Chapter 3

The Potential Role of the MCHR1 in Diagnostic Imaging: Facts and Trends

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Abstract

The neuropeptide melanin-concentrating hormone (MCH) plays a key role in energy maintenance by decreasing energy expenditure and stimulating feeding behavior. Furthermore, it is involved in diabetes, gut inflammation, sleep, depression, and cilia beat function. The biological function of MCH is mediated by two G-protein coupled receptors, MCH receptor 1 and 2 (MCHR1 and MCHR2). Since only the MCHR1 is functional in rodents, the physiological importance of MCHR2 remains unknown due to the lack of appropriate animal models. The involvement of the MCHergic system in a variety of pathologies, especially endocrinological diseases, such as obesity and diabetes, makes it interesting as a new target to treat human disorders. Many pharmaceutical companies have pursued the development of MCHR1 antagonists for the treatment of obesity. Moreover, positron emission tomography (PET) tracers targeting the MCHR1 have been developed in order to gain a deeper understanding of the role and distribution of the MCHR1. As a high-end technique, PET allows noninvasive in vivo visualization and quantification of receptor systems, as well as monitoring and following hormone receptor status and related pathologies. Therefore, a MCHR1 PET tracer could help to guide pharmacological intervention via the MCHR1.

Keywords: MCHR1, PET, imaging, tracer, antagonist

1. Introduction

Melanin-concentrating hormone (MCH) was first referenced as "melanophore-concentrating hormone" in studies examining the possible origin of a factor leading to lightning of fish skin color in 1955 [1]. Although speculations regarding the existence of such a factor date back to the 1930s—when studies of pigmentation changes in amphibians were performed [2]—the isolation of MCH succeeded only in 1983 [3]. It was gained from the pituitary gland of

the salmon and characterized as a cyclic 17-amino acid polypeptide with a cysteine-cysteine disulfide bond [3]. In teleost fish, MCH is synthesized as a preprohormone in the pituitary gland and is secreted into the circulation, where it acts as the opponent of melanocyte-stimulating hormone (α-MSH) by lightning the skin color in response of the environmental background. This effect is due to the aggregation of pigment granules within melanophores [4, 5].

Several years after the discovery in fish, MCH was identified in mammalian brain, too. It was first isolated from rat hypothalamic fragments and characterized as a 19-amino acid peptide [6], which was found to be identical to human MCH [7] (structure shown in **Figure 1**). Generally, MCH is present in all groups of vertebrates from lampreys to humans and exhibits considerable structural coherence among different species [8]. MCH is derived by posttranslational cleavage from the C terminus of a 165 amino-acid precursor, pre-proMCH (ppMCH). The preprohormone is also generating two additional peptides, neuropeptide-glutamic acid-isoleucine (NEI), and neuropeptide-glycine-glutamic acid (NGE). The gene encoding MCH is called Pmch [7].

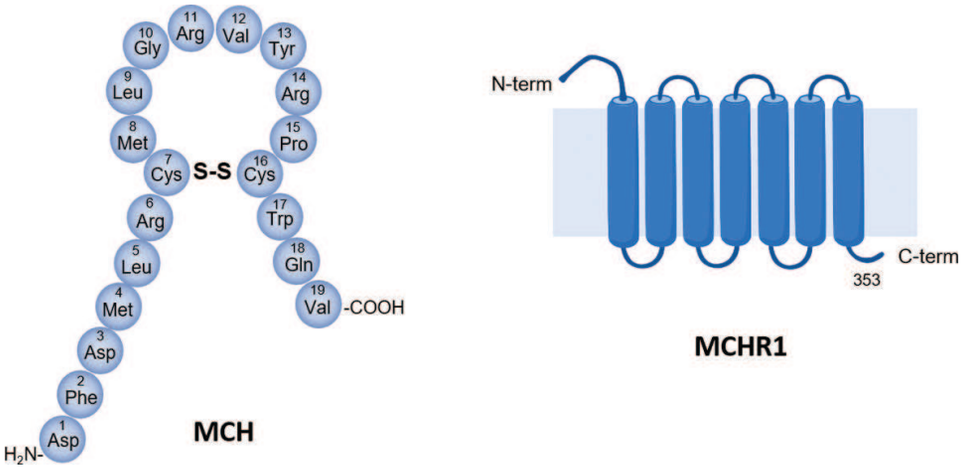

Figure 1. Structure of MCH and MCHR1.

In mammals, MCH is predominantly expressed in the lateral hypothalamus and zona incerta and projects broadly throughout the central nervous system (CNS) [9, 10]. Furthermore, it is also found in peripheral tissues, such as colonic epithelial cells [11], adipocytes [12], or beta-cells of the islets of Langerhans [13]. Although it is expressed in human melanocytes too, it has not been shown to affect human pigmentation [14]. In mammals, MCH operates as a neuropeptide, playing a key role in energy maintenance by decreasing energy expenditure and stimulating feeding behavior [15–17].

Initial efforts to identify a MCH receptor were based on binding assays by using radiolabeled MCH. MCH-binding sites were detected in a variety of cells and in rat brain [18, 19]. However, the existence of the MCH receptor remained obscure until 1999, when it was found to be identical to the previously cloned orphan G protein-coupled receptor somatostatin-like clone 1 (SLC-1), which exhibited about 40% homology to the five somatostatin receptors in its hydrophobic domains. The first MCH receptor (MCHR1) was identified simultaneously by several groups using different pharmacological approaches [20–24]. MCHR1 is 353 amino acids long and has all hallmark features of the G protein-coupled receptors, including seven

	Rat		Human	
Brain region				
Hypothalamus	++	[23]	+++	[29]
Thalamus	+++	[30]	++	[29]
Hippocampus	+++	[23]	++	[31]
Amygdala	++	[23]	+	[31]
Pons	+	[22]	++	[29]
Medulla oblongata	?		++	[29]
Substantia nigra	++	[23]	++	[32]
Nucleus accumbens	+++	[23]	++	[33]
Locus coeruleus	++	[23]	?	
Olfactory system	+++	[23]	?	
Cerebral cortex	++	[22]	+	[29]
Cerebellum	++	[34]	+	[29]
Peripheral tissues				
Pituarity	+	[23]	++	[33]
Eye	++	[23]	?	
Tongue	+	[23]	?	
Sceletal muscle	++	[23]	–	[32]
Adipose tissue	+	[23]	+	[33]
Liver	–	[23]	+	[32]
Heart	–	[23]	–	[32]
Thymus	?		–	[32]
Spleen	?		–	[32]
Kidney	–	[23]	–	[32]
Adrenal	+	[35]	+	[31]
Testis	+	[36]	+	[32]
Ovary	++	[36]	++	[32]
Placenta	?		–	[32]
Prostate	?		–	[32]
Stomach	?		–	[33]
Pancreas	+	[37]	+	[13]
Colonic epithelial cells	?		+	[11]

+++, high abundance; ++, moderate abundance; +, low abundance; –, not detectable; ?, not investigated.

Table 1. Binding sites of MCH/MCHR1 mRNA distribution pattern.

transmembrane helices, a DRY motif at the end of the third intracellular loop, and three potential glycosylation sites at the N-terminus [25] (structure shown in **Figure 1**).

Comparison of the human and the rodent receptors shows a high degree of conservation between species (human-rat 96% identity; human-mouse 95% identity), which is not unexpected knowing that the ligand structure is identical in human, rat, and mouse [25, 26].

Activation of MCHR1, which couples to multiple G proteins (G_i, G_o, and G_q), leads to an increase in intracellular Ca^{2+} accumulation via stimulation of phospholipase C, lowered cyclic adenosine monophosphate levels (cAMP) via inhibition of adenylate cyclase, and stimulation of extracellular-signal-regulated kinase [27]. In the CNS, activation of these signaling pathways has diverse effects, ranging from changes in gene expression to modulation of ion channel activity [28].

MCHR1 is predominately expressed in the brain; besides, it is also found in moderate to weak concentration in other tissues. An overview of the widespread MCHR1 distribution is given in **Table 1**.

In 2001, a second MCH receptor (MCHR2) was identified with 340 amino acids of length [32, 33, 38, 39]. The overall homology between the two MCH receptors is quite low; they share only 38% identical amino acids. It also seems that the signal transduction mechanism of MCHR2 is limited to the G_q protein, resulting in increased intracellular Ca^{2+} levels. Its expression profile is similar to MCHR1, with the highest expression in the brain, notably in the frontal cortex, amygdala, hippocampus, nucleus accumbens, and putamen [38]. Low levels were found in the thalamus, hypothalamus, medulla oblongata, and no expression was found in the cerebellum. Peripheral expression was shown in adipocytes, pancreas, prostate, and intestine [40]. MCHR2 is found to be a pseudogene in rodent species, but—interestingly—is known to be functional only in dogs, ferrets, rhesus monkeys, and humans [41]. Due to the lack of appropriate animal models, the physiological importance of MCHR2 remains unknown until now.

2. Physiological function of the MCHergic system

MCH plays a major role in energy homeostasis, e.g., the control of food intake, body weight, and metabolism [15–17]. It has been shown that MCH-deficient (MCH-KO) mice are leaner than wild-type mice and their body weight deficit is about 25% at 4 months of age. The decrease in body weight is the result of reduced food intake (hypophagia) and a slight increase in energy expenditure. Leptin levels are low, as would be expected in a lean mouse model. Otherwise, the mice appear to be normal, with normal levels of activity and normal fertility [42].

In contrast, MCH overexpressing (MCH-OE) mice developed—when placed on a high-fat diet—excessive obesity compared with wild-type mice. The reason, therefore, is that MCH-OE mice are hyperphagic. Furthermore, these animals had elevated blood glucose levels, significant hyperinsulinemia, and islet cell hyperplasia [43]. Chronic infusion of MCH in mice reproduced the hyperphagic obese phenotype seen in the transgenic mice (MCH-OE mice) [17].

Considering the receptor, MCHR1 knockout (MCHR1-KO) mice are—when maintained at regular feed—lean and have a reduced fat mass. The leanness is due to hyperactivity,

increased energy expenditure, and altered metabolism. A dramatic 250% increase in running-wheel activity was reported [44]. Paradoxically, they were found to be hyperphagic compared with wild-type mice. This effect was interpreted as a compensatory response. When placed on a high-fat diet, they gain significantly less weight and are less susceptible to diet-induced obesity (DIO). Chronic infusion of MCH did not show any effects in MCHR1-KO mice [16].

Furthermore, MCH plays an important role in mediating the effects of leptin on energy homeostasis. Leptin is predominantly secreted from adipocytes and is referred as "adiposity signal," circulating in proportion to body-fat content [45]. Leptin-deficient (ob/ob) mice are obese, hyperphagic, insulin resistant, and had significantly increased MCH expression [15].

Crossing the ob/ob mice to the MCH-KO mice caused a significant reduction in body weight with increased energy expenditure, thermogenesis, and locomotor activity. Further, they showed improved glucose homeostasis [46].

In MCHR1-KO mice, which were crossed with the ob/ob mice, body-fat mass decreased and locomotor activity increased. No differences in body weight, food intake, or energy expenditure could be observed compared with the ob/ob mice. Despite being obese, MCHR1-KO ob/ob mice had improved insulin sensitivity [47].

All these findings illustrate the central role of MCH in regulating energy homeostasis: MCH promotes the conservation of body energy and the loss of MCH function leads to leanness. Conservation of energy is also one of the main functions of sleep. Hence, it seems likely that MCH has also a function in sleep regulation. Several research groups described the role of MCH as a sleep promoter (reviewed by Torterolo et al. [48]). MCHergic neurons project throughout the central nervous system, including areas involved in the control of sleep, such as the dorsal and median raphe nuclei. The fact the MCHergic neurons are active during sleep, especially during rapid eye movement (REM) sleep, indicates the MCH plays a critical role in the generation and maintenance of sleep. An increase in the duration of REM sleep is considered as an important biological marker for depression [49]. Furthermore, the expression of MCHR1 in serotonergic neurons, as well as MCHergic projections toward the limbic system, suggest a relevant role of MCH in the control of emotional states [50]. Several preclinical studies demonstrated the antidepressant and anxiolytic effects of MCHR1 antagonists (i.e. [51, 52]).

Furthermore, it has been shown that MCH contributes to maintain cerebrospinal fluid (CSF) homeostasis: MCHR1 is expressed in the ependymal cells of the third ventricle, where it is involved in the regulation of cilia beat frequency [53, 54]. This beating facilitates cerebrospinal fluid (CSF) circulation, which is crucial for brain function, as defects in ventricular cilia result in hydrocephalus. A lack of MCH receptor provokes a ventricular size increase as observed in MCHR1-KO mice. Brain penetrating MCHR1 antagonists may thus alter CSF flow, limiting their potential use as therapeutic agents.

Since both, MCH and MCHR1 are expressed in islets and clonal beta-cell lines [13], some peripheral effects of MCH were also observed. MCH has a direct effect on islet signaling pathways, insulin secretion, and insulin sensitivity [13]. As mentioned above, MCH-OE mice

have substantial hyperinsulinemia and islet hyperplasia that is out of proportion with their degree of obesity [43]. In contrast, MCH-KO mice have normal or improved glucose tolerance, despite having less insulin release in response to a glucose load [55]. Furthermore, MCH stimulates leptin production in adipocytes, where the MCHR1 is present too [12]. MCH was also found to be a mediator of intestinal inflammation. MCH and MCHR1 mRNA expression are increased in human colitis. MCH-KO mice had a significant protection from induced colitis, suggesting that MCH has a proinflammatory role in the development of colitis [11]. Pmch and MCHR1 were also found in human immune cells. This may provide a link between allergic inflammation, asthma, and obesity [56, 57].

An overview of the multiple involvement of the MCHergic system is given in **Figure 2**.

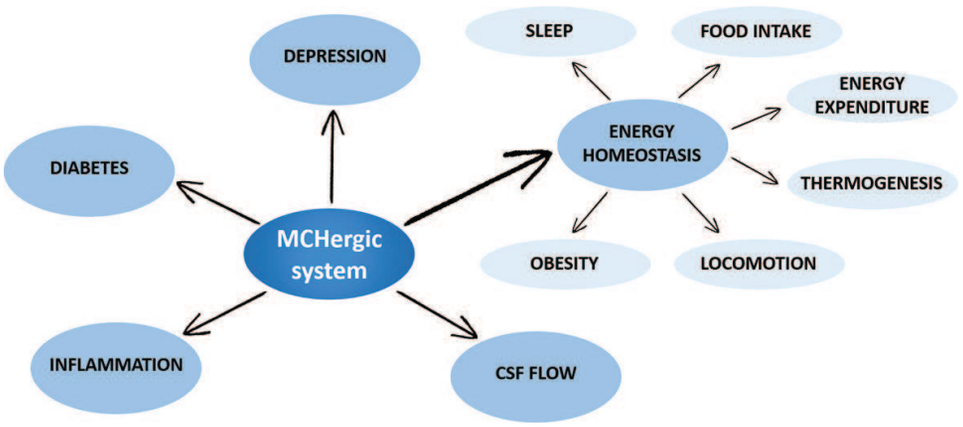

Figure 2. Involvement of the MCHergic system.

3. Targeting the MCHR1

The involvement of the MCHergic system in a variety of pathologies, especially endocrinological diseases such as obesity and diabetes, makes it interesting as a new target to treat human disorders. Since it has been shown that MCHR1 antagonists reduce body weight in rodents (reviewed by MacNeil [58]), several MCHR1 antagonists were developed in the last 15 years; some of them have entered clinical trials for the treatment of obesity [59], while some are in discussion of becoming anti-diabetic drugs [60].

The first functional, competitive MCHR1 antagonist was the $_{D\text{-}}Ala^{11}$ analog of hMCH [61]. Subsequently, a series of analogs with antagonist activity were generated, such as Ac-(Ava$^{9\text{-}10}$, Ava$^{14\text{-}15}$)-hMCH(6-16)-NH_2 (also known as PMC-3881-PI) [62]. However, peptide MCHR1 antagonists are not able to cross the blood-brain barrier (BBB) and interact with the MCHR1 in the CNS. Therefore, small molecule MCHR1 antagonists were developed. The first nonpeptide antagonist was T-226296 (Takeda), an orally active compound that demonstrated high affinity and selectivity to the MCHR1 (Ki = 5.5 nM) [63].

Screening of a G protein-coupled receptor-based compound library against the human MCHR1 in a functional assay measuring intracellular Ca^{2+} mobilization resulted in the

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discovery of a second nonpeptide antagonist, SNAP-7941 ((+)-methyl (4S)-3-{[(3-{4-[3-(acetylamino)phenyl]-1-piperidinyl}propyl)amino]carbonyl}-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate hydrochloride) (Synaptic/Lundbeck, **Figure 3** (1)) [51]. SNAP-7941 has an excellent binding affinity (Kd = 0.18 nM) and selectivity (>1000-fold) to the MCHR1. In rat brain sections, binding of radiolabeled SNAP-7941 ([^{3}H]SNAP-7941) was detected in the cerebral cortex, olfactory tubercle, claustrum, piriform cortex, hippocampus, amygdala, caudate-putamen, accumbens nucleus, hypothalamus, dorsal raphe, and locus coerulus [51]. This distribution pattern parallels the widespread MCHR1 expression in the brain [30]. Further, systemic pretreatment with SNAP-7941 (10 mg/kg, intraperintoneal (i.p.)) inhibited the increase in food intake induced by intra-cerebroventricular (i.c.v.) injection of MCH (3 nmol). Rats treated with SNAP-7941 (10 mg/kg, i.p.) twice a day for seven days gained 26% less weight compared with their littermates. SNAP-7941 was also capable to decrease milk consumption in satiated rats: 13% less milk consumption in rats treated with 3 mg/kg (i.p.), 41% with 10 mg/kg (i.p.), and 59% with 30 mg/kg (i.p.) compared with vehicle-treated rats. These results suggest that SNAP-7941 acts as an anorectic agent. To rule out that this anorectic effect was due to malaise, a taste aversion study was performed, which confirmed that the anorectic effect of SNAP-7941 was not a result of malaise. In DIO rats, SNAP-7941 (10 mg/kg, i.p., twice daily over four weeks) produced a sustained and consistent decrease in food consumption and body weight. This effect was reversible insofar as two weeks after the termination of the treatment, DIO rats previously treated with SNAP-7941 showed an increase in body weight and food consumption. A toxic effect of SNAP-7941 as a causal role for reduction in food intake and weight gain was ruled out by blood tests of the hepatic and renal function of the drug treated rats [51]. All these findings render the MCHR1 a viable target for the treatment of obesity. Additionally to the reported anorectic effects, SNAP-7941 evinced antidepressant and anxiolytic properties. A single oral dose of SNAP-7941 (3, 10, and 30 mg/kg) significantly decreased the duration of immobility and increased the swimming time of rats in the forced-swim test. Unfamiliar male rats showed increased social interaction time after acute treatment with SNAP-7941. Finally, the high-frequency vocalizations emitted from guinea pig pups separated from their mothers were significantly reduced after treatment with SNAP-7941 [51]. These anxiolytic effects were not supported by another group [64].

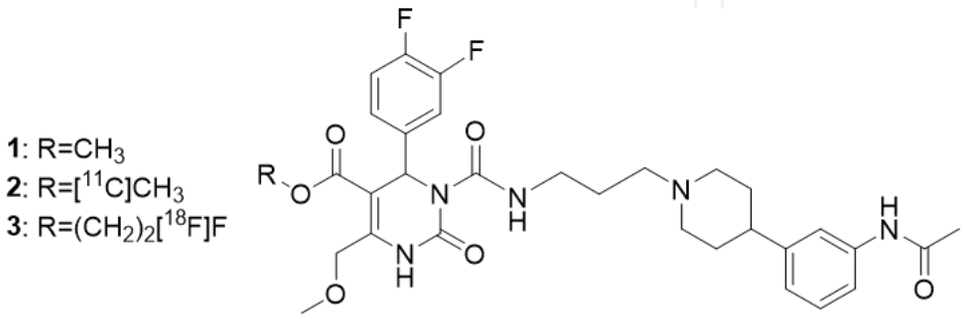

Figure 3. SNAP-7941 derivatives (**1**: SNAP-7941; **2**: [^{11}C]SNAP-7941; **3**: [^{18}F]FE@SNAP).

Several other small molecule antagonists were developed from pharmaceutical companies, e.g., ATC0065 and ATC0175 (Arena/Taisho collaboration) [65, 66], GW803430 (GlaxoSmithKline) [67], SNAP 94847 (Synaptic/Lundbeck) [52], AMG-076 (Amgen) [68], and NGD-4715 (Neurogen) [69]. All these drugs are BBB-penetrating compounds, which is mandatory to reduce body weight [70].

Due to medical need for oral anti-diabetics that give weight loss, a dual MCHR1 antagonist/dipeptidyl peptidase-4 (DPPIV) inhibitor had been developed recently [60].

Nevertheless, none of these molecules reached market authorization so far. Unfortunately, a significant number of MCHR1 antagonists showed a cardiovascular risk involving human ether-a-go-go gene (hERG) potassium channel inhibition and QT prolongation. hERG blockers are associated with lethal arrhythmias known as torsade de pointes. Structural requirements, such as a positively charged group and at least one distal aromatic/hydrophobic region, for MCHR1 potency correlate with hERG inhibition. Efforts in designing MCHR1 antagonists with improved selectivity over hERG are undertaken by several pharmaceutical companies; a few candidates have progressed to clinical development [71].

4. Diagnostic imaging

It has been described that changes of expression of the MCHR1 are related to various diseases, such as obesity, diabetes, gut inflammation, hydrocephalus, and depression. Thus, the MCHR1 seems to be a promising target for various clinical questions.

In the last decades, positron emission tomography (PET) has become a vital and versatile modality for modern medicine, as well as for applied medicinal research. At present, it belongs to the most sensitive methods for the purpose of molecular imaging [72]. However, the potential of nuclear molecular imaging and its capabilities strongly depends on the supply of potent and specific radiotracers for specific applications. Hence, the evaluation and development of new highly affine and selective radioligands is an indispensable part to increase the scope of application for molecular imaging.

A PET tracer for the MCHR1 comprises several advantages for clinicians and patients as the in vivo monitoring and following of the hormone receptor status and related pathologies. Moreover, it could support dose selection of MCHR1 antagonists in drug development [59] and would provide a deeper understanding of the involvement and distribution of the MCHR1. Therefore, specific MCHR1 imaging is of high clinical interest for status monitoring in endocrine pathologies such as obesity and diabetes.

As mentioned before, Borowsky et al. [51] presented the evaluation of the very potent MCHR1 antagonist SNAP-7941, which contains a methyl ester (**Figure 3**(1)), making it suitable for radiolabeling introducing either a [^{11}C]methyl moiety or a 2-[^{18}F]fluoroethyl moiety. On this basis, two potential PET tracers for the visualization of the MCHR1 were developed so far: [^{11}C]SNAP-7941 (**Figure 3**(2)) and [^{18}F]FE@SNAP (**Figure 3**(3)) [73–77].

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The radiosynthesis of [^{11}C]SNAP-7941 could be conducted in a conventional synthesis module and consisted of a [^{11}C]methylation of the precursor SNAP acid. The optimal reaction conditions were found to be 2 min reaction time in acetonitrile at ≤25°C reaction temperature using 2 mg/ml precursor and [^{11}C]CH_3OTf as a methylation agent. Under these conditions, 2.9 ± 1.6 GBq (11.5 ± 6.4% at end of bombardment (EOB)) [^{11}C]SNAP-7941 could be produced. Radiochemical purity always exceeded 99% [73]. The specific radioactivity for the preclinical in vivo evaluation was 108.2 ± 56 GBq/μmol at the end of synthesis (EOS) [74]. The full radiosynthesis, purification procedure, and physiological formulation could be automated to guarantee a safe and reliable production. All quality control parameters were in accordance with the standards for human application [73]. In vitro binding assays on CHO-K1 cell membranes expressing the human MCHR1 and MCHR2, respectively, evinced high-binding affinity (Ki = 4.52 ± 0.7 nM for the MCHR1) and selectivity (Ki > 1000 nM for the MCHR2) of [^{11}C] SNAP-7941. The metabolic stability of [^{11}C]SNAP-7941 in plasma and against liver microsomes and carboxylesterases was very high: no degradation in human plasma over 60 min; <10% degradation by liver microsomes (human and rat) over 60 min and no decomposition by porcine carboxylesterases. Interestingly, in rat plasma, [^{11}C]SNAP-7941 was metabolized considerably: 50.4 ± 1% of intact compound were found after 60 min. The formation of a hydrophilic metabolite was observed. The plasma free fraction was found to be sufficient for imaging: f1 = 21.0 ± 1% in human plasma and even 32.4 ± 1% in rat plasma. The lipophilicity was in a range, where a passive diffusion through the BBB would be expectable: log $D^{7.4}$ = 3.29. However, in the in vivo experiments in healthy rats, [^{11}C]SNAP-7941 evinced to be a P-glycoprotein (P-gp) substrate, since after blocking with the P-gp inhibitor Tariquidar (TQD), the [^{11}C]SNAP-7941-uptake in the brain raised 3–5 times [74].

Of note, Borowsky et al. [51] observed a significant reduction in food intake and body weight in rats after i.p. application of SNAP-7941. Knowing that drugs have to cross the BBB to reduce body weight via central mechanisms [70], it is quite surprising that [^{11}C]SNAP-7941 evinced to be a P-gp substrate.

Nevertheless, no metabolite was found in the rat brains of the baseline and TQD-pretreatment group [74].

The biodistribution experiments showed both uptake in kidneys and in intestines. On the basis of the conducted experiments, a specification of the major way of excretion was not possible.

Uptake in MCHR1 expressing organs (adrenals, pancreas, eyes, muscle, and ovary) could be observed. Low uptake was found in peripheral fat tissue of the healthy rats [74].

Due to the advantage of the longer half-life of fluorine-18 (110 min) compared with carbon-11 (20 min), [^{18}F]FE@SNAP, the [^{18}F]fluoroethylated derivative of SNAP-7941 was developed as the second PET tracer for the MCHR1. Its radiosynthesis was challenging; no vessel-based approach succeeded. Only the preparation within a microfluidic device was successful, consisting of the direct [^{18}F]fluorination of the tosylated precursor (Tos@SNAP). Harsh reaction conditions had to be applied: high reaction temperature of 170°C and a short reaction time using an overall flow rate of 150 μl/min. Since the microfluidic device was not equipped

for purification steps, the crude reaction mixture was purified in a conventional synthesis module. The radiosynthesis as well as the purification and physiological formulation were automated to guarantee safe and reliable production. The radiochemical yield ranged between 100 and 650 MBq, which was sufficient for every subsequent preclinical experiment. Specific radioactivity was 24.8 ± 12 GBq/μmol EOS. All quality control parameters were in accordance with the standards for human application [75].

[^{18}F]FE@SNAP evinced high-binding affinity and selectivity to the MCHR1: Kd = 2.9 ± 2.5 nM for the MCHR1; Ki > 1000 nM for the MCHR2. Similar to [^{11}C]SNAP-7941, it is highly stable in human plasma (only 3.9 ± 4% metabolism after 120 min), against liver microsomes (<10% metabolism after 60 min) and porcine carboxylesterases (Km = 347.3 μM) and rapidly metabolized in rat plasma (completely after 120 min). The plasma-free fraction was lower (f1 = 12.6 ± 0.2%) than for [^{11}C]SNAP-7941, but can still be considered high enough for imaging. Compared with SNAP-7941, the lipophilicity was slightly higher: $logD^{7.4}$ = 3.83 [76].

After IV administration of [^{18}F]FE@SNAP into healthy and conscious rats, ex vivo autoradiography of the brains evinced specific tracer uptake in the hypothalamic region and the ventricular system. In addition, preliminary small-animal PET measurements in healthy rats showed a high tracer uptake in the ventricular system (**Figure 4**) [77].

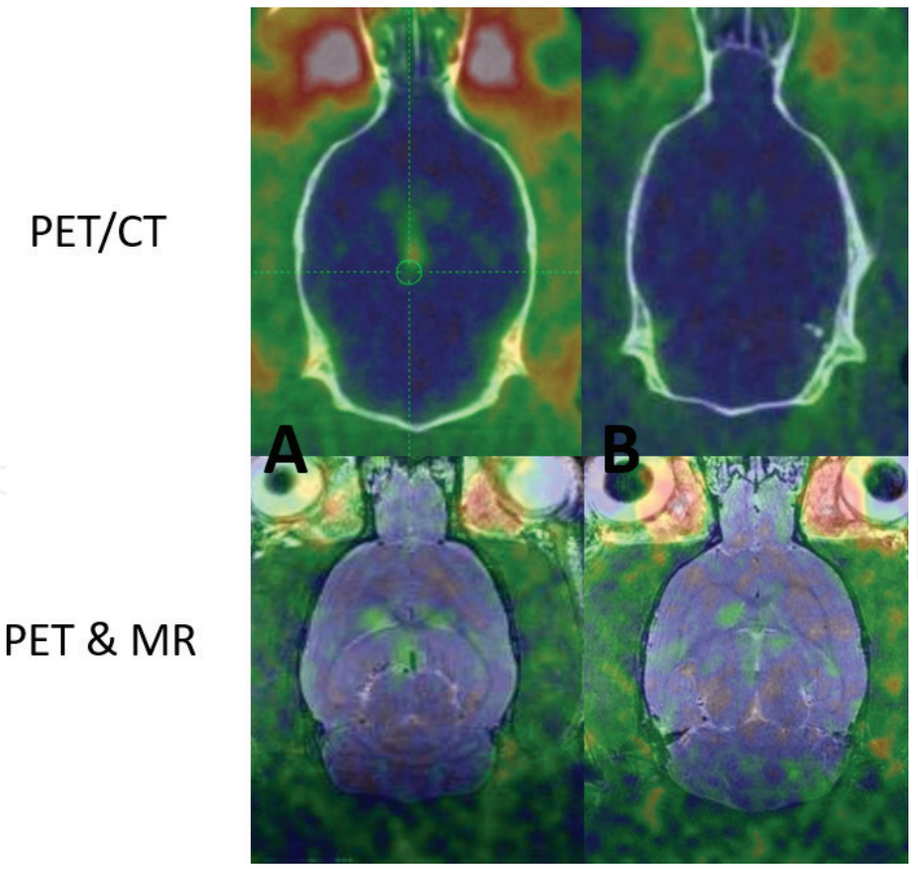

Figure 4. Exemplary small-animal PET/CT and PET and MR image of a rat brain with [^{18}F]FE@SNAP. Rats were anesthetized by isoflurane. 25 min after [^{18}F]FE@SNAP iv injection, vehicle (A) or 15mg/kg SNAP-7941 (B) were administered through the tail vein. 75 min after tracer injection, the rats were sacrificed. A significant reduction in tracer uptake could be observed after the administration of SNAP-7941.

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Biodistribution experiments showed—similar to [^{11}C]SNAP-7941—uptake in kidneys as well as in the intestines. Uptake in MCHR1 expressing organs (adrenals, pancreas, eyes, muscle, and tongue) could be observed too [77].

So far, [^{11}C]SNAP-7941 and [^{18}F]FE@SNAP are the only described potential PET tracers for the MCHR1. Both proved high affinity and selectivity for the MCHR1; could be prepared in a reproducible and feasible way; evinced high metabolic stability in human plasma and against human and rat liver microsomes and showed specific uptake in preclinical in vivo experiments in healthy rats. Since the extent of MCHR1 expression in obese or diabetic rats is unknown, further experiments with [^{11}C]SNAP-7941 or [^{18}F]FE@SNAP in obese and diabetic rats will show the applicability of the MCHR1 concept. Furthermore, the quantitative analysis and evaluation of the preclinical data may provide high-impact predictive values upon further clinical application in PET imaging for diagnosis and further treatment of MCHR1-related diseases. A more detailed insight and better understanding of the involvement of the MCHR1 in various neurotransmitter systems can be obtained, which potentially provides the basis for the development of novel pharmaceuticals and eventually, may serve as new working standard for the evaluation of the MCHR1 as a potential binding site of atypical antipsychotic drugs, using PET.

5. Conclusion

MCH was initially characterized as a factor mediating color change in teleost fish. In response to the environmental background, MCH causes a concentration of pigment in melanophores, thus producing a lighting of pigmentation and has the opposite effect of α-MSH, which causes darkening of fish pigmentation. This phenomenon is crucial for fish to camouflage themselves from predators.

Although MCH is expressed in human melanocytes too, it has not been shown to affect human pigmentation so far. In mammals, MCH operates as a neuropeptide and involvement of MCH/MCHR1 was reported in obesity and diabetes, and MCHR1 has also been related to depression, colitis, and hydrocephalus. Therefore, MCHR1 imaging is of high clinical interest for monitoring these pathologies and guide pharmacological interventions. Specific MCHR1 PET tracers could serve as a useful tool for diagnostic imaging. So far, the first two PET tracer for the MCHR1, [^{11}C]SNAP-7941, and [^{18}F]FE@SNAP are evaluated in preclinical settings.

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