PET imaging of brain sex steroid hormone receptors and the role of estrogen in depression
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Chapter 2

PET and SPECT Imaging of Steroid Hormone Receptors

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Abstract
Steroid hormones like estrogens, progestins, androgens and corticosteroids are involved in normal brain function. They are able to exert both neuroprotective and neurotrophic effects. In addition, steroid hormones play a crucial role in mood disorders by interacting with different neurotransmitter systems in the brain. Steroid hormones produce their physiological effects by binding to their corresponding hormone receptors. To better understand the role of steroid hormones, knowledge of the expression of steroid hormone receptors in the brain may provide important insights. In animal experiments, it is possible to perform invasive measurement of steroid hormone receptors both in healthy and in pathological conditions, but noninvasive measurement of steroid receptors in the brain is required in humans. PET and SPECT are techniques that may allow non-invasive measurements of the expression of steroid hormone receptors. This chapter addresses the role of steroid hormone receptors in both physiological and pathological conditions, and provides an overview of the current status of PET and SPECT imaging methods for steroid hormone receptors.
Introduction
Hormones are messenger molecules that are produced and secreted by endocrine glands in the body. Hormones travel through the bloodstream to those parts of the body where they induce their specific cellular responses. Hormones are generally classified into two classes: steroidal and nonsteroidal hormones. Structurally all steroid hormones consist of a steroidal scaffold, which is composed of three six-membered rings and one five-membered ring; nonsteroidal hormones lack this steroid scaffold. Examples of steroid hormones are estrogens, progestins, androgens, and corticosteroids. Steroid hormones are responsible for biological responses in a wide range of endocrine processes, including sexual differentiation, reproductive physiology, glucose metabolism, and maintenance of salt and water balance. Examples of nonsteroidal hormones are insulin, glucagon, thyroid stimulating hormone, follicular-stimulating hormone, catecholamines, and eicosanoids.

The brain is an important target organ for circulating steroid hormones that are secreted from peripheral organs, such as adrenal cortex, testes, and ovaries. Steroid hormones are highly lipophilic and therefore can easily pass through the blood-brain barrier by passive diffusion. However, the brain itself is now known to synthesize steroid hormones de novo from cholesterol (Figure 1). After surgical removal of peripheral organs that produce steroid hormones (e.g., castration, like orchietomy or ovariectomy), constant levels of these neurosteroids are maintained in the brain\textsuperscript{1,2}. The most important neuroactive steroids include not only neurosteroids produced by the brain like pregnenolone, dehydroepiandrosterone, and 3α-hydroxy-5α-pregnane-20-one but also classical steroid hormones, such as 17β-estradiol, testosterone, and progesterone. Neurosteroids produce their effects by autocrine or endocrine pathways\textsuperscript{3}. Steroid hormones produced in the CNS are allosteric modulators of different neurotransmitter receptors. The major functions of neuroactive steroids have been reviewed by Rupprecht\textsuperscript{4}.

In the central nervous system (CNS), neuroactive steroids/neurosteroids play a crucial role in neuronal development and plasticity. Neuroactive steroids can act as allosteric modulators of ligand-gated ion channels (GABA\textsubscript{A}), NMDA, and sigma receptors. Because of these interactions, neuroactive steroids have been implicated to have sleep-inducing, anticonvulsant, anesthetic, nootropic, and antipsychotic properties\textsuperscript{4}. They are also associated with processes like learning, memory, emotion, behavior, synaptic transmission, and neuroprotection\textsuperscript{5}. Because of these neuroprotective properties, steroid hormones may have a beneficial effect in neurodegenerative diseases, including Alzheimer’s disease, multiple sclerosis, Parkinson’s disease, and Huntington’s disease. However, steroid hormones are also implicated in psychiatric disorders, due to their role in cognition and behavior.

Steroid Hormones in Brain Disorders
Estrogens
Women have a higher prevalence of reduced cognitive function, depression, panic disorder, generalized anxiety disorder, social phobia, eating disorders, and some
personality traits than men. This difference in prevalence between sexes suggests that female sex steroid hormones may be involved in these conditions. This hypothesis is supported by the observation that several mental changes occur during the transition of women from pre- to post-menopause. These changes include reduced sexual drive, pre-menstrual and peri-menopausal dysphoria induced by oral contraceptives or hormone replacement therapy. These symptoms are associated with altered levels of circulating estrogens. At menopause, levels of circulating estrogens are strongly reduced. This reduction in estrogen levels is associated with social and psychological changes in women, like anxiety, irritability, stress, memory loss, lack of concentration, and loss of libido. Eventually, this may culminate into depression. The effects of estrogen changes are likely the result of an altered interaction of estrogens with other neurotransmitters like acetylcholine, dopamine, noradrenaline, and serotonin. Moreover, prolonged deficiency of estrogens increases the risk to develop dementia and Alzheimer’s disease.

Figure 1: Neurosteroidogenesis: Steroidogenesis follows a sequential, highly compartmentalised reaction, with the translocation of cholesterol from cytoplasm to mitochondria in the cells of CNS, which is mediated by Steroidogenic acute regulatory protein (STAR) and an 18 kDa Translocator protein (TSPO). In the mitochondria, P450 side chain cleavage (P450SCC) cleaves the side chain to form cholesterol, resulting in the formation of pregnenolone. Pregnenolone is subsequently converted to progesterone and dehydroepiandrosterone in endoplasmic reticulum. The lipophilic nature of these compound allows them to diffuse from one cell to another. Progesterone and dehydroepiandrosterone are further metabolized to form other neuroactive metabolite like testosterone, estrone, and estradiol.
As a consequence, maintenance of steady levels of estrogens seems essential for normal physiological and mental status. In fact, estrogen replacement therapy was found to improve learning, memory, and cognition in postmenopausal women\textsuperscript{14} and to prevent depression both in peri- and post-menopausal women\textsuperscript{15}. Furthermore, estrogen replacement therapy was also found to have a protective effect against neurodegenerative disorders. This protective effect was ascribed to the anti-inflammatory activity of estrogens\textsuperscript{16–18}. Neurosteroids produced by activated microglia are able to shift a pro-inflammatory immune response into an anti-inflammatory phenotype\textsuperscript{5}. The shift between pro- and anti-inflammatory effects of estrogens seems to be dependent upon both the expression level and the extent of stimulation of estrogen receptors (ER) in the CNS. It is also evident from recent literature that the anti-inflammatory effects are associated with suppression of ER-mediated pro-inflammatory cytokine and chemokine production\textsuperscript{19,20}.

**Progestins**

Progestins have been demonstrated to play an important role in neuroprotection as observed in experimental models and clinical trials in patients with stroke and traumatic brain injury\textsuperscript{21,22}. Progestins can easily pass through the blood-brain barrier and exert their neuroprotective effects inside the brain. A few studies were performed to assess the role of PR in experimental animal models of stroke and traumatic brain injury. Liu et al. found that ischemia to the brain for 6 h resulted in a rapid increase in the progesterone and 5α-dihydroprogesterone levels both in wild-type and PR knockout mice, suggesting a possible role of progestins in the salvage of neurons at risk\textsuperscript{23}. Changes in steroid hormone levels affected the expression of membrane PR, specifically PR\(_A\), in rats and mice. Upon treatment with estradiol or progesterone, significant expression of PR\(_A\) was observed in neurons of olfactory bulb, striatum, cortex, thalamus, hypothalamus, septum, hippocampus, and cerebellum, but not on oligodendrocytes or astrocytes. Traumatic brain injury induced the expression of PR\(_A\) not only on neurons but also on oligodendrocytes, astrocytes, and reactive microglia, suggesting a role of progestins and PR in inflammation in the injured brain\textsuperscript{24}.

The neuroprotective mechanisms and anti-inflammatory effects of progestins have been reviewed by several authors\textsuperscript{5,25–29}. Progestins may prevent brain damage by controlling edema formation (vasogenic or cytogenic) via modulation of the expression of the aquaporin-4 water transporter, moderating Ca\(^{2+}\) flux caused by excitotoxicity, and reconstitution of the blood-brain barrier. Progestins also have antioxidant properties that can prevent cellular insults by oxidative stress induced by free radical formation. Progestins can inhibit the activation of microglia, which prevents NO and TNF-α production and the release of other inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, compliment factor C\(_3\) and C\(_5\), and macrophage inducing factor-1. In addition, progestins have anti-apoptotic properties. Besides the aforementioned roles in neuroprotection, progestins also play a role in neuronal remodeling by up regulating several neurotrophic factors, such as brain derived...
neurotrophic factor (BDNF), Na/K ATPase, microtubule-associated protein 2 (MAP-2), choline acetyl transferase (ChAT), and glial-derived neurotrophic factor (GDNF).

To investigate progestin as neuro protectant in patients, a clinical trial (phase IIa) was conducted in 100 male and female patients with blunt head trauma with moderate- to-severe damage. Treatment with progesterone showed significant reduction in mortality compared to vehicle group30. Two large scale studies on progesterone treatment are now in process. A phase III clinical trial investigates the effects in moderate-to-severe traumatic brain injury in 1,200 patients. Another phase III trial studies the effect on brain injury in pediatric patients21. Administration of progestins in combination with estrogens was found to be an effective treatment for postmenopausal symptoms. The combination of progestins and estrogens showed efficacy in the treatment of multiple sclerosis in both animal models and in patients. The beneficial effect was mediated by modulation of peripheral and brain-intrinsic immune responses and regulation of local growth factor supply, oligodendrocytes, and astrocytes31.

**Androgens**

The most common central effect of androgens is the induction of aggression. Excessive levels of testosterone are known to induce aggression in both sexes. Exposure to high testosterone levels at young age is associated with a reduction in feminine characteristics in women. Moreover, testosterone is converted to estradiol in the CNS, which plays a pivotal role in the feedback regulation in the hypothalamus. The hypothalamus plays a positive role in hormone release by endocrine system through the pituitary. In analogy to menopause in women, aging men may experience andropause (hypogonadism), which is a condition characterized by very low circulating androgen concentrations. This reduction in androgen levels may be accompanied by decreased cell survival in the hippocampus32 and a decrease in cognitive functions and increased risk to develop depression and Alzheimer’s disease33. Testosterone treatment was found to reduce many mood- and cognition-related symptoms in hypogonadal men34 and to enhance hippocampal neurogenesis through increased cell survival in rodents32. Androgen treatment combined with estrogens in postmenopausal women provides more improvement in psychologic and sexual symptoms than does estrogen alone35.

**Corticosteroids**

Corticosteroids, such as glucocorticoids and mineralocorticoids, are produced by the adrenal glands, liver, and during pregnancy by placenta and maternal glands. In stressful conditions, the glucocorticoid, cortisol, is rapidly synthesized and secreted in response to adrenocorticotropic hormone released from the pituitary and corticotrophin- releasing hormone secreted by the hypothalamus. Cortisol stimulates the production of energy-rich compounds such as glucose, free fatty acids, and amino acids. The mineralocorticoid aldosterone is produced in response to angiotensin II and promotes sodium reabsorption and fluid retention. Besides their role in glucose
and mineral metabolism, corticosteroids are also implicated in the regulation of sleep, ingestive behavior, behavioral adaptation, learning, and memory. In addition, corticosteroid receptors play a significant role in brain damage, aging\textsuperscript{36}, mood, mental performance, and the pathogenesis of neuropsychiatric disorders, such as depression and Alzheimer’s disease\textsuperscript{37,38}. Both cortisol and aldosterone release are controlled by the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is a neuroendocrine system that has complex interactions with brain serotonergic, noradrenergic, and dopaminergic systems. An important role of the HPA axis is the regulation of the body’s response to stress. Overactivity of the HPA axis or enlargement of the pituitary or adrenal gland causes an increase in cortisol levels, which in turn leads to hypercortisolemia. The overactivity of the HPA axis in stressful conditions may lead to dysregulation of the serotonergic system and is one of the most important predictors of suicide attempts in depressed patients\textsuperscript{39}. Depression, on the other hand, is one of the major causes of hypercortisolemia, characterized by increased cortisol levels. Hypercortisolemia may lead to neurotoxicity and reduced neurogenesis in the hippocampus in depressed patients\textsuperscript{40}.

**Steroid Hormone Receptors in Brain Disorders**

Steroid hormones exert their biological effects through specific steroid hormone receptors (SHR) that are expressed by the target cells. To date, two estrogen receptor subtypes (ER\textsubscript{α} and ER\textsubscript{β}) with several isoforms\textsuperscript{41–44}, two progesterone receptors (PR) subtypes (PR\textsubscript{A} and PR\textsubscript{B}) with several splice variants\textsuperscript{45,46}, and two types of androgen receptor (AR) subtypes have been identified\textsuperscript{47,48} (AR\textsubscript{α} and AR\textsubscript{β}). The corticosteroid receptors may be divided into two classes: mineralocorticoid receptors\textsuperscript{49} (MR) and glucocorticoid receptors\textsuperscript{50} (GR). All SHR share similar functional domains but differ in the length of the amino acid chain (Figure 2).

In steroid-responsive cells, SHR are mainly present in the cytoplasm and the nucleus, although SHR are also found on the cell membrane\textsuperscript{51,52}. When SHR are activated by the corresponding steroid hormone, they dimerize and move into the nucleus of the cell, where they bind to hormone responsive element in the promoter region of specific target genes. SHR may act as transcriptional activators or transcriptional repressors, resulting in the induction or suppression of the expression of hormone-responsive genes. These responsive genes may evoke a wide variety of physiological responses. Some rapid actions of estrogens and progestins are directly mediated by cell surface receptors in a non-genomic manner (Figure 3). Although the involvement of steroid hormones in various brain disorders has been demonstrated, the mechanisms with which they exert their effects are still largely unknown.
Western blotting and immunohistochemical studies in experimental animals and postmortem human brains have shown that receptors for different steroid hormones are expressed in different regions of the brain. ER, PR, and AR are expressed in those brain areas that are associated with emotion, cognition, and behavior, such as the hypothalamus, amygdala, cerebral cortex, hippocampus, and brainstem. This expression pattern is in agreement with the association of sex hormones with psychiatric disorders. The neuroprotective effects of estrogens are mainly due to ER α-mediated signaling, whereas the effect on mood and cognitive functions in depression and schizophrenia is mainly mediated by ERβ. A study on patients with depression or schizophrenia, who committed suicide, showed down regulation of ERβ expression in the limbic system. To our knowledge, no data exist on altered expression of PR and AR in the human brain in mood and behavioral disorders.

Not only SHR expression, but also polymorphisms in the SHR genes were found to be implicated in psychiatric diseases. SHR polymorphisms have been associated with an increased risk for schizophrenia, depression, anxiety traits, and cognitive impairment. Association of polymorphisms in estrogen and androgen receptors associated with psychiatric disorders has been reviewed recently by Westberg and Eriksson.

Corticosteroids affect behavioral changes by engaging with either MR or GR. MR are mainly expressed in the limbic system, hypothalamus, and circumventricular organs and to lesser extent in other parts of the brain. The expression of GR, on the other hand, is mainly observed in the subfields of the cerebral cortex, olfactory cortex, hippocampus, amygdala, dorsal thalamus, hypothalamus, cerebellar cortex, trapezoid body, locus coeruleus, and dorsal raphe nucleus in rats.
Figure 3: Mode of action of steroid hormone receptors. All the steroid hormone receptors mediate their action by a common genomic pathway. In the cytoplasm, they exist as complexes with heat shock proteins in an inactive form. When a steroid hormone binds, the receptor complex releases the heat shock proteins and becomes activated. The activated receptor forms a homodimer or heterodimer, which subsequently enters into the nucleus. The dimer binds to the specific hormone response element in DNA and initiates or inhibits the process of gene transcription.

Both the corticosteroid receptors are co-expressed in the hippocampus, amygdala, inferior frontal gyrus, cingulate gyrus, and nucleus accumbens in human brain, whereas predominantly MR were found in the hippocampus. A reduction in both MR and GR expression and an increase in corticosteroid levels were observed in the brains of patients with bipolar disorder or schizophrenia who committed suicide and in subjects exposed to stressful conditions. Furthermore, decreased MR expression in the hippocampus of suicide victims was observed in another study. Decreased MR expression was also demonstrated in depressed subjects after treatment with the MR antagonist, spironolactone. Spironolactone treatment led to an increase in cortisol levels in both controls and depressed patients. However, in depressed patients, cortisol levels were significantly higher than in controls.

Increased production of the cortisol also causes desensitization of the GR, resulting in a down regulation of these receptors. Down regulation of GR in turn leads to an increase in the levels of cortisol. Prolonged stress has been reported to down regulate the expression of GR in the prefrontal cortex in rats. Likewise, stress...
leads to a reduction in the GR mRNA in the basolateral/lateral nuclei in patients with schizophrenia or bipolar disorder\textsuperscript{64,65}.

**Imaging of Steroid Hormone Receptors**

Hitherto, almost all information about the role of SHR in healthy and diseased brain is obtained from experimental animals and postmortem human studies, because brain biopsy in patients is generally not feasible or highly undesirable. To better understand the role of steroid hormones in neurodegenerative and psychiatric diseases, it is therefore of invaluable importance to have a noninvasive tool to measure the expression of SHR in the brain. PET and SPECT are noninvasive nuclear imaging techniques that allow measurement of receptor expression and receptor occupancy in the living brain. Until now, several PET and SPECT tracers have been developed to image the SHR. Most of these radiopharmaceuticals, however, were developed for applications in oncology, in particular for imaging of receptor expression and occupancy in steroid hormone-sensitive tumors like breast and prostate cancer\textsuperscript{66,67}. So far, only a few studies on imaging of SHR in the brain have been reported. However, it is expected that most radiopharmaceuticals that have been developed for tumor imaging may also be applied in brain imaging. Although many tracers have been described for each SHR, most of these tracers did not provide satisfactory results and consequently did not enter clinical studies. In the following paragraphs, we will not provide a complete overview of all tracers for SHR that have been reported, but only discuss the most promising candidate tracers for PET and SPECT imaging of SHR in the brain.

**Radiopharmaceuticals for Estrogen Receptor Imaging**

ER is the most widely studied SHR. Although literature exists on Western blotting and in situ hybridization studies to determine the expression of the ER in the rodent brain, hardly any data exists on ER expression in the human brain. For this purpose, imaging methods to measure ER expression could certainly be of added value. Several tracers have been developed for PET and SPECT imaging of ER, in particular for imaging breast cancer.

**PET**

16α-[\textsuperscript{18}F]fluoro-17β-estradiol ([\textsuperscript{18}F]FES) was introduced for imaging of ER in the 1980 and is now used in both clinical trials and in patient care for diagnosis and monitoring of anticancer treatment efficacy in ER-positive breast cancer. In rats and mice, highest [\textsuperscript{18}F]FES uptake was observed in tissues with high ER expression, such as the uterus and ovaries\textsuperscript{68–72}. [\textsuperscript{18}F]FES uptake in ER-rich organs could be blocked with unlabeled estradiol in a dose-dependent manner, indicating that the tracer uptake is ER-mediated\textsuperscript{73}. A recent study demonstrated that treatment with fulvestrant, an irreversible ER antagonist, also reduced the uptake of [\textsuperscript{18}F]FES in ER-positive breast tumors in mice\textsuperscript{74}. PET imaging studies in rodents showed a good correlation of [\textsuperscript{18}F]FES tumor uptake with ER density, as determined in vitro\textsuperscript{68}. In
breast cancer patients, [18F]FES PET has been applied successfully to determine the ER status of tumor lesions. ER expression was clearly visualized in primary breast tumors and in metastases. The accumulation of [18F]FES in these tumors correlated well with ER density, as determined by immunohistochemistry. The radiation burden associated with [18F]FES PET is within the normal range of other clinical nuclear medicine procedures: a typical dose of 200 MBq (6 mCi) causes a radiation burden to the patient of 4.4 mSv. [18F]FES preferentially binds to the α subtype of the ER, as its affinity is 6.3-fold higher for ERα than for ERβ. ERα is overexpressed in many breast tumors, where it is associated with tumor growth and development. The ERβ isoform was found to be co-expressed with ERα in breast tumors, but the function of ERβ in breast cancer is not well understood yet. The discovery of ERβ in breast cancer initiated the search for ER β-selective PET tracers. Several attempts have been made to develop ERβ-selective tracers. Recently, 8β-[18F]fluoroethyl estradiol (8β-[18F] FEE), a derivative of the potent ERβ-selective steroid 8β-vinylestradiol, was evaluated as a selective PET tracer for ERβ. In addition, the nonsteroidal ERβ ligand ERB-041 was labeled with 76Br, yielding [76Br]BrERB-041 as a potential ERβ-selective PET tracer. Although both 8β-[18F]FEE and [76Br]BrERB-041 showed high binding affinities in a radiometric assay, ex vivo biodistribution studies in rats and mice could not demonstrate ER β-mediated uptake. So far, no suitable PET tracer of imaging of ERβ is available.

Besides [18F]FES, several radiolabeled estradiol derivatives and ER-targeting anticancer drugs have been evaluated as candidate PET tracers for imaging ER density and occupancy (Figure 4). The potent estrogen 17α-ethynyl-11βmethoxy-estradiol ([18F]βFMOX) showed promising results in rodents with a fourfold higher uptake in immature rat uterus than [18F]FES. [18F]βFMOX was considered to be a highly sensitive tracer for imaging of the ER, as [18F]βFMOX also exhibited specific binding in organs with low ER density, such as the kidney, muscle, and thymus. Despite the promising results in rodents, [18F]βFMOX PET studies failed to detect ER-positive lesions in human breast cancer patients. This lack of sensitivity in humans may be due to the fast metabolism of the tracer, because it exhibited low binding to sex hormone-binding protein (SHBG), which protects steroids from metabolic degradation. Other ethynl analogues of FES also showed better target-to-background ratios but were also associated with faster degradation in vivo, because of low SHBG binding.

In order to increase the binding affinity and in vivo stability of the tracer, several analogues of [18F]FES were developed. One of these candidates, 11β-methoxy-4,16α-[18F]difluoroestradiol (4F-M-[18F]FES), showed high uptake and high target-to-background ratios in ER-rich organs like the uterus. 4F-M-[18F]FES has a low affinity towards the SHBG, but studies in humans showed a significant, potentially ER-mediated uterus uptake in both pre- and post-menopausal women. However, no other human studies with 4F-M-[18F]FES have been published since.

In addition to estradiol derivatives, radiolabeled derivatives of anticancer drugs, such as tamoxifen and fulvestrant, were evaluated for imaging of ER. Tamoxifen is a partial agonist of the ER and used as a drug in the treatment of ER-
positive breast cancer. $^{18}$F-labeled tamoxifen, $[^{18}\text{F}]	ext{fluoromethyl-N,N-dimethyltamoxifen} ([^{18}\text{F}]\text{FTX})$, exhibited specific uptake in the uterus and mammary tumors, which could be blocked with an excess of estradiol$^{89}$. In a clinical study in 10 ER-positive breast cancer patients, $[^{18}\text{F}]\text{FTX}$ uptake appeared to correlate with tamoxifen treatment outcome$^{90}$. So far, no additional studies have been performed to prove the clinical utility of $[^{18}\text{F}]\text{FTX}$. Labeling of fulvestrant, a full antagonist of the ER, with $^{18}$F reduced its binding affinity. Consequently, $^{18}$F-labeled fulvestrant is not suitable for PET imaging of ER$^{91}$.

**Figure 4:** Chemical structures of tracers that have been evaluated for PET or SPECT imaging of estrogen receptors.

**SPECT**

In addition to PET tracers, some SPECT tracers were developed for imaging of ER (Figure 4). Amongst the promising SPECT tracers for ER was $16\alpha-[^{125}\text{I}]\text{iodo-11β-}
PET and SPECT of Steroid Hormone Receptors

methoxy-17β-estradiol\(^{92}\) ([\(^{125}\)I]MIE). In rodents, [\(^{125}\)I]MIE was found to accumulate in ER-rich areas, such as the uterus. [\(^{125}\)I]MIE showed higher uterus-to-blood ratios than 16α-[^123]I]iodeoestradiol. 16α-[\(^{123}\)I]iodo-17β-estradiol ([\(^{123}\)I]IES) and (20Z)-11β-methoxy-17α-[\(^{123}\)I]iodovinylestradiol (Z-[\(^{123}\)I]MIVE) have not only been applied in animals but also in clinical studies. [\(^{123}\)I]IES showed ER-mediated uptake in the rabbit reproductive system and in ER-positive tumors in breast cancer patients, but no specificity or sensitivity data were reported\(^{93–96}\). Both stereoisomers of [\(^{123}\)I]MIVE were evaluated for ER imaging. (Z)-[\(^{123}\)I]MIVE showed highest ER-mediated specific uptake in rodents and in clinical studies in breast cancer patients. The tracer uptake could be blocked by saturation of the ER with tamoxifen\(^{97–100}\). Although both [\(^{123}\)I]IES and (Z)-[\(^{123}\)I]MIVE showed ER-mediated specific uptake, these tracers also displayed fast metabolism and low SHBG binding\(^{101,102}\). For both tracers, no further studies are available to support their utility for brain imaging.

Attempts have been made to generate a SPECT tracer for ER by labeling derivatives of the anticancer drug tamoxifen. In rodents, the uptake of [\(^{123}\)I]iodotamoxifen ([\(^{123}\)I]TAM) was found to be high in ER-rich organs. In clinical studies, [\(^{123}\)I]TAM showed ER-specific uptake in breast tumors\(^{103,104}\). Recently tamoxifen was also labeled with \(^{131}\)I ([\(^{131}\)I]TAM). Biodistribution studies in rodents proved that the uptake of this tracer was ER-mediated in the uterus and breast tissue\(^{105}\). No further studies on iodine-labeled tamoxifen have been published lately. Estradiol and anticancer drug derivatives have also been labeled with \(^{99m}\)Tc. A few of them have even been successfully evaluated in rodents\(^{106–112}\). However, the usefulness of these tracers for brain imaging would be questionable, because of the high hydrophilicity of the \(^{99m}\)Tc conjugates, which likely precludes efficient brain penetration.

Consequently, at this moment [\(^{18}\)F]FES remains the only validated tracer for molecular imaging of ER expression that is currently used in clinical studies. Even though its characteristics are not ideal, [\(^{18}\)F]FES still is an adequate tracer for PET imaging of ER in humans\(^{113}\). Efforts to develop better alternatives for [\(^{18}\)F]FES are still made but yielded disappointing results so far.

Radiopharmaceuticals for Progesterone Receptor Imaging

PET

A few substrates of PR have been labeled with \(^{18}\)F, \(^{76}\)Br, \(^{123}\)I, and \(^{125}\)I for imaging of PR with PET and SPECT (Figure 5). The 18 F-labeled candidate PET tracers for PR include 21-[\(^{18}\)F]fluoro-16a-ethyl-19-norprogesterone\(^{114–117}\) ([\(^{18}\)F]FENP, 21-[\(^{18}\)F]fluoro-16a-methyl-19-norprogesterone\(^{118}\) ([\(^{18}\)F]FMNP), and 21-[\(^{18}\)F]fluoro-16α,7α-[(R)-(1′α-furylethylidene)dioxyl]-19-norpregn-4-ene-3,20-dione\(^{119}\).

[\(^{18}\)F]FMNP exhibited PR-mediated uptake in the uterus and tumors in rats\(^{118}\), but no further studies in humans were reported. [\(^{18}\)F]FENP showed highly selective PR-mediated uptake in the uterus of estrogen-primed rats\(^{116}\) and in PR-positive carcinoma in mice\(^{117}\). In eight breast cancer patients, however, [\(^{18}\)F]FENP could only detect 50 % of PR-positive lesions, and tracer uptake did not correlate with PR
expression\textsuperscript{14}. The major reason for failure of $[^{18}\text{F}]$FENP in clinical studies was its extensive metabolism in humans\textsuperscript{120}. To overcome this problem, several ketals of 16α,17α-dihydroxyprogesterone were labeled with positron-emitting isotopes\textsuperscript{119,121,122}. One of these ketals is 21-$[^{18}\text{F}]$fluoro-16α,17α-[(R)-(\textempty AUTHORITY)\textempty AUTHORITY]-19-norpregn-4-ene-3,20-dione ($[^{18}\text{F}]$FFNP). In a study performed in mice with mammary tumors, treatment with estradiol, letrozole, or fulvestrant showed treatment-induced changes in the uptake of $[^{18}\text{F}]$FFNP, suggesting that early evaluation of response to the anticancer treatment could be feasible\textsuperscript{74}. Recently, a study in breast cancer patients showed that $[^{18}\text{F}]$FFNP PET is a safe, noninvasive method to evaluate the tumor’s PR status in vivo\textsuperscript{123}. Brain uptake of $[^{18}\text{F}]$FFNP seems to be acceptable, but further studies are needed to prove its suitability for brain imaging.

Another series of candidate PET tracers for PR imaging were the derivatives of the nonsteroidal PR agonist tanaproget. Several derivatives of tanaproget were evaluated\textsuperscript{124}, and 4-$[^{18}\text{F}]$fluoropropyl-tanaprog et ($[^{18}\text{F}]$FPTP) demonstrated highest uptake in the target tissues like uterus and ovaries. The biodistribution pattern of $[^{18}\text{F}]$FPTP in rats was comparable with other PR tracers, such as FENP and FFNP\textsuperscript{125}.

SPECT
A few iodinated tracers for PR imaging have been developed, but none of these candidate tracers showed promising results. (20Z)-17α-$[^{125}\text{I}]$iodovinyl-19-nortestosterone ($[^{125}\text{I}]$IVNT) had interesting binding properties but lacked selectivity in vivo\textsuperscript{126}. Later, both isomers of 17α-iodovinyl-18-methyl-11-methylene-19-nortestosterone ($[^{125}\text{I}]$IVMMNT) were investigated in rats and rabbits. (Z)-$[^{125}\text{I}]$IVMMNT displayed highest in vivo binding in target organs, such as in uterus and ovaries. The uptake of (Z)-$[^{125}\text{I}]$IVMMNT was found to be PR-mediated\textsuperscript{127}. So far, no human data exist to prove the feasibility of PR imaging with these tracers.

At the moment, $[^{18}\text{F}]$FFNP seems to be the most promising candidate tracer for imaging PR, but more studies are required to validate the utility of this tracer in humans.

Radiopharmaceuticals for Androgen Receptor Imaging
PET
The existing PET tracers for imaging AR expression are depicted in Figure 6. 20-$[^{18}\text{F}]$fluoromibolerone (20-$[^{18}\text{F}]$Fmib) was the first radiolabeled PET tracer for AR that showed promising uptake in the prostate of diethylstilbestrol (DES)-primed rats\textsuperscript{128}. Several other fluorinated compounds have been developed, and some of them showed promising results, such as 16β-$[^{18}\text{F}]$fluorodihydrotestosterone ($[^{18}\text{F}]$FDHT), 16β-$[^{18}\text{F}]$fluorotestosterone (16β-$[^{18}\text{F}]$FT), 16β-$[^{18}\text{F}]$fluoro-7α-methyl-19-nortestosterone (16β-$[^{18}\text{F}]$FMNT), 16α-$[^{18}\text{F}]$fluoro-7α-methyl-19-nortestosterone (16α-$[^{18}\text{F}]$FMNT), and 20-$[^{18}\text{F}]$fluormetribolone\textsuperscript{129} (20-$[^{18}\text{F}]$R1881). Most of these tracers showed quick clearance from the body and rapid metabolism. Best results in baboons and rats were obtained for $[^{18}\text{F}]$FDHT. Uptake of $[^{18}\text{F}]$FDHT in the prostate
was specific and AR-mediated. Metabolism of $[^{18}F]$FDHT was slower than metabolism of the other candidate tracers\textsuperscript{130,131}. $[^{18}F]$FDHT was able to detect AR-positive tumor lesions in prostate cancer patients, and tracer uptake was proven to be AR-mediated in humans as well\textsuperscript{132,133}. Another interesting candidate PET tracer is 7α-$[^{18}F]$fluoro-17- methyl-5-dihydrotestosterone ($[^{18}F]$FMDHT), although the first results reported for this tracer were not very promising. The uptake of $[^{18}F]$FMDHT in the prostate was low; results were not reproducible and not comparable with other labeled steroids like $[^{18}F]$FDHT. In these first experiments, $[^{18}F]$FMDHT was investigated in rats treated with DES to suppress endogenous testosterone production\textsuperscript{134}. The same authors reevaluated the suitability of $[^{18}F]$FMDHT for AR imaging in chemically castrated rats. In this animal model, uptake in the prostate was proven to be AR-mediated. Prostate uptake was comparable to other $^{18}$F-labeled steroids and twofold higher than $[^{18}F]$FMDHT uptake in DES-treated rats\textsuperscript{135}.

![Chemical structures of tracers](image)

\textbf{Figure 5:} Chemical structures of tracers that have been evaluated for PET or SPECT imaging of progesterone receptors.

Currently, $[^{18}F]$FDHT is the only PET tracer that has proceeded into the clinical evaluation phase\textsuperscript{132,133,136,137}. The radiation burden associated with $[^{18}F]$FDHT PET is
within the normal range of other clinical nuclear medicine procedures: 0.018 mSv/MBq; for the maximum administered dose of 331 MBq, the total radiation burden is 6.0 mSv. The major drawback of \[^{18}\text{F}]\text{FDHT}\) is its rapid metabolism. This led to the investigation of nonsteroidal derivatives with better in vivo stability, like propanamide derivatives a selective androgen receptor modulator\(^{138}\) (SARM) with \(^{11}\text{C}\).

Some nonsteroidal antagonists of AR have been radiolabeled, such as a \(^{11}\text{C}\)-labeled diethylamineflutamide derivative\(^{139}\), a \(^{18}\text{F}\)-labeled hydroxyflutamide derivative\(^{140}\), 3-\(^{76}\text{Br}\)bromohydroxyflutamide\(^{141}\), \(^{18}\text{F}\)bicalutamide, 4-\(^{76}\text{Br}\)bromobicalutamide, and \(^{76}\text{Br}\)bromo-thiobicalutamide\(^{142}\). However, none of these compounds showed promising results that warranted further evaluation.

\[\text{C}_6\text{H}_3\text{O} + \text{C}_3\text{H}_3\text{OH} \rightarrow \text{R}_{1}\text{R}_{2}\] 20-\[^{18}\text{F}]\text{FMib}: R_1 = \text{CH}_2\text{F}, R_2 = \text{H}

16-\[^{18}\text{F}]\text{FMib}: R_1 = \text{CH}_3, R_2 = \text{F}

16-\[^{18}\text{F}]\text{FMNT}: R_1 = \text{H}, R_2 = \text{F}

\[\text{C}_6\text{H}_3\text{O} + \text{C}_3\text{H}_3\text{OH} \rightarrow \text{R}_{1}\text{R}_{2}\] 16j-\[^{18}\text{F}]\text{FT}

\[\text{C}_6\text{H}_3\text{O} + \text{C}_3\text{H}_3\text{OH} \rightarrow \text{R}_{1}\text{R}_{2}\] \[^{18}\text{F}\]\text{R1881}

\[\text{C}_6\text{H}_3\text{O} + \text{C}_3\text{H}_3\text{OH} \rightarrow \text{R}_{1}\text{R}_{2}\] \[^{18}\text{F}\]\text{FDHT}

\[\text{C}_6\text{H}_3\text{O} + \text{C}_3\text{H}_3\text{OH} \rightarrow \text{R}_{1}\text{R}_{2}\] \[^{18}\text{F}\]\text{FMDHT}

**Figure 6:** Chemical structures of tracers that have been evaluated for PET or SPECT imaging of androgen receptors.

**SPECT**

The radio iodinated steroid 2α-[\(^{125}\text{I}\)]dihydrotestosterone was the first SPECT tracer showing high uptake in AR-rich organs like the prostate, epididymis, and testis in
rats. Pretreatment with dihydrotestosterone reduced the uptake in these organs, suggesting that tracer uptake is specific and AR-mediated\textsuperscript{[43]}. 7α-[\textsuperscript{125}I]iodo-5a-dihydrotestosterone (7α-[\textsuperscript{125}I]IDHT) is another analogue of testosterone that was labeled with \textsuperscript{125}I. 7α-[\textsuperscript{125}I]IDHT showed AR-mediated uptake in the prostate of rats. In vitro autoradiography of 7α-[\textsuperscript{125}I]IDHT produced excellent autoradiograms with low nonspecific binding in the prostate of rats\textsuperscript{[44]}, but no further studies were published to demonstrate the use of this tracer in vivo.

Some steroid and flutamide derivatives have been labeled with \textsuperscript{99m}Tc and tested as SPECT tracers for AR. However, in vivo evaluation in rats did not show any AR-mediated specific binding for any of these compounds\textsuperscript{[45,46]}. So far, \textsuperscript{[18}F\textsuperscript{]}FDHT is the only AR tracer that has proceeded into the clinical evaluation phase. Clinical studies confirmed that this tracer is suitable for AR imaging in cancer patients. However, it still remains to be evaluated whether \textsuperscript{[18}F\textsuperscript{]}FDHT PET is also able to monitor AR expression in the human brain. Preclinical data of \textsuperscript{[18}F\textsuperscript{]}FMDHT suggest that it might have favorable characteristics for AR imaging as well, but further evaluation is still required to establish the merit of this tracer.

### Radiopharmaceuticals for Corticoid Receptor Imaging

So far, only a few GR ligands have been synthesized and evaluated for the potential use as imaging tracer (Figure 7). Most of these candidate tracers showed disappointing results in rodents and baboons. The first labeled compound that was introduced as ligand for the imaging of GR was 21-[\textsuperscript{18}F]fluoroprednisone. 21-\textsuperscript{[18}F\textsuperscript{]}fluoroprednisone was rapidly metabolized, leading to low uptake in rat brain\textsuperscript{[47]}. The biodistribution of \textsuperscript{[18}F\textsuperscript{]}RU 52461, an analogue of the selective GR agonist RU28362, showed high GR-mediated uptake in the adrenals and pituitary in rats. PET imaging studies in baboons, however, showed low uptake of \textsuperscript{[18}F\textsuperscript{]}RU 52461 in the brain\textsuperscript{[48]}. In another study in rats, \textsuperscript{[18}F\textsuperscript{]}RU 52461 uptake in the hippocampus could only be partially blocked with an excess of the unlabeled ligand, whereas complete blocking of tracer uptake in peripheral organs was observed\textsuperscript{[49]}. The potent GR ligand \textsuperscript{[18}F\textsuperscript{]}ORG 6141 was evaluated in adrenalectomized and sham-operated rats. Ex vivo biodistribution 3 h post-injection revealed higher uptake of tracer in the hippocampus and brain stem of adrenalectomized animals as compared to sham-operated controls. However, GR-mediated specific retention of activity in these brain areas could not be demonstrated\textsuperscript{[50]}. Wuest et al. synthesized a series of novel 4-fluorophenylpyrazolo steroids and tested their binding affinities to GR. Some of these compounds showed binding affinities up to 56 % relative to dexamethasone\textsuperscript{[51]} (100 %). One of these compounds, 2′-(4-fluorophenyl)-21-[\textsuperscript{18}F]fluoro-20-oxo-11β,17α,21-trihydroxy-pregn-4-eno[3,2-c]pyrazole, was evaluated in autoradiography and small animal PET imaging. Brain uptake of this tracer was found to be constant between 5 and 60 min after tracer injection. However, brain uptake was not specifically GR-mediated\textsuperscript{[52]}, but only due to nonspecific binding.
The high-affinity GR antagonist Org 34850 was labeled with $^{11}$C. $[^{11}\text{C}]$Org 34850 was found to rapidly metabolize in rats. Ex vivo biodistribution and small animal PET studies demonstrated that $[^{11}\text{C}]$Org 34850 was not able to penetrate the blood-brain barrier\textsuperscript{153}.

The nonsteroidal selective GR modulator AL-438 was labeled with $^{11}$C. The biodistribution of $[^{11}\text{C}]$AL-438 showed high uptake in the pituitary and the brain, but treatment with a high dose of the GR antagonist corticosterone did not result in any blocking of tracer uptake, suggesting that the uptake was not GR-mediated\textsuperscript{154}.

Thus, none of the aforementioned studies were successful, and consequently suitable tracers for imaging GR expression are currently not available.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chemical_structures.png}
\caption{Chemical structures of tracers that have been evaluated for PET or SPECT imaging of glucocorticoid receptors.}
\end{figure}
Radiopharmaceuticals for Mineralocorticoid Receptor Imaging

There is only one report that describes a series of MR-specific compounds that have been labeled with fluorine-18 for PET imaging. These compounds include 21-[¹⁸F]fluoroprogesterone, 21-[¹⁸F]fluoro-11β-hydroxyprogesterone, and 3’-fluoro-RU26752 (Figure 8). Unfortunately, none of these compounds displayed the characteristics that are required for PET imaging of MR.

![Figure 8: Chemical structures of tracers that have been evaluated for PET imaging of mineralocorticoid receptors.](image)

**Imaging of Steroid Hormone Receptors in the Brain**

Despite several tracers for imaging of SHR have now been applied in humans, hardly any studies on imaging of these receptors in the brain have been published. So far, only tracers for ER have been successfully used in rodents for imaging SHR in the brain. 16α-[¹²⁵I]iodoestradiol and 11β-methoxy-16α-[¹²⁵I]iodoestradiol ([¹²⁵I]MIE₂) have only been used in autoradiography studies, whereas [¹⁸F]FES has also been used for ex vivo biodistribution and PET imaging of the rat brain.

An ex vivo brain autoradiography study in prepubertal Sprague Dawley rats injected with 16α-[¹²⁵I]iodoestradiol showed high concentrations of activity at the marginal zone of the mid-region anterior lobe of the pituitary at 1 h post tracer injection, whereas the intermediate lobe and most cells in the anterior lobe showed only a weak signal. Also the dorsocaudal paraventricular nucleus and the medial amygdaloid region showed only a weak signal, whereas a high signal was observed in preoptic neurons. Long-term exposure of the photographic plate allowed topographical recognition of tracer binding to cells in medial amygdala, mediodorsal and cortical nuclei, and the piriform cortex. However, 16α-[¹²⁵I]iodoestradiol uptake in the brain was not significantly blocked by an excess of unlabeled estradiol, which was ascribed to de-iodination of the tracer, leading to nonspecific binding of ¹²⁵I within the myelin sheaths.

11β-methoxy-16α-[¹²⁵I]iodoestradiol ([¹²⁵I]MIE₂) has been evaluated in binding and displacement studies in rat, rabbit, and human brain slices. [¹²⁵I]MIE₂ showed specific binding to the ER with no cross-reactivity with the other SHR. Moreover, a dose-dependent uptake of [¹²⁵I]MIE₂ in pituitary and brain cell nuclei was observed after in vivo administration in 25-day-old female rats. In another
study, ER expression during the brain development was studied with $[^{125}\text{I}]\text{MIE}_2$ in mice of both sexes. This study demonstrated the presence of ER-positive cells in the early postnatal cortex and showed a profound change in the topography and number of ER-positive cells during development\textsuperscript{157}. Recently, the effect of long-term treatment (21–60 days) with estradiol and tamoxifen on ER occupancy in the brain was evaluated by ex vivo autoradiography with $[^{125}\text{I}]\text{MIE}_2$. The distribution of $[^{125}\text{I}]\text{MIE}_2$ uptake was in agreement with the expected ER distribution in the ovariectomized rats: highest uptake in the preoptic and hypothalamic nuclei, followed by the amygdala, hippocampus, midbrain, and frontal cortex. In the tamoxifen-treated rats, a reduction in $[^{125}\text{I}]\text{MIE}_2$ binding was mainly seen in ERα-dominated regions like the cortical amygdala, central gray, and anterior paraventricular thalamus. A moderate inhibition of tracer uptake was found in the regions where both ER subtypes are expressed, like the ventrolateral-ventromedial hypothalamus, medial preoptic area, medial amygdala, and arcuate nucleus. After estradiol treatment, $[^{125}\text{I}]\text{MIE}_2$ showed a low and homogenous uptake in the brain, with an overall reduction in ER binding of 87% as compared to untreated controls\textsuperscript{158}.

Fluoroestradiol ($[^{18}\text{F}]\text{FES}$) is the only PET tracer that has been used to assess ER expression in rat brain. In a very detailed study, the suitability of $[^{18}\text{F}]\text{FES}$ for in vivo quantification of ER was performed by both equilibrium and dynamic kinetic analysis\textsuperscript{159}. The uptake of $[^{18}\text{F}]\text{FES}$ was mainly seen in ER-rich regions in the brain, such as in the pituitary and hypothalamus. Maximum uptake was observed between 25 and 30 min post-injection reaching a pseudo-equilibrium at 30 min. Blocking with increasing doses of unlabeled estradiol reduced the accumulation in the pituitary and hypothalamus in a dose-dependent manner, whereas no effect was observed in the hippocampus, cortex, and striatum. The specific binding of $[^{18}\text{F}]\text{FES}$ was calculated by equilibrium analysis considering the striatum as a reference tissue where the expression of the ER was expected to be very low. The equilibrium analysis showed saturable binding in the pituitary and hypothalamus with highest binding potential ($B_{\text{max}}/K_d$) in the pituitary (16.11) and hypothalamus (1.97). The $B_{\text{max}}$ and the $K_d$ were found to be much higher in pituitary (124.01 ± 12.36 pmol/g and 7.70 ± 1.07) then in hypothalamus (11.85 ± 0.16 pmol/g and 6.01 ± 0.41). The in vivo quantification of ER gave similar results in the pituitary and hypothalamus when either equilibrium or graphical analysis was used\textsuperscript{159}. In another study, the effect of long-term treatment of estradiol and tamoxifen on ER occupancy in rat brain was studied by ex vivo autoradiography with $[^{18}\text{F}]\text{FES}$. Although this study showed marked reduction in the uptake of $[^{18}\text{F}]\text{FES}$ in ER-rich areas, such as the hypothalamus, preoptic area, amygdala, and frontal cortex in the treatment groups, no differences in cerebellar uptake was observed\textsuperscript{158}.

All the aforementioned studies were performed by ex vivo measurement of tracer uptake, without the use of in vivo imaging. We recently studied the feasibility of $[^{18}\text{F}]\text{FES}$ to monitor ER in the rat brain by small animal PET. The brain time activity curves of $[^{18}\text{F}]\text{FES}$ showed a quick peak uptake immediately after intravenous tracer injection, which was followed by a washout leading to a state of pseudoequilibrium after 25 min. Highest uptake was seen in the pituitary gland,
followed by the hypothalamus. All other areas of the brain showed low uptake. Blocking of the receptor with an excess of estradiol resulted in a statistically significant reduction in tracer uptake only in the pituitary gland (90%, \( p<0.001 \)) and hypothalamus (70%, \( p<0.001 \)). A statistically significant higher volume of distribution and binding potential was found in the pituitary, when compared to other brain regions. \([^{18}\text{F}]\text{FES}\) uptake was not significantly affected by differences in plasma estrogen levels.

So far, \([^{18}\text{F}]\text{FES}\) is the only tracer that was tested for in vivo visualization of ER in the brain of rats. \([^{18}\text{F}]\text{FES}\) showed promising results, as it displayed highest uptake in the regions of the brain with high expression of ER. In an ongoing study in breast cancer patients at University Medical Center Groningen, it was found that \([^{18}\text{F}]\text{FES}\) can be used to visualize the brain metastases (Figure 9 ). But further research is necessary to validate this tracer for ER imaging in human brain. Moreover, the availability of a new ER \( \beta \)-selective tracer would be highly desirable, since the different isoforms of ER have different expression patterns and different functions in neuroprotection, mood, and memory\textsuperscript{53,54}.

\([^{18}\text{F}]\text{FPTP}\) is the only tracer that could visualize PR both in humans and in experimental animals so far, but further evaluation of the tracer for brain imaging is required. More recently, \([^{18}\text{F}]\text{FFNP}\) PET was found to be a safe, noninvasive method to evaluate tumor PR in vivo in patients with breast cancer. This tracer may also be of interest for brain research. \([^{18}\text{F}]\text{FDHT}\) is the only tracer that has successfully been applied for AR imaging in humans but still needs to be validated for its use in brain imaging. Unfortunately, no selective tracers for the different isoforms of the PR and AR are available yet. No suitable tracers for GR and MR imaging are available yet either.

\textbf{Figure 9:} \([^{18}\text{F}]\text{FES}\) PET image of a patient with metastasized breast cancer. (A) Maximum intensity projection (MIP) coronal \([^{18}\text{F}]\text{FES}\)-PET image, showing the physiological uptake in the liver and normal excretion by gall bladder and bile ducts into the intestines and some excretion via kidneys and urinary bladder. Multiple bone, lymph node and cerebral metastases, (B) fused FES-PET and CT sagittal slice showing two cerebral metastases, and (C) fused FES-PET and CT transversal slice showing two cerebral metastases.
Conclusion and Perspectives

Despite a growing insight into several functions of SHR, many questions still remain unanswered. PET and SPECT imaging are attractive tools to investigate SHR function in the brain in living subjects. Several PET and SPECT tracers have been already evaluated for detection of SHR in various applications in oncology, and few of them have already entered into the clinical settings. It is evident that SHR are not only associated with cancers, but they are also associated with neurological and psychiatric disorders, such as depression and neurodegenerative disorders. Research on brain SHR is still a largely unexplored area, in which these PET and SPECT tracers may be valuable tools. Tracers that are already used for diagnosis and monitoring of therapy response in hormone-sensitive cancers may probably easily be validated for applications in neurological and psychiatric disorders as well. So far, \[^{18}\text{F}]\text{FES}, \[^{18}\text{F}]\text{FFNP}, \text{and }[^{18}\text{F}]\text{FDHT} \text{have been used successfully in cancer patients for imaging of } \text{ER, PR, and AR, respectively. These compounds are now available as potential tracers for imaging of SHR in the human brain. In addition, new tracers for SHR are still under development.}

Development of tracers for corticoid receptors has long been attempted, but these efforts did not produce any promising results yet. When tracers for corticoid receptors finally become available, however, they will be valuable assets for research in stress, mood, and neuropsychiatric disorders that are known to be associated with overactivity of the HPA axis.

Aging and the lifestyle-associated stress are known to change SHR expression. Imaging of SHR in the brain could be a valuable tool to study the disease mechanisms associated with the age and stress-related changes in expressional levels of SHR, which can ultimately culminate into neurological and psychiatric disorders. Understanding the disease mechanism could provide a rationale for treatment regimens based on hormone replacement or the use of selective SHR modulators. PET and SPECT imaging of SHR could also be helpful in drug discovery for individual SHR-associated disorders. Based on the occupancy studies of a new drug, PET and SPECT may provide information about the amount of drug that binds to the target and about the residence time of the drug in the brain. Such information about a new drug is highly valuable for decision making in drug development and optimizing the dose and route of administration. Another benefit of PET and SPECT imaging could be patient stratification based on the receptor status of a patient before inclusion in a clinical trial. Thus, studies can be performed in a more homogenous population, which reduces variability and may reduce the costs of drug development.

In the future, PET and SPECT imaging of SHR will not only be helpful in the diagnosis of neurological and psychiatric disorders associated with altered SHR expression, but could also be instrumental in providing a better understanding of disease mechanisms and the development of new intervention strategies.
References

Chapter 2


