligands are used to mark this receptor and there are more being developed. The two that have proven most suitable until now are [^{18}F]altanserin and the carbon labeled [^{11}C]MDL100,907 which are both derived from 5-HT_{2A} antagonists. They have somewhat superseded the older but less selective [^{18}F]setoperone. Another PET radioligand for the 5-HT_{2A} receptor that has already been used in humans is the spiperone-derived [^{18}F]FESP. Recently two more potential PET radiotracers for the human brain appeared. [^{18}F]MH.MZ and its revised version ((R)-[^{18}F]MH.MZ) have been tested in rodents (Debus et al. 2010) yielding good results for the latter. Another promising PET tracer, [^{11}C]CIMBI-36, showed good results in pig studies (Ettrup et al. 2011), advocating its application in the human brain.

5-HT_{2B}/5-HT_{2C}

In contrast to the other 5-HT receptors, the 5-HT_{2B} receptor is mainly present in the periphery and only scarcely expressed in the brain, questioning its role in the cerebral serotonergic system. The 5-HT_{2C} receptor, however, is so far thought to be restricted to the CNS and has not yet been detected in the periphery.

In the CNS, low levels of 5-HT_{2B} binding sites were found in the human cortex (Bonhaus et al. 1995) and immunoreactivity that can possibly be ascribed to the 5-HT_{2B} receptor was observed in the rat cerebellum, lateral septum, amygdala and hypothalamus (Duxon et al. 1997). Highest densities of 5-HT_{2C} receptor's binding sites were found in the choroid plexus, but were also well detected in the hypothalamus and nucleus accumbens (Pandey et al. 2006). Lowest levels were present in the PFC and cerebellum.

Since it has been convincingly suggested to play a role in eating behavior of 5-HT_{2C} knockout mice (Tecott et al. 1995), developing PET ligands to study the 5-HT_{2C} receptor in vivo is of high interest. Apart from its potential function in eating disorders (Halford 2011), the receptor has also been implicated in mood behavior, e.g., by mediating effects of SSRIs, (Serretti et al. 2004) and effects of atypical antipsychotics (e.g., Meltzer 1999).

Nonlabeled ligands for the 5-HT_{2C} receptor do exist but labeled PET ligands still have low selectivity (Paterson et al. 2011) complicating the search for its function in the CNS.

5-HT_3 receptors

In contrast to all other 5-HT receptors which are metabotropic, the 5-HT_3 receptor group consists of ligand-gated ion channels comprising five different subunits, 5-$HT_{3A–E}$, that form functional homomers (3A only) and heteromers. The 5-HT_{3A} subunit on its own only shows low conductance and low response amplitude. Combined with the 3D or 3E subunit, however, the efficacy of the ion channel is markedly increased. Combinations of 3A/3C and 3A/3Ea are less efficient, compared with the two above (Hannon and Hoyer 2008).

The receptor is most densely distributed in the dorsal vagal complex of the brain stem (nucleus tractus solitarius, area postrema and dorsal motor nucleus of the vagus nerve). In the forebrain, 5-HT_3 receptor binding sites are found at lower overall densities, being highest in the hippocampus, the upper layers of the cerebral cortex and the amygdala (Hannon and Hoyer 2008).

Development of PET radioligands for humans would be well received, given the ionotropic receptor's empirically tested function in illnesses such as nausea, vomiting, gastrointestinal disorder (Machu 2011) and treatment of irritable bowel syndrome with 5-HT_3 agonists and antagonists (Jarcho et al. 2008). 5-HT_3 antagonists have further successfully been applied in treatment of drug and alcohol abuse (Enoch et al. 2010; Machu 2011; Rodd et al. 2010) as well as fibromyalgia (Seidel and Müller 2011) and depression (Mahesh et al. 2010). In a rodent model of

Parkinson's disease, 5-HT_3 agonists have been linked to neuronal firing in the medial PFC (Zhang et al. 2011).

So far, 5-HT_3 selective antagonists and agonist could be identified, but hardly any yield promising results when tested in rodent or primate PET studies. Derivatives of the ligand [^{11}C]NMQ for example could potentially be used for PET in humans (Paterson et al. 2011). Also carbon-11 labeled benzoxazole derivatives have been synthesized (Gao et al. 2008), but remain to be tested in vivo.

5-HT_4

Another metabotropic receptor of the serotonergic system is the excitatory 5-HT_4 receptor. Apart from its positive coupling to adenylate cyclase, 5-HT_4 receptors have been suggested to be directly linked to potassium channels (Bockaert et al. 1998) and voltage-sensitive calcium channels (Dunlap and Fischbach 1981). High levels of 5-HT_4 binding sites in the human brain were identified in the substantia nigra, ventral pallidum, septum, striatum (putamen, caudate, globus pallidus), amygdala, hippocampus, nucleus accumbens, island of Calleja and the olfactory tubercle. The receptor could thus be classified as belonging to two main systems in the brain: the striato-nigrotectal pathway and the septo-hippocampo-habenulo-peduncular pathway (Hannon and Hoyer 2008), in line with its suggested functions in the healthy as well as the pathological brain.

Mice lacking the 5-HT_4 receptor show markedly low locomotor activity and hypophagia when faced with a stressful or novel situation (Compan et al. 2004). 5-HT_4 knockout mice have also been shown to develop stronger scopolamine-induced memory impairments (Segu et al. 2010). Clinical studies further point towards the 5-HT_4 receptor's role in diseases such as Alzheimer's and depression, in which amongst others treatment with 5-HT_4 agonist is investigated (Lucas et al. 2010; Madsen et al. 2011b; Russo et al. 2009). Recent findings suggest a potential function of the receptor in the treatment of cancer (Nishikawa et al. 2010).

There exists at least one PET compatible radioligand for this receptor that has already been tested in pigs (Kornum et al. 2009) and humans (Marner et al. 2010), namely, [^{11}C]SB207145. Another group of ligands, derived from the 5-HT_4 receptor antagonist SB207710, has recently been tested in guinea pigs by Xu et al. (2010). The novel ([methoxy-^{11}C]1-butylpiperidin-4-yl)methyl 4-amino-3-methoxybenzoate ([^{11}C]**13**), showing high affinity and selectivity for the guinea pig 5-HT_4 receptor, for example, has yet to be validated in human PET studies.

5-ht_5

Like the 5-ht_{1E} receptor, the 5-ht_5 receptor is still written in lower case due to the insufficient understanding of its preferential coupling and role in the serotonergic system. It has been shown to be negatively coupled to forskolin-stimulated cAMP production, but has also been suggested to be positively coupled to cAMP itself (Hannon and Hoyer 2008). The presence of 5-ht_5 receptor binding sites in the human brain were so far only observed for the 5-ht_{5A} subtype, but not the 5-ht_{5B}.

Binding sites of the 5-ht_{5A} receptor are widely spread across the brain. High levels of binding site density can be found in the raphe nuclei (DRN and MRN), cerebral cortex, hippocampus, amygdala, hypothalamus, habenula, locus coeruleus, nucleus tractus solitarius and cerebellum (Thomas 2006).

In 5-ht_{5A} knockout mice, an increase in exploratory activities in a novel environment was observed. Such mice were also less reactive to the highly 5-ht_{5A} affine lysergic acid diethylamide (LSD) (Hannon and Hoyer 2008) and antagonists of this receptor were reported to have antidepressant and antipsychotic effects in rodents (Hannon and Hoyer 2008).

In an interaction study with citalopram, the 5-ht_{5A} receptor has recently been proposed to be implicated in inhibition of the circadian rhythm in hamsters (Gannon et al. 2009). Another study found a weak connection between the 5-ht_{5A} receptor and bipolar disorder. The authors, however, indicate that replication of this association is necessary to support their results (Yosifova et al. 2009).

Although highly 5-ht_{5A} selective antagonists were tested in guinea pig (SB699551-A, Thomas et al. 2006) and rodent (A843277, Volk et al. 2010), no selective PET ligand has yet been successfully synthesized, obscuring the receptor's function in vivo.

5-HT_6

Like the 5-HT_4 and 5-HT_7 receptors, 5-HT_6 receptors preferentially couple to G_S and by activating adenylate cyclases promote cAMP formation. It is of special interest due to its empirically suggested role in a variety of cognitive functions and disorders. Its distribution is limited to the CNS, where it is found at highest levels in the striatum, nucleus accumbens, olfactory tubercle and cerebral cortex. Moderate density of binding sites were observed in the amygdala, hypothalamus, thalamus, cerebellum and hippocampus.

Most prominently, the 5-HT_6 receptor has been found to be pivotal for memory and learning (Costa-Aze et al. 2011; Meneses et al. 2008) and has thus been subject to studies testing its antagonists' potency as cognitive enhancers (Gravius et al. 2011; Holenz et al. 2006) as well as treatment of Alzheimer's disease (Codony et al. 2011; Tsai et al. 1999). Other studies found an advantageous 5-HT_6-mediated GABA activation and suggested 5-HT_6

antagonists in the treatment of psychiatric disorders such as schizophrenia (Marsden et al. 2011; Pouzet et al. 2002; Vogt et al. 2000). Both, agonists and antagonists, have been implicated in the treatment of depression (Kishi et al. 2010; Nikiforuk et al. 2011; Wesolowska 2010) and anxiety disorders (Wesolowska 2010) as well as feeding behavior and obesity (Heal et al. 2008; Holenz et al. 2006). Further, 5-HT_6 receptor genes have been linked to bipolar disorder (Vogt et al. 2000).

Currently, the most promising PET agent for this excitatory 5-HT receptor is the antagonist derived [^{11}C]GSK210583 which has been tested in pig (Martarello et al. 2005) and human brain (Parker et al. 2008). Most recently, a novel PET ligand, [^{11}C]SB399885, has been tested in baboons (Liu et al. 2011) but showed poor blood–brain-barrier penetration and inconsistent brain uptake motivating the search for other more suitable ligands.

5-HT_7

The excitatory 5-HT_7 receptor is one of the most versatile 5-HT receptors. Apart from its activation of cAMP formation via G_S, this receptor further positively couples to the mitogen-activated protein kinase ERK (Errico et al. 2001). Density of 5-HT_7 receptor binding sites has been found to be high in the thalamus, hippocampus, caudate, putamen, hypothalamus and DRN. Moderate levels were detected in the inner layer of the frontal cortex, superior colliculus, subthalamic nucleus and dendate gyrus of the hippocampus (Martin-Cora and Pazos 2004).

The receptor has been shown to play an important role in numerous functions of the CNS in healthy as well as clinical populations (for review, see Leopoldo et al. 2011). Studies found it to mediate SSRI-induced REM sleep suppression in rodents (Monti et al. 2008; Shelton et al. 2009) and to be involved in regulating the circadian rhythm in hamster and rat (Ehlen et al. 2001; Lovenberg et al. 1993). Further, the 5-HT_7 receptor has been linked to thermoregulation (Guscott et al. 2003), as well as learning and memory (Roberts and Hedlund 2011), with 5-HT_7 knockout mice exhibiting impaired learning. Mice lacking the 5-HT_7 receptor were further found to be more prone to induced seizures, suggesting the receptor's implication in epilepsy (Bourson et al. 1997; Witkin et al. 2007). Clinical studies have suggested 5-HT_7 receptor's antagonists to act as a treatment option in depression and mood disorders (Mnie-Filali et al. 2011), OCD (Hedlund and Sutcliffe 2007) as well as anxiety disorders (Wesolowska et al. 2006). The receptor has also been linked to migraine (Wang et al. 2010b), pain (Leopoldo et al. 2011) and irritable bowel syndrome (Zou et al. 2007).

A number of selective ligands for the 5-HT_7 receptor exist, but none have so far successfully been tested in vivo as labeled PET ligand in humans. The carbon-labeled [^{11}C]DR4446 ligand, however, has been tested in the monkey brain yielding mixed results (Zhang et al. 2002). Very recently, SB269970-derived potential in vivo PET tracers have been synthesized and tested in vitro by Andries et al. (2011) showing promising results.

Transporters

Serotonin transporter (SERT, 5-HTT)

Owing to its successful application as target for treatment of major depression and anxiety disorders, the SERT has been subject to extensive research over the past two decades (for review, see Huang et al. 2010). SERT is located presynaptically on serotonergic neurons and removes serotonin from the synaptic cleft and other extracellular space. It was detected at high levels in the raphe nuclei, thalamus, hypothalamus and striatum. Moderate levels were found in the hippocampus and cingulate cortex, while it is low in other cortical areas. In the cerebellum SERT levels are barely detectable (see Fig. 4, for anatomical labeling see Fig. 5).

Due to its central role in the serotonergic system, SERT has been associated with many different functions in the healthy and clinical population.

It was linked to differences in personality traits, yielding negative associations between levels of SERT binding in different brain regions and the personality trait openness (Kalbitzer et al. 2009), (but see Burke et al. 2011). SERT binding in the hypothalamus was observed to be negatively associated with pain (Kupers et al. 2011), while cognitive functioning was found to be positively correlated to SERT levels in right dorsolateral PFC, caudate and left ventrolateral PFC (Madsen et al. 2011a). Another negative association was found between SERT binding in the thalamus and stress and anxiety (Ichise et al. 2006; Reimold et al. 2011).

Most prominently in the clinical population (for review, see, e.g., Daws and Gould 2011), SERT has been found to play a major role in depression (e.g., Tsao et al. 2006) and bipolar disorder (e.g., Lesch et al. 1995). Other studies suggested SERT to be implicated in OCD (Hesse et al. 2011; Simpson et al. 2003) and substance abuse (Brown et al. 2007), especially MDMA (McCann et al. 2005; Selvaraj et al. 2009). SERT has further been linked to obesity (Erritzoe et al. 2010) and Parkinson's disease (e.g., Wang et al. 2010a).

Although the treatment of major depression (Kasper et al. 2009; for review, see, e.g., Meyer 2007) with SSRIs has long shown to be quite effective, the exact mechanism is still not fully understood.

A number of PET ligands were thus developed among which the diarylsulfides [^{11}C]DASB (for comparison with

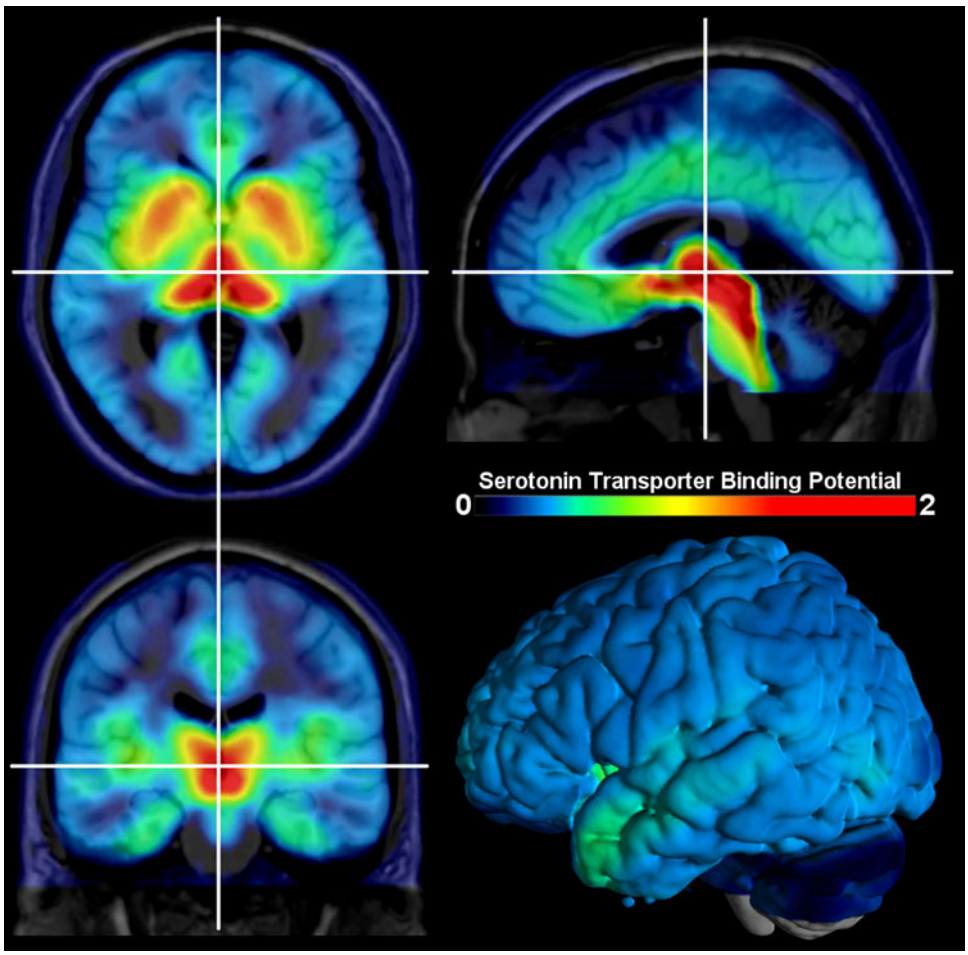

Fig. 4 Distribution of the serotonin transporter (SERT, 5-HTT) in the human brain as measured with PET, using the SERT-specific radioligand [^{11}C]DASB based on 16 healthy subjects. In contrast to the receptors in Figs. 1, 2 and 3, SERT levels in cortical areas are very low. High levels of SERT, however, are detected in the raphe nuclei, thalamus, hypothalamus and striatum, while SERT concentration in the hippocampus and cingulate cortex is moderately low. *Color table* indicates receptor binding potentials. For anatomical labeling of the same brain sections and brain surface image see Fig. 5

[^{11}C]DAPP, see Houle et al. 2000) and [^{11}C]MADAM have become the most successful and superseded the older and less suitable [^{11}C]McN5652. Another two promising new fluor-18 labeled ligands, [^{18}F]FPBM (Wang et al. 2010a) and [^{18}F]ADAM (Huang et al. 2010), have recently been successfully tested in rat, and rat and monkey, respectively, supporting the ligands' validation in the human brain.

Vesicular monoamine transporter 2 (VMAT2)

The VMAT2 enables neurotransmitters such as serotonin to be stored in vesicles, which are then released into the synaptic cleft and does hence play an important role in the serotonergic system.

High levels of VMAT2 were localized in the striatum (putamen and caudate), while moderately high levels were found in nucleus basalis Meynert, hypothalamus, substantia nigra (pars compacta). Lowest levels were observed in white matter regions such as the corpus callosum and internal capsule as well as cerebellar regions (Tong et al. 2011).

The transporter itself has been implicated in effects of drug addiction (Schwartz et al. 2005), mood disorder (Fukui et al. 2007) and stress (Tillinger et al. 2010) as well as Parkinson's disease (Okamura et al. 2010; Taylor et al. 2009) and Alzheimer's disease (Villemagne et al. 2011). For a recent comprehensive review of the VMATs' function and pharmacology, see Wimalasena (2011).

A few PET ligands have been successfully validated in humans to measure VMAT2 density in vivo. Already quite early, [^{11}C]DTBZ was evaluated by Koeppe et al. (1996) and is still in use today (e.g., Boileau et al. 2010). Another [^{11}C] tetrabenazine (see Canney et al. 1995, for early evaluation of tetrabenazines) that has already been tested in humans over a decade ago is the carbon-labeled methoxytetrabenazine [^{11}C]MTBZ (Vander Borght et al. 1995), but which has, to our knowledge, not been used recently to measure VMAT2 in vivo. A new, more promising ligand is the fluorine-labeled [^{18}F]AV133, which has recently been tested in mice (Zhu et al. 2010) and humans (Okamura et al. 2010).

Monoamine oxidase type A (MAO-A)

MAO-A is an enzyme which is, amongst other things, in charge of the degradation of 5-HT in the brain. MAO-A has been found to be most highly concentrated in the thalamus,

Fig. 5 Structural magnetic resonance image (MRI) showing selected regions of interest and anatomical labels. The three brain sections and the 3D brain surface image correspond to the Figs. 1–4. *Cau* caudate, *Cing* cingulum, *CC* corpus callosum, *Cer* cerebellum, *Cun* cuneus, *Front* frontal lobe, *Fus* fusiform gyrus, *Hipp* hippocampus, *Ins* insular cortex, *Occ* occipital lobe, *Pall* pallidum, *Par* parietal lobe, *Pit.gl* pituitary gland, *Put* putamen, *Prec* precuneus, *Temp* temporal lobe, *Thal* thalamus, *Raph* raphe nuclei, *subgen. ACC* subgenual anterior cingulate cortex

yielding moderate levels in the striatum and cortical regions. Lowest levels were found in the cerebellum (Ginovart et al. 2006).

It has been suggested to play an important role in the pathogenesis of depression (Livingston and Livingston 1996; Meyer et al. 2006) and modulation of aggression (Shih et al. 1999), as well as personality traits (Soliman et al. 2011) and habitual smoking (Fowler et al. 2005b; Leroy et al. 2009).

A fairly large number of ligands have proved valuable for in vivo imaging of MAO-A using PET which is why we will limit ourselves to the most important MAO-A PET ligands (for review, see Fowler et al. 2005a). The most successful ligands which have been validated in humans are [^{11}C]harmine (e.g., Bergström et al. 1997; Ginovart et al. 2006; Jensen et al. 2006; Soliman et al. 2011), [^{11}C]clorgyline and [^{11}C]clorgyline-D2 (Fowler et al. 1987, 2002; Logan et al. 2002) and [^{11}C]befloxatone (Bottlaender et al. 2003; Leroy et al. 2009). Another promising carbon-labeled PET ligand, [^{11}C] (R)-*N*-(α-cyclohexylethyl)-*N*-methyl-1H-pyrrole-2-carboxamide ([^{11}C]RS 2360), has recently been tested in mice by De Bruyne et al. (2010) but remains to be validated in primates and humans.

Serotonin synthesis

In order to measure synthesis of serotonin, different approaches using PET have been proposed. Serotonin is synthesized from tryptophan by the aromatic acid decarboxylase (AAAD), which is also involved in the biosynthesis of dopamine and norepinephrine. Since the rate-limiting step in serotonin-synthesis, however, is the amount of TPH available (Hasegawa and Nakamura 2010), measuring concentrations of TPH offers one possibility to quantify serotonin synthesis.

As measured with PET, high serotonin synthesis capacity rates were observed in the putamen, caudate, thalamus and hippocampus. In cortical regions, rectal gyrus of the inferior frontal lobe, transverse temporal gyrus, anterior and posterior cingulate gyrus yielded high synthesis rates. Moderate levels were measured in the middle, superior and frontal gyri, parietal cortex and occipital cortex (Chugani et al. 1998).

These synthesis rates are subject to gender differences of up to 50% (Nishizawa et al. 1997) with males showing significantly higher synthesis rates than females. Differences in 5-HT synthesis have also been observed to be

negatively linked to blood oxygen levels (Nishikawa et al. 2005).

Most prominently, changes in 5-HT synthesis have been associated with the treatment of major depression, showing lower 5-HT synthesis rates in patients with major depression (Rosa-Neto et al. 2004). Decrease of TPH has also been associated with Parkinson's disease, especially in the caudate (Kish et al. 2008). Leyton and colleagues found borderline personality disorder to be negatively linked to 5-HT synthesis rates as measured with PET in the medial frontal gyrus, anterior cingulate gyrus, superior temporal gyrus and corpus striatum. They also found reduced synthesis rates in the medial frontal gyrus, anterior cingulate gyrus, temporal gyrus and striatum in subjects scoring high on measures of impulsivity (Leyton et al. 2001).

To measure 5-HT synthesis in vivo, the most common ligand in use is α-[^{11}C]methyl-L-tryptophan ([^{11}C]AMT or α[^{11}C]MTrp). [^{11}C]AMT uptake has been shown to be stable (Rosa-Neto et al. 2005) and suitable for statistical mapping analysis (Okazawa et al. 2000), supporting its preferential application. Another ligand, used to trap TPH is the carbon-labeled [^{11}C]5-hydroxytryptophan ([^{11}C]5-HTP). It is proposed to be more suitable to actually measure 5-HT synthesis, but is still less widely used due to its complicated radiosynthesis (for review, see Visser et al. 2011).

Endogenous serotonin levels

Measuring endogenous serotonin levels with PET is of high relevance, seeing the successful and informative implementation of such measurements in the dopaminergic system (e.g., Narendran et al. 2009). It has proven difficult, though, to translate this success to the serotonergic system.

In general, measurement of endogenous neurotransmitter levels with PET can be realized based on differences in availability of the system's target receptors (in this case the 5-HT receptors discussed above). These availabilities differ according to fluctuations of the neurotransmitter in the extracellular concentration, which in turn changes after a pharmacological challenge. Such a challenge causes increased binding of the endogenous neurotransmitter and therefore reduced binding of the radioligand. Thus, comparing binding potentials across different conditions and regions with different receptor densities yields information about endogenous neurotransmitter levels (for review, see Paterson et al. 2010).

Different PET ligands have been tested to measure such endogenous 5-HT levels in the human brain, producing mixed results. Derry et al. (2006) as well as Sibon et al. (2008) found the 5-HT$_{1A}$ ligand [^{18}F]MPPF to be sensitive to synaptic 5-HT levels, while the latter found fluoxetine-induced changes only in the raphe nuclei. Also the 5-HT$_{2A}$ tracer [^{18}F]-setoperone was shown to visualize fluctuations in endogenous 5-HT following tryptophan depletion (Yatham et al. 2001), but methodological difficulties call these results into question. Promising first results, though, have been published by G. Knudsen and co-workers (Paterson et al. 2010) and by the Karolinska Institutet (Varnäs et al. 2011b) using agonistic radioligands of the 5-HT$_{1B}$ receptor.

Conclusion

From the chapters above, it becomes evident that serotonin is an important modulatory neurotransmitter which is involved in numerous processes in the CNS. Most prominently, many different brain regions are influenced via G$_{i/o}$-mediated inhibition of adenylate cyclase by the 5-HT$_{1A}$ receptor as well as 5-HT$_{2A}$-induced increase of inositol phosphates and cytosolic [CA^{2+}] via Gq/11.

Amongst other things, the 5-HT receptors are involved in pivotal processes such as memory consolidation and learning, modulation of sleep patterns and mood regulation. The serotonergic system has further been implicated in a variety of illnesses ranging from migraine to psychiatric disorders such as major depression.

When looking at the current state in PET measurement in vivo, great differences in the progress of PET radioligand development for imaging the different receptor subtypes become evident.

For the 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{2A}$ and 5-HT$_4$ receptors as well as SERT, VMAT2, MAO-A and 5-HT synthesis PET radioligands have been successfully applied in a number of PET studies.

5-HT receptor subtypes for which validation of suitable PET ligands for application in the human brain still lack include the 5-HT$_3$, 5-HT$_6$ and the 5-HT$_7$. For the 5-HT$_{1D}$, 5-ht$_{1E}$, 5-HT$_{1F}$, 5-HT$_{2C}$ and 5-ht$_5$, no radiotracers for PET were yet found.

The most successful PET radioligands to visualize 5-HT receptor binding are [^{18}F]altanserin and [^{11}C]MDL100,907 (both 5-HT$_{2A}$), [*Carbonyl*-^{11}C]-WAY and [^{11}C]WAY100635 and [^{18}F]MPPF (all 5-HT$_{1A}$), [^{11}C]AZ10419369 (5-HT$_{1B}$) as well as [^{11}C]SB207145 (5-HT$_4$). For the SERT [^{11}C]DASB and [^{11}C]MADAM have seen most successful application, while [^{11}C]DTBZ and [^{11}C]harmine are well-validated tracers to quantify VMAT2 and MAO-A, respectively.

Although an impressive number of PET radioligands have already been successfully synthesized and validated, there is still a lack of suitable PET ligands for a large part of the serotonergic system. Closing this gap in order to further understand the functioning of this important neurotransmitter on a systems level motivates further research of the human serotonergic system using PET and emphasizes the important role of radiochemists in the progress of molecular neuroimaging in vivo.

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