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Molecular Imaging of $\alpha 7$ Nicotinic Acetylcholine Receptors *In Vivo*: Current Status and Perspectives

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1. Introduction

Nicotine, named after the French diplomat Jean Nicot who brought the tobacco plant (*Nicotiana tabacum*) to France, isolated in 1828 as the major pharmacologically active compound in this plant (Posselt & Reimann, 1828), structurally identified between 1890 and 1893 (Pinner, 1893; Pinner & Wolffenstein, 1891), and first synthesized chemically in 1903 (Pictet, 1903), acts on various subtypes of nicotinic acetylcholine receptors (nAChRs) in the brain and in the periphery (Changeux, 2010; Langley, 1906).

Besides tobacco, nicotine is found in plants of the nightshade family (solanaceae) such as tomato, potato, peppers and aubergine (eggplant) but also in tea plants (Schep et al., 2009). Accordingly, it is regularly taken up by the great majority of the human population with a mean daily dietary intake of approximately 1.4 μg per day (Siegmund et al., 1999). The alkaloid is readily absorbed by the lung or intestinal tissue, distributed by the blood and transported across the blood-brain barrier (Allen & Lockman, 2003; Oldendorf et al., 1979). When inhaled it takes about seven seconds for nicotine to reach the brain (Rose et al., 2010), where it binds with high affinity to the heteromeric $\alpha 4\beta 2$ and the homomeric $\alpha 7$ nAChRs, the two most abundant nAChR populations (Changeux, 2010). In the brain, nAChRs are involved in attention and cognition, locomotion, vigilance control, and rewarding mechanisms (Changeux, 2010; Graef et al., 2011), and they are suggested to play a major role in brain development (Hruska et al., 2009; Ross et al., 2010).

Notably, nicotinic receptors, and in particular $\alpha 7$ nAChR, are not only expressed on neurons but virtually on all cell types present in the brain including astrocytes (Sharma & Vijayaraghavan, 2001), microglia (De Simone et al., 2005; Suzuki et al., 2006), oligodendrocyte precursor cells (Sharma & Vijayaraghavan, 2002), and endothelial cells (Hawkins et al., 2005). Accordingly, neuronal and non-neuronal expression of $\alpha 7$ nAChR has also been found in peripheral organs (Albuquerque et al., 2009; Sharma & Vijayaraghavan, 2002).

Molecular imaging *in vivo* as considered in this review relates exclusively to the use of radiolabelled receptor ligands, although occasionally optical imaging has been used to investigate the cholinergic system (Prakash & Frostig, 2005). Molecular imaging of $\alpha 4\beta 2$ nAChR *in vivo* has recently been reviewed (Horti et al., 2010; Sabri et al., 2008). Therefore, the current review is focussed on neuroimaging of $\alpha 7$ nAChRs.

2. Role of $\alpha 7$ nicotinic receptors in normal brain function

$\alpha 7$ nAChRs, discovered in 1990 (Couturier et al., 1990), belong to the superfamily of multisubunit ligand-gated ion channels and mediate the effects of the endogenous neurotransmitter acetylcholine. Homomeric $\alpha 7$ nAChR is functionally distinct from the heteromeric nAChRs due to lower affinity to the agonists acetylcholine and nicotine, and higher affinity to the antagonistic snake venom α -bungarotoxin (α -BGT). Agonist binding induces a change in conformation of all five subunits of the $\alpha 7$ nAChR and leads to opening of the cation-conducting channel across the plasma membrane, probably by cis-trans prolyl isomerisation (Lummis et al., 2005). Regarding ion selectivity, $\alpha 7$ nAChR is known to have the highest permeability to Ca^{2+} ions within all nAChR subtypes (Dajas-Bailador et al., 2002; Gilbert et al., 2009; Sharma & Vijayaraghavan, 2001). Therefore, the activation of $\alpha 7$ nAChR changes the intracellular Ca^{2+} homeostasis both directly as well as indirectly, the latter via voltage-dependent membrane-spanning Ca^{2+} channels as well as Ca^{2+} release channels and pumps in the endoplasmic reticulum. Downstream events of this Ca^{2+} signalling result in (i) immediate effects, such as neurotransmitter release, (ii) short-term effects, such as receptor desensitisation and recovery, and (iii) long-lasting adaptive effects, such as neuroprotection or changes in the plasticity of the brain via gene expression (Leonard, 2003; Radcliffe & Dani, 1998; Shen & Yakel, 2009). Dependent on the cell-specific pattern of intracellular signalling in neurons with $\alpha 7$ nAChRs located post-, pre- and extrasynaptically (Berg & Conroy, 2002; Frazier et al., 1998; Schilström et al., 2000), these complex functional properties explain the involvement of the $\alpha 7$ nAChR in physiological processes of neurotransmission as well as its role in both acute and chronic neuropathologies (Fig. 1).

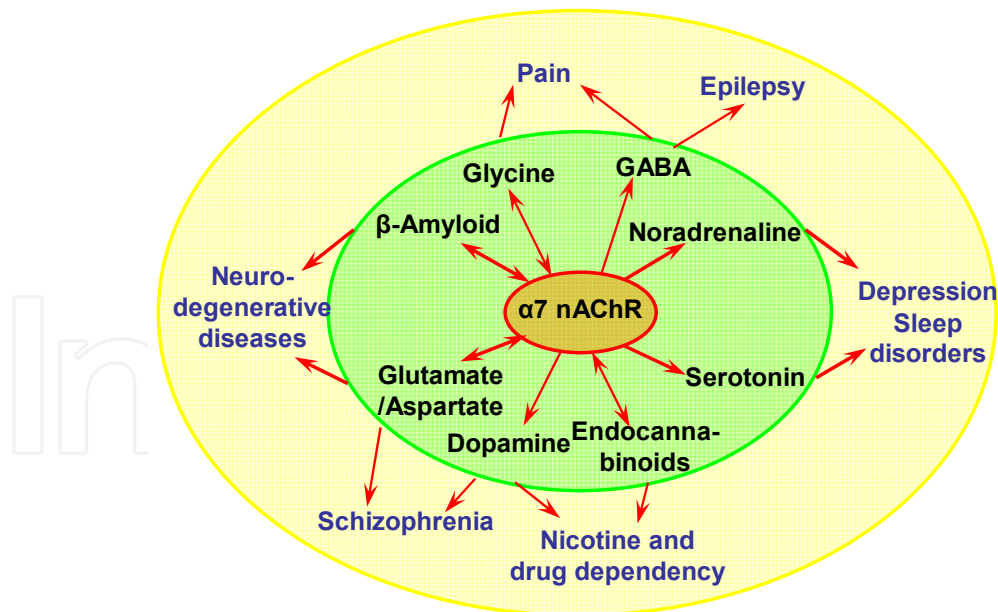


Fig. 1. Involvement of $\alpha 7$ nAChRs in physiological and pathophysiological processes of neurotransmission.

For example, presynaptic $\alpha 7$ nAChRs regulate, either directly or via modulation of glutamate release, the activity profiles of neurotransmitters such as GABA (Albuquerque et al., 1997; Liu et al., 2001), noradrenaline (Fu et al., 1999; Li et al., 1998), or dopamine (Kulak

et al., 1997; Northrop et al., 2010) and thereby mediate neuronal adaptation related to development, learning, memory, attention, pain perception, and reward. Furthermore, $\alpha 7$ nAChRs mediate postsynaptic responses in serotonergic neurons involved in maintaining the waking state (Galindo-Charles et al., 2008). An assumed contribution of $\alpha 7$ nAChRs to the formation of endocannabinoids (Stella & Piomelli, 2001) and a proposed regulation of $\alpha 7$ nAChR activity by anandamide (van der Stelt & Di Marzo, 2005) is consistent with a functional interaction of neuromodulating systems involved in drug dependency (McPartland et al., 2008).

Species	Brain region	Radioligand, concentration	Receptor binding*	Referenz
Human	Nucleus reticularis	[¹²⁵ I] α -BGT, 1 nM	5-12 nM	(Spurden et al., 1997)
	Nucleus geniculatis lat.	[¹²⁵ I] α -BGT, 1 nM	2 nM	(Spurden et al., 1997)
	Dorsolateral prefrontal cortex	[¹²⁵ I] α -BGT, 5 nM	9-12 nM	(Mathew et al., 2007)
	Cingulate cortex	[¹²⁵ I] α -BGT, 2.6 nM	~ 16 nM	(Marutle et al., 2001)
	Temporal cortex	[¹²⁵ I] α -BGT, 2.6 nM	~ 8 nM	(Marutle et al., 2001)
	Hippocampus	[¹²⁵ I] α -BGT, 1.2 nM	2-8 nM	(Hellström-Lindahl & Court, 2000)
Monkey	Cerebellum	[¹²⁵ I] α -BGT, 1 nM	1-3 nM	(Lee et al., 2002)
	Cortex	[¹²⁵ I]iodo-MLA	6 nM (B _{max})	(Kulak et al., 2006)
	Striatum	[¹²⁵ I]iodo-MLA	3-4 nM (B _{max})	(Kulak et al., 2006)
Rat	Cortex	[¹²⁵ I] α -BGT, 3 nM	7.5 nM	(Quik et al., 2005)
		[³ H]MLA, 5 nM	6-16 nM	(Mugnaini et al., 2002)
		[³ H]MLA, 20 nM	~30 fmol/mg protein	(Davies et al., 1999)
		[¹²⁵ I] α -BGT, 10 nM	~40 fmol/mg protein	(Davies et al., 1999)
	Thalamus	[¹²⁵ I] α -BGT	~ 1.1 nM (B _{max})	(Christensen et al., 2010)
		[³ H]MLA, 5 nM	0.9 - 21 nM	(Mugnaini et al., 2002)
	Hippocampus	[³ H]MLA, 5 nM	6-182 nM	(Mugnaini et al., 2002)
		[³ H]MLA, 20 nM	~ 70 fmol/mg protein	(Davies et al., 1999)
		[¹²⁵ I] α -BGT, 10 nM	~ 70 fmol/mg protein	(Davies et al., 1999)
		[¹²⁵ I] α -BGT	~1.2 nM (B _{max})	(Christensen et al., 2010)
	Hypothalamus	[³ H]MLA, 5 nM	14-34 nM	(Mugnaini et al., 2002)
		[³ H]MLA, 20 nM	~ 55 fmol/mg protein	(Davies et al., 1999)
Mouse	Cortex	[¹²⁵ I] α -BGT, 10 nM	~ 50 fmol/mg protein	(Davies et al., 1999)
		[³ H]MLA, 2 nM	1-5 fmol/mg protein	(Whiteaker et al., 1999)
		[¹²⁵ I] α -BGT, 1.2 nM	~ 8 nM	(Svedberg et al., 2002)
		[¹²⁵ I] α -BGT, 2 nM	0-3 fmol/mg protein	(Whiteaker et al., 1999)
	Thalamus	[³ H]MLA, 2 nM	1-20 fmol/mg protein	(Whiteaker et al., 1999)
		[¹²⁵ I] α -BGT, 2 nM	0-12 fmol/mg protein	(Whiteaker et al., 1999)
		[¹²⁵ I] α -BGT, 1.2 nM	~ 3 nM	(Svedberg et al., 2002)
		[³ H]MLA, 2 nM	0-9 fmol/mg protein	(Whiteaker et al., 1999)
	Hippocampus	[¹²⁵ I] α -BGT, 2 nM	0-4 fmol/mg protein	(Whiteaker et al., 1999)
		[¹²⁵ I] α -BGT, 1.2 nM	~ 12 nM	(Svedberg et al., 2002)
		[³ H]MLA, 2 nM	1-12 fmol/mg protein	(Whiteaker et al., 1999)
	Hypothalamus	[¹²⁵ I] α -BGT, 2 nM	1-6 fmol/mg protein	(Whiteaker et al., 1999)

Table 1. Quantitative *in vitro* autoradiographic studies on $\alpha 7$ nAChR binding of various radioligands in the brains of different species, *nM = fmol/mg wet weight

Qualitatively, the expression pattern of $\alpha 7$ nAChR is similar in rodent and primate brain (Han et al., 2000), although a comprehensive and parallel quantitative analysis of $\alpha 7$ nAChR protein expression in the brain of different species, expected to facilitate the translation of experimental data on the imaging of $\alpha 7$ nAChR from *in vitro* and *in vivo* animal models into clinical application, is still warranted. In general, regions with high- to moderate-density of $\alpha 7$ nAChR gene expression and [125 I] α -BGT binding are related to learning and memory such as thalamic and hippocampal structures, the horizontal limb of the diagonal band of Broca, and the nucleus basalis of Meynert (Alkondon et al., 2007; Breese et al., 1997; Fabian-Fine et al., 2001; Hellström-Lindahl et al., 1999; Schulz et al., 1991; Spurden et al., 1997). However, species differences exist regarding the total number of binding sites of $\alpha 7$ nAChR specific radioligands (Han et al., 2003) with for example a lower amount of [125 I] α -BGT binding in the monkey hippocampus or the human thalamus and cortex compared with the same regions of rat brain (Breese et al., 1997) (Tab. 1).

3. Alterations of $\alpha 7$ nAChR in diseased brain

The World Health Organization has classified dependence on the use of drugs including tobacco as a disease in 1965. During the following decades convincing evidence was obtained that nicotine is the key factor in tobacco addiction and that nicotinic acetylcholine receptors are of importance (Stolerman, 1990). It has been suggested that $\alpha 7$ nAChRs in the ventral tegmental area mediate nicotine's stimulatory effect on mesolimbocortical dopaminergic function and consequently its reinforcing and dependence-producing properties (Nomikos et al., 2000). As shown in rats, exposure to tobacco smoke not only induced nicotine dependence but increased the $\alpha 7$ nAChR density in the CA2/3 area (+ 25%) and the stratum oriens (+ 18%) of the hippocampus (Small et al., 2010).

With respect to clinical considerations, a close association between nicotine addiction and schizophrenia has been found (Lohr & Flynn, 1992). Consistent with the hypothesis, that a gene-mediated dysfunction of $\alpha 7$ nAChR (Dome et al., 2010; Freedman et al., 1997; Stephens et al., 2009) underlies impairments seen in schizophrenia (Nomikos et al., 2000), the density of hippocampal [125 I] α -BGT binding sites was decreased in schizophrenic patients (Freedman et al., 1995) but was at control levels in schizophrenic smokers (Mexal et al., 2010).

Evidence for an involvement of $\alpha 7$ nAChR in Alzheimer's disease (AD) was obtained at about 30 years ago from data showing a significantly reduced number of [125 I] α -BGT binding sites in the mid-temporal gyrus from demented patients (Davies & Feisullin, 1981). During the last decade, comparable results were obtained by analysing other neurodegenerative diseases. Lewy body dementia (DLB) and Parkinson's disease have also been associated with alterations in the transcription or translation of the $\alpha 7$ subunit (Burghaus et al., 2003; Court et al., 2000; Nordberg, 2001; Wevers & Schröder, 1999), indicating a hypocholinergic tone due to for example reduced levels of $\alpha 7$ mRNA and protein in the hippocampus and reticular nucleus in AD and DLB (Court et al., 1999; Guan et al., 2000; Hellström-Lindahl et al., 1999). Functional interactions of β -amyloid with $\alpha 7$ nAChR, revealed *in vitro* (Wang et al., 2000), and the colocalization of both in AD support the hypothesis that neuronal degeneration in AD might also be triggered by β -amyloid-initiated and $\alpha 7$ nAChR-mediated inflammatory processes (Bencherif & Lippiello, 2010).

Interestingly, also in traumatic brain injury (TBI), regarded as risk factor for AD (Fleminger et al., 2003), significantly lowered $\alpha 7$ nAChR densities were found in rats and pigs (Hoffmeister et al., 2010). The resulting cholinergic hypofunction may attenuate the anti-inflammatory effect of acetylcholine (Rosas-Ballina & Tracey, 2009) and thus contribute to the process of neurodegeneration (Conejero-Goldberg et al., 2008).

Other diseases with potential involvement of $\alpha 7$ nAChR include epilepsy and attention deficit hyperactivity disorder (ADHD). While some forms of epilepsy have recently been associated with alterations of $\alpha 4$ subtype expression (Raggenbass & Bertrand, 2002), there is experimental evidence that $\alpha 7$ nAChR may play a role in epileptogenesis (Dobelis et al., 2003). Based on similarities between schizophrenia and ADHD with regard to a number of disturbances in attention it has been hypothesized that the $\alpha 7$ subunit gene may be of significance in ADHD although experimental data are still missing (Kent et al., 2001). Previous attempts to treat ADHD patients with nicotine (Levin et al., 1996; Potter & Newhouse, 2004) are currently repeated in a Phase II study with the selective $\alpha 7$ nAChR ligand TC-5619 by Targacept Inc.

4. $\alpha 7$ nAChR as target for drug development

Because the activation of $\alpha 7$ nAChR persistently affects synaptic transmission, multiple neurotransmitter and neuropeptide systems, and eventually brain plasticity (Leonard, 2003; Radcliffe & Dani, 1998; Shen & Yakel, 2009), $\alpha 7$ nAChR has been assessed as a potential target for the rational design of drugs for neuroprotective and neuropsychiatric indications. The large number of studies on receptor structure and pharmacology makes $\alpha 7$ nAChR an extensively investigated receptor protein and the continued development of orthosteric ligands and allosteric modulators by the pharmaceutical industry testifies the importance of efforts to assess $\alpha 7$ nAChR expression and functionality in the living human brain (Bunnelle et al., 2004; Mazurov et al., 2006).

Evidence of a correlation between $\alpha 7$ nAChR properties and brain performance has been provided by studies on the attentional and cognitive enhancement obtained by $\alpha 7$ nAChR agonists (Feuerbach et al., 2009; Levin et al., 1999; Roncarati et al., 2009) and positive allosteric modulators (Faghih et al., 2008; Timmermann et al., 2007) as well as on $\alpha 7$ nAChR related pharmacotherapeutic approaches for schizophrenia (Freedman et al., 2008; Olincy et al., 2006; Tregellas et al., 2011), and dementia (Bacher et al., 2010; Kitagawa et al., 2003; Thomsen et al., 2010). Furthermore, electrophysiological (Hurst et al., 2005; Ng et al., 2007) and behavioural data (Bitner et al., 2010; Pacini et al., 2010; Tietje et al., 2008) highlight the potential of $\alpha 7$ nAChR as therapeutic target for neurodegenerative diseases. The close connection between $\alpha 7$ nAChR signalling, inflammation, and neurodegeneration makes $\alpha 7$ nAChR auspicious also for medicinal control of inflammation as an epiphenomenon of many brain disorders (Conejero-Goldberg et al., 2008; de Jonge & Ulloa, 2007; Rosas-Ballina & Tracey, 2009).

5. Noninvasive imaging of $\alpha 7$ receptors in normal and diseased brain

Far beyond what can be analysed postmortem, the non-invasive and real-time investigation of $\alpha 7$ nAChR by means of molecular imaging techniques provides the assessment of temporal and spatial changes in receptor distribution and density during disease progression and drug treatments.

5.1 Technical requirements

The most advanced system for non-invasive diagnostic and therapeutic neuroreceptor imaging is positron emission tomography (PET) (Antoni & Langström, 2008; Hagooly et al., 2008; Heiss & Herholz, 2006). In PET, the quantitative detection of the distribution of radiolabeled molecules *in vivo* with high resolution and sensitivity leads to functional images of brain biochemistry and physiology (Spanoudaki & Ziegler, 2008). PET has now become an advanced nuclear medicine imaging technique integrated into routine clinical use (Galban et al., 2010) and a highly sophisticated tool for experimental animal research (Lancelot & Zimmer, 2010; Xi et al., 2011).

Receptor ligands used for PET are radiolabelled with short-lived positron-emitting isotopes such as ^{15}O , ^{13}N , ^{11}C , and ^{18}F with half-lives of 2, 10, 20.4, and 109.6 min, respectively. The spatial resolution of recently developed clinical PET systems with about 2-3 mm allows tracing of radioligand distribution even within small cerebral nuclei in human brain (Heiss et al., 2004; Lecomte, 2009; Wienhard et al., 2002), and a detailed regional analysis also in rodents (Lancelot & Zimmer, 2010; Lecomte, 2009; Xi et al., 2011) can be achieved with dedicated small-animal PET scanners. To overcome the problem of the anatomic classification of areas with increased or diminished radioligand accumulation, co-registration of brain anatomy with MRI or CT is needed. Software-based approaches used for computerized anatomical alignment have been very successful in brain imaging because of the relatively fixed and uniform structure of the head, and both manual and automated systems have been developed in the last years (Slomka & Baum, 2009). Through the use of multimodal approaches delineation of small-sized but receptor-rich brain areas is considerably improved (Heiss, 2009). During the last decade hybrid PET-CT scanners have been developed, where two gantries for PET and CT are placed back-to-back (Mawlawi & Townsend, 2009). Technically even more challenging is the development of hybrid PET-MRI scanners because of the sensitivity of the photomultiplier tubes of the standard PET detectors to even low magnetic fields. This problem has been solved only recently (Pichler et al., 2008; Pichler et al., 2006) and was first successfully accomplished for small-animal designs (Judenhofer et al., 2008). Very recently, fully integrated PET-MRI systems which allow simultaneous data acquisition have been developed as clinical research instruments, and four prototypes of integrated hybrid PET-MRI scanners were installed at two PET centres in Europe (Germany) and the United States so far. However, several technological and methodical issues have to be addressed before PET-MRI can establish itself as a routine clinical tool (von Schulthess & Schlemmer, 2009).

5.2 Radiotracer development

PET technology, using radionuclides with high specific radioactivity and the opportunity to specifically label a chemical compound by substituting a stable atom with its radioactive counterpart, combined with quantitative measurements of radioactivity, is the preferred modality for molecular imaging (Antoni & Langström, 2008). Despite of some of the limitations in instrumentation discussed above, the bottleneck for broad clinical applications in neuroimaging is the limited availability of suitable radioligands. Among positron-emitting isotopes only ^{11}C and ^{18}F are applicable for imaging of neurotransmitter-related components in the brain. Their short half-life (^{11}C : $t_{1/2} = 20.4$ min, ^{18}F : $t_{1/2} = 109.6$ min) allows repeated investigations in the same patient or the same animal with short time intervals. Accordingly, the patient or the animal can be considered as its own reference

following a pharmacological intervention. For use in a satellite concept (i.e. with no on-site cyclotron available at the PET center), there is a special demand for PET radioisotopes with longer half-life such as ^{18}F .

Even though the basic mechanisms of radioligand-target interactions *in vitro* and *in vivo* are identical, *in vivo* imaging requires some additional factors that have to be taken into account. In addition to high-affinity binding and supreme selectivity towards the biological target, key requirements for all types of radioligands, suitable physicochemical properties gain special importance for brain imaging with PET. For example not only the transfer of the radioligand across the blood-brain barrier (BBB) is determined by its lipophilicity (Davson & Segal, 1996; Liu et al., 2010) but also the non-specific binding (Waterhouse, 2003). High accumulation and prolonged retention in the target region with target-to-background ratios of desirably more than 5 are closely related to both the affinity of the radioligand and the density of its potential binding sites, which are small compared to the concentration of non-target proteins. Because saturation of binding sites may be obtained at comparably low radioligand concentrations, the concentration of the radioligand applied has to be about 1000-fold lower than the pharmacological threshold. In other words, high specific activity in the range of 50-500 GBq/ μmol has to be achieved, feasible nowadays with both ^{11}C - and ^{18}F -labeled radioligands (Antoni & Langström, 2008).

In summary, high target affinity, specificity, sensitivity, metabolic stability and appropriate pharmacokinetics are among the most important features for a good *in vivo* neuroreceptor-imaging agent. Despite the fact that over the past decade a great variety of $\alpha 7$ nAChR selective agents have been developed, so far there are only a few radioligands which fulfil at least some of these criteria and will be discussed below.

5.3 Imaging of $\alpha 7$ nAChR in animal and human brain

Although a radiopharmaceutical for PET imaging of $\alpha 7$ nAChR that fulfills all the above-mentioned pre-conditions is still missing, there is general agreement to develop ligands, which bind to the orthosteric site of the $\alpha 7$ nAChR. The steric and electronic requirements of this site are met by structurally diverse classes of compounds as reviewed recently (Toyohara et al., 2010a), and potential ligands originate from for example benzyldene anabasein compounds such as GTS-21 (Meyer et al., 1998), or the quinuclidine framework such as AR-R-17779, both shown in Fig. 2 (Bodnar et al., 2005; Mazurov et al., 2005; Mullen et al., 2000; Tatsumi et al., 2005). A recently developed highly selective fluorescent $\alpha 7$ nicotinic receptor ligand is restricted to *in vitro* studies because of its chemical structure (Hone et al., 2010).

Despite this basic knowledge and promising experimental data obtained *in vitro*, the imaging of $\alpha 7$ nAChR *in vivo* is still in its infancy. This is not only due to the inadequate *in vivo* performance caused by an insufficient target specificity of radioligands such as the non-negligible 5HT₃R binding of otherwise promising quinuclidine-based tracers (Pomper et al., 2005) (Table 2).

Compared to the heteromeric $\alpha 4\beta 2$ nAChRs, imaging of $\alpha 7$ nAChR is challenged by the much lower expression of this target, which is illustrated by the up to 100-fold lower density of binding sites of $\alpha 7$ -specific [^{125}I] α -BGT in comparison to $\alpha 4\beta 2$ -specific [^3H]nicotine in different nuclei of human thalamus (Spurden et al., 1997). Furthermore, the outcome of preclinical studies in primates can hardly be predicted from biodistribution studies in rodents. While in the monkey brain high target-to-nontarget ratios were obtained for the

diazabicyclooctane derivatives [^{11}C]A-582941 and [^{11}C]A-844606, both failed with regard to regional distribution and selectivity in the mouse brain (Toyohara et al., 2010b) (Tab. 2).

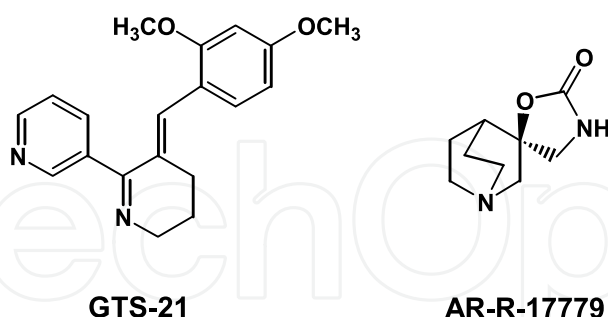


Fig. 2. Lead structures for development of radioligands for neuroimaging of $\alpha 7$ nAChR

Recently, the 1,4-diazabicyclo-[3.2.2]nonane skeleton (Bunnelle et al., 2004) has been identified as new structure to improve the receptor-ligand interaction, and both ^{18}F -substituted compounds such as [^{18}F]NS10743 (Peters et al., 2007) and those for labelling with ^{11}C such as [^{11}C]CHIBA-1001 (Hashimoto et al., 2008; Toyohara et al., 2009) and [^{11}C]NS12857 (Lehel et al., 2009) have been designed (Table 2). As illustrated by the data in Tab. 2, the general suitability of these derivatives for imaging of $\alpha 7$ nAChR is supported by preclinical PET studies in pigs (Deuther-Conrad et al., 2011; Lehel et al., 2009) and non-human primates (Hashimoto et al., 2008) as well as a first clinical study (Toyohara et al., 2009). However, substantial enhancement in the affinity of the $\alpha 7$ nAChR PET ligands is required to improve image analysis, modelling, and eventually quantification of $\alpha 7$ nAChR in brain diseases. Considering the low density of $\alpha 7$ nAChR in brain, the target affinity of the currently most promising tracers [^{11}C]CHIBA-1001 ($K_i \sim 35$ nM; (Hashimoto et al., 2008; Toyohara et al., 2009) and [^{18}F]NS10743 ($K_i \sim 10$ nM; (Deuther-Conrad et al., 2009) has proved insufficient, because dissociation constants of ≥ 10 nM result in baseline binding potential values considerably lower than the threshold value of 2 (Koeppe, 2001). NS14490, a novel diazabicyclononane derivative which has been developed by NeuroSearch and radiolabelled in collaboration with the authors, possesses a K_i value of ~ 3 nM *in vitro* (Deuther-Conrad and colleagues, unpublished), and the ligand distribution pattern of [^{18}F]NS14490 has been assessed in a first proof-of-principle experiment (Fig. 3).

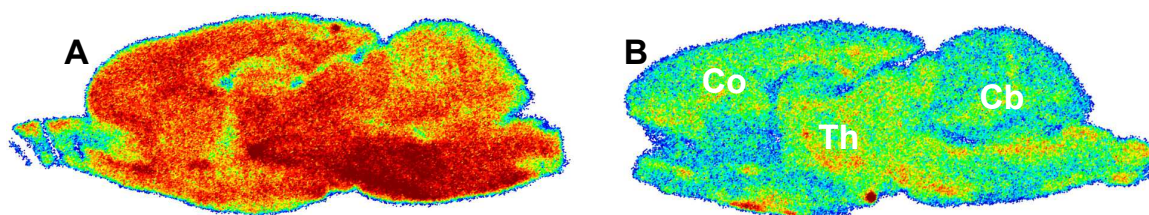


Fig. 3. *In vitro* autoradiography on the distribution of [^{18}F]NS14490 in rat brain (sagittal slices, 12 μm). A = [^{18}F]NS14490, total binding; B = Co-incubation of [^{18}F]NS14490 with 20 μM methyllycaconitine; Abbreviations: Co=cortex; Cb=cerebellum; Th=thalamus.

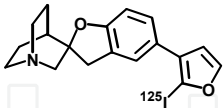
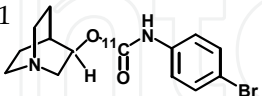
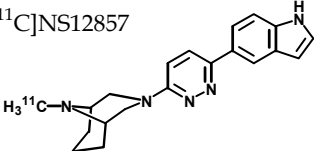
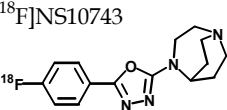
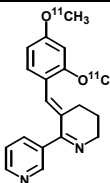
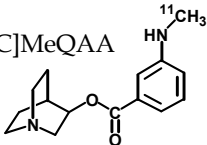
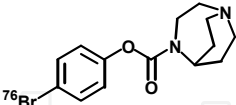
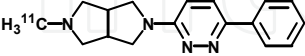
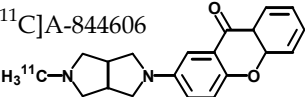
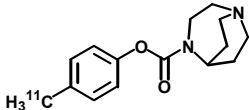
PET radioligand	Species; Study type	Main findings	Reference
[¹²⁵ I]4 	CD1 mice Biodistribution	Very limited uptake of radioactivity in the brain; No evidence of receptor blockade	(Pomper et al., 2005)
[¹¹ C]1 	SPRD rats Biodistribution	No regionally selective or specific binding	(Dolle et al., 2001)
[¹¹ C]NS12857 	<i>Sus scrofa domestica</i> Dynamic PET scan	High uptake in the pig brain; Distribution as reported in primates; Lack of <i>in vivo</i> displacement	(Lehel et al., 2009)
[¹⁸ F]NS10743 	<i>Sus scrofa domestica</i> Dynamic PET scan	High uptake in the pig brain; Blocking significantly reduced binding potential in regions with high radioactivity uptake	(Deuther-Conrad et al., 2011)
[2/4-methoxy- ¹¹ C]GTS-21 	<i>Papio anubis</i> Dynamic PET scan	Very high initial uptake followed by rapid clearance; Radiometabolites penetrate the BBB; High nonspecific binding consistent with the low affinity for α7 nAChR	(Kim et al., 2007)
[¹¹ C]MeQAA 	<i>Macaca mulatta</i> Dynamic PET scan	<i>R</i> -enantiomer with high uptake of radioactivity in the brain and α7 nAChR-related distribution	(Ogawa et al., 2010)
[⁷⁶ Br]SSR180711 	<i>Macaca mulatta</i> Dynamic PET scan	Substantial and heterogeneous brain accumulation; Uptake reduced to background level of the cerebellum by pretreatment with the α7 nAChR agonist SSR180711	(Hashimoto et al., 2008)
[¹¹ C]A-582941 	<i>Macaca mulatta</i> Dynamic PET scan	Regional distribution consistent with α7 nAChR expression	(Toyohara et al., 2010b)
[¹¹ C]A-844606 			
[¹¹ C]CHIBA-1001 	Clinical PET study (one healthy male subject)	Selective uptake in the regions of the hippocampus, cortex and basal ganglia; gradual washouts; cerebellum with lowest binding	(Toyohara et al., 2009)

Table 2. Findings on *in vivo* biodistribution and PET imaging studies on the binding of $\alpha 7$ nAChR specific radioligands in brain of different species.

6. Noninvasive imaging of $\alpha 7$ nAChR in other diseases – Reality and vision

For another derivative, NS14492, an IC_{50} value of 4.5 nM was reported. It was radiolabelled with ^{11}C and investigated in pigs, where the radioligand showed the capability of measuring *in vivo* occupancy at $\alpha 7$ nAChR (Ettrup et al., 2010).

With regard to molecular imaging, the development of quantitative approaches to visualise $\alpha 7$ nAChR outside the brain is another big challenge because comparably low receptor densities have to be expected also in peripheral organs. Experimental radiotracer studies discussed above provided evidence of specific $\alpha 7$ receptor binding not only in the adrenals with reported receptor densities of less than 10 fmol/mg in human tissue (Mousavi et al., 2001) but also in heart, muscle, gut, kidney, thymus, pancreas and liver (Deuther-Conrad et al., 2009).

In general, imaging the concentration, distribution and occupancy of neuroreceptors involved in respiratory and cardiovascular disorders is a very attractive research area as it can provide new insights in the aetiology of these diseases as well as means to diagnose them (Hagooly et al., 2008). Regarding $\alpha 7$ nAChR, the presence of these receptors in microvascular endothelial cells has been shown and their involvement in the regulation of microvascular permeability and angiogenesis has been suggested (Egleton et al., 2009; Li & Wang, 2006; Moccia et al., 2004).

Furthermore, nicotinic $\alpha 7$ receptors are part of a neural circuit where acetylcholine transmitted via the vagus nerve is thought to control cytokine release as part of the cholinergic anti-inflammatory pathway (Tracey, 2002). This pathway may protect organs such as heart or kidney from ischemic injury (Li et al., 2010; Sadis et al., 2007; Yeboah et al., 2008) and could be of importance in patients with autoimmune diseases known to be characterized by suppressed vagus nerve activity (Bruchfeld et al., 2010). Accordingly, neuroimmunomodulation mediated by $\alpha 7$ nAChR agonists is regarded as a future therapeutic approach (Bencherif et al., 2011; Kumar & Sharma, 2010).

Nicotinic $\alpha 7$ receptors are also regarded as a powerful regulator of responses that stimulate cancer cells (Egleton et al., 2008; Schuller, 2009). In particular, evidence of the involvement of nicotinic $\alpha 7$ receptors in the control of basal cell proliferation and differentiation pathways in lung and the participation of these receptors in airway remodelling during bronchopulmonary diseases led to the assumption that $\alpha 7$ nAChRs are of relevance for lung development, injury, repair, and carcinogenesis (Maouche et al., 2009). Because the $\alpha 7$ nAChR is the most predominantly expressed nAChR subtype in bronchial epithelial cells (Paleari et al., 2009) and mRNA for $\alpha 7$ nAChR has been detected not only in normal lung cells but in most human lung cancer cell lines (Egleton et al., 2008; Plummer et al., 2005), it has been hypothesized that a desensitization of $\alpha 7$ nAChR in heavy smokers with a prolonged exposure to nicotine could lead to squamous metaplasia (Tournier & Birembaut, 2011). While in an early investigation of small cell carcinomas of the lung no specific [^{125}I]- α -bungarotoxin binding could be demonstrated, probably due to a sub-threshold density of the $\alpha 7$ receptor protein related to this particular type of cancer (Cunningham et al., 1985), not only all of 50 investigated non-small cell lung cancer (NSCLC) cell lines expressed the $\alpha 7$ subtype (Paleari et al., 2009) but also all out of 52 investigated NSCLC patients expressed $\alpha 7$ receptor mRNA and protein and the values were higher in smoking patients with squamous carcinomas than those with adenocarcinomas (Paleari et al., 2008).

Besides lung cancer, $\alpha 7$ nAChR-mediated signalling has been implicated in the growth and metastasis of colon cancer (Wei et al., 2009; Wei et al., 2011; Ye et al., 2004), probably due to

the activity of the endogenous allosteric $\alpha 7$ nAChR modulator SLURP-1 and the upregulation of the downstream signalling molecule NF- κ B (Chernyavsky et al., 2010; Pettersson et al., 2008; Ye et al., 2004). Also the development of keratinocyte carcinoma, the most prevalent skin cancer and the most common cancer in United States (Albert & Weinstock, 2003), may depend on $\alpha 7$ nAChR expression and regulation. Interestingly, antagonisation of nAChR activity by SLURP-1 and -2 prevented the tobacco nitrosamine-induced malignant transformation of oral keratinocytes (Arredondo et al., 2007), cells known to express $\alpha 7$ nAChR (Chernyavsky et al., 2010). Further cancers with known $\alpha 7$ nAChR expression include breast, pancreas, and prostate carcinomas (Al-Wadei et al., 2009; Dasgupta et al., 2009; Hirata et al., 2010; Hruska et al., 2009). Based on this evidence, $\alpha 7$ nAChR is considered a primary target in ongoing research on pathogenesis of a variety of cancers. Furthermore, the quantitative imaging of disease-related changes in the expression of peripheral $\alpha 7$ nAChR by PET is highly desirable for the validation of novel approaches in diagnostics and development of cancer-specific therapy.

7. Conclusion

Generally, the development of imaging approaches to non-invasively quantify $\alpha 7$ nAChR receptors in and outside the brain is expected to help in the generation and testing of novel hypotheses supporting the understanding of pathogenetic processes and promoting novel diagnostic and therapeutic concepts. The clinical significance of a malfunction of $\alpha 7$ nAChR, involved in particular cell-type and pathology specific modulating and signalling cascades, can be assessed on molecular level with an imaging-supported spatiotemporal quantification of $\alpha 7$ nAChR protein. In this context, the imaging technique must be sensitive enough not only to identify but also to assess the dynamics and quantity of even subtle changes in the amount of functional $\alpha 7$ nAChR, which is despite its physiological importance expressed at comparably low levels in the brain and periphery. PET techniques offer the highest achievable resolution of functional processes in the body in four dimensions by imaging of $\alpha 7$ nAChR with further optimised PET radiotracers, which might be based for instance on the currently most promising diazabicyclononane derivatives.

8. References

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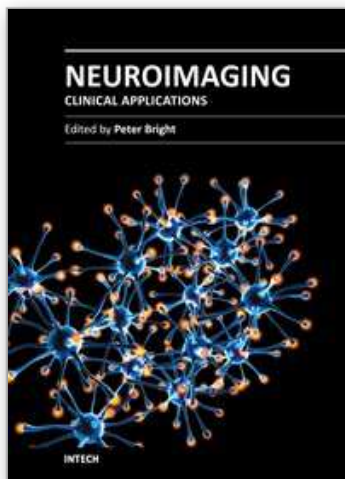
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