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PET Imaging of Beta-Adrenoceptors in Human Brain: A Realistic Goal or a Mirage?

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Abstract: Beta-adrenoceptors are predominantly located in the cerebral cortex, nucleus accumbens and striatum. At lower densities, they are also present in amygdala, hippocampus and cerebellum. Beta-2 sites regulate glial proliferation during ontogenic development, after trauma and in neurodegenerative diseases. The densities of beta-1 adrenoceptors are changed by stress, in several mood disorders (depression, excessive hostility, schizophrenia) and during treatment of patients with antidepressants.

A technique for beta-adrenoceptor imaging in the human brain is not yet available. Although 24 (ant)agonists have been labeled with either ¹¹C or ¹⁸F and some of these are successful myocardial imaging agents, only two (*S*-1'-¹⁸F-fluorocarazolol and *S*-1'-¹⁸F-fluoroethylcarazolol) could actually visualize β -adrenoceptors within the central nervous system. Unfortunately, these radiopharmaceuticals showed a positive Ames test. They may be mutagenic and cannot be employed for human studies.

Screening of more than 150 beta-blockers described in the literature yields only two compounds (exaprolol and L643,717) which can still be radiolabeled and evaluated for β -adrenoceptor imaging. However, other imaging techniques could be examined. Cerebral β -adrenoceptors might be labeled after temporary opening of the blood-brain barrier (BBB) and simultaneous administration of a hydrophilic ligand such as *S*-¹¹C-CGP12388. Another approach to target β -adrenoceptor ligands to the CNS is esterification of a myocardial imaging agent (such as ¹¹C-CGP12177), resulting in a lipophilic prodrug which can cross the BBB and is split by tissue esterases. BBB opening is not feasible in healthy subjects, but the prodrug approach may be successful and deserves to be explored.

Key Words: Beta-adrenoceptors, positron emission tomography, human, brain, depression, multiple sclerosis, radiopharmaceuticals, imaging.

INTRODUCTION

In the autonomic nervous system, two networks can be distinguished which regulate the internal environment to maintain a steady-state (homeostasis): the sympathetic and the parasympathetic system. The latter network maintains basal functions (heart rate, respiration, etc.) under normal conditions, whereas the former responds to threatening situations (hypoglycemia, hypoxia, sudden changes in the environment). Sympathetic activation results e.g. in increased cardiac output, body temperature and blood glucose in order to respond adequately in case of an emergency.

The physiological responses resulting from activation of the sympathetic nervous system are mediated by the neurotransmitter noradrenalin and the hormone adrenalin. These catecholamines originate from the amino acid tyrosine. Noradrenalin is synthesized in nerve endings, while adrenalin is produced mainly in the chromaffin cells of the adrenal medulla. Both compounds activate specific membrane receptors called adrenoceptors. The interaction of noradrenalin with these receptors was discovered by Sir Henry Dale

in the first decade of the twentieth century [51]. Later, it was shown that the adrenoceptor family could be divided in two populations, called β_1 - and β_2 -adrenoceptors [8]. The former induce activation of the uterus and vasoconstriction, the latter inhibition of the uterus and vasodilation. Later still, β -adrenoceptors were classified in two different subtypes: β_1 and β_2 [136]. Beta-1 agonists stimulate cardiac contractility and lipolysis, whereas beta-2 agonists cause bronchodilation and vasodilation. Since then, β_1 -adrenoceptors involved in lipolysis have been reclassified as 'atypical' or β_3 -adrenoceptors [14]. A fourth subtype, the putative β_4 -adrenoceptor, has been suggested to exist in myocardial and adipose tissue [84, 127]. Blocking this subtype requires much higher concentrations of β -adrenoceptor antagonists than those required to block β_1 - or β_2 -adrenoceptors.

Since responses to stressful situations occur all over the body, β -adrenoceptors are present in many different organs. Stimulation of myocardial receptors increases heart rate and contractile force, resulting in enhanced cardiac output [32]. Stimulation of pulmonary β -adrenoceptors causes bronchodilation and increased blood flow, resulting in enhanced oxygen uptake [16]. Beta-adrenoceptors in the pancreas regulate the secretion of glucagon [135], while those in the liver and kidney control glycogenolysis and glucose release [125, 91]. The overall effect of stimulation of these receptors is an increased availability of glucose and an increased

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capacity of tissues to use glucose as a fuel. Beta-adrenoceptors in the spleen are involved in the stress-induced augmentation of circulatory blood volume and lymphoid cell mobilization [232, 196]. The secretion of many glands, including the lacrimal [1], salivary [188], thyroid [9] and pituitary [210] glands, is also under β -adrenergic control.

Physiological and behavioral responses to noradrenalin in the central nervous system are regulated predominantly by two different nuclei in the brain stem: the locus coeruleus and the lateral tegmental neurons. The former has very broad projections throughout the brain. Much less noradrenergic neurons project from the lateral tegmental neurons to the brain stem, spinal cord and thalamus. While the lateral tegmental neurons contribute to the integration of autonomic functions (blood pressure and heart rate), the projections of the locus coeruleus play an important role in behavioral responses such as orientation, and reactions to sudden contrasting or aversive sensori stimuli [167].

Cerebral β -adrenoceptors are involved in several physiological functions, such as respiratory [12, 81], cardiovascular [231] and renal [132] sympathetic nervous control. Furthermore, β -adrenoceptors located on glial cells regulate (injury-induced) astrogliosis and microglial proliferation [224, 85, 104, 83]. These processes contribute to neuronal regeneration after injury, but they can also play a negative role in neurodegenerative diseases and contribute to ischemia-induced neuronal death [116, 154]. Biological rhythms, such as the diurnal activity cycle [251, 122], the sleep/wakefulness cycle [217] and annual hibernation [182] are accompanied by changes of β -adrenoceptor density and/or β -adrenoceptor signalling in particular brain areas.

Cerebral β -adrenoceptors are essential to various memory functions, such as memory storage of emotional events [159, 36], motor learning [102], conditioned olfactory [145] and taste [20] learning. They also regulate the processing of visual information [170]. Memory functions, processing of external information and the ability to hibernate are required to respond correctly in case of emergencies.

Studies in rodents have revealed changes of regional β -adrenoceptor density and of the activity of β -adrenoceptor-coupled second messenger systems after exposure of the animals to stress. Acute or unpredictable stress is thought to be accompanied by an increase of β -adrenoceptor density, probably in order to assess the danger of a situation [179]. In contrast, a predictable form of chronic stress is often accompanied by a reduction of β -adrenoceptor numbers [80, 103]. This reduction may be interpreted as an adaptation of the animal to recurrent stressful events and the accompanying release of large amounts of catecholamines. In some studies, there were no changes of β -adrenoceptor density after exposure of animals to stress [29, 93, 100]. These conflicting results may be due to the different stress paradigms and test procedures that were employed.

Postmortem studies in humans have provided evidence for abnormal β -adrenoceptor density and function in mood disorders such as depression. Initial studies in suicide victims reported either increases [13, 23], no alteration [162, 221, 48], or decreases [54] in various brain areas, such as the frontal cortex and hippocampus. The data were difficult to

interpret because of the heterogeneity of the patient groups (e.g., large differences in medication) and the fact that many different radioligands were used in the receptor assays. Later studies employing more stringent inclusion criteria demonstrated β -adrenoceptor decreases in several cortical areas, not only in antidepressant-treated but also in drug-free depressed patients [55, 149, 202]. After long-term treatment with antidepressants, cerebral β -adrenoceptors are downregulated in human brain [56, 11].

Several other disorders of mood and behavior, such as schizophrenia [130, 121], excessive hostility [256, 222], premenstrual dysphoria [95] and chronic alcohol abuse [94] have been reported to be accompanied by abnormal β -adrenoceptor densities and/or coupling of β -adrenoceptors to the G_s protein. Low doses of lipophilic β -blockers proved often effective in the suppression of psychosis or anxiety and the reduction of aggressive behavior in chronic psychiatric patients [96, 15, 75].

Neurodegenerative diseases may also be associated with abnormal β -adrenoceptor function. In some patients with Parkinson's disease, an increased number of β_1 adrenoceptors was found in the pre-frontal cortex [38]. Alzheimer's dementia has been reported to be accompanied by changes of the relative sizes of β -adrenoceptor subpopulations (decrease of β_1 , increase of β_2) [123, 247] and impaired β -adrenoceptor coupling to adenylyl cyclase [47] in various regions of the brain. An almost complete loss of β_1 -adrenoceptors in basal ganglia of patients suffering from Huntington's disease is observed only in late stages of the disease. This loss is accompanied by a strong increase of β_2 -adrenoceptor density in the posterior putamen, probably as a result of gliosis [249]. Normal aging is accompanied by a slow decrease of β_1 -adrenoceptor densities in human brain [123, 202]. Apparently, this loss is accelerated in certain forms of neurodegeneration.

POSITRON EMISSION TOMOGRAPHY (PET) OF CEREBRAL β -ADRENOCEPTORS

If a method could be developed to image and quantify β -adrenoceptors in the human brain, this would allow investigators to answer several questions:

- (a) *Beta-adrenoceptor occupancy* of novel and existing CNS drugs could be measured and related to plasma levels of the drug, to the desired therapeutic effect and to undesired side effects.
- (b) Changes in *β -adrenoceptor availability* after administration of noradrenalin reuptake inhibitors could be assessed in the intact human brain, reduced β -adrenoceptor availability indicating increased occupancy of the β -adrenoceptor population by endogenous noradrenalin.
- (c) The time course of *β_1 -adrenoceptor downregulation* in patients during treatment with antidepressants could then be assessed and related to mood changes in the same subjects.
- (d) It would become possible to make a *differential diagnosis* between multiple sclerosis and other neurodegenerative diseases in an early stage of the disease. White

matter in the brain of healthy subjects is virtually devoid of β -adrenergic sites [257], but glial cells possess β_2 -adrenoceptors [154]. Gliosis after neurodegeneration might therefore be visualized with a suitable β_2 -adrenoceptor ligand and PET. Proliferation of microglia results normally in increased β_2 -adrenoceptor densities in white matter, but astrocyte proliferation in multiple sclerosis is not accompanied by such increases because astrocytes in MS have lost their β_2 -adrenoceptors [52, 257].

Myocardial and pulmonary β -adrenoceptors in patients and healthy volunteers have already been quantified, using the radiolabeled antagonists S- ^{11}C -CGP12177 [98, 139, 161, 185, 186, 206, 239] and S- ^{11}C -CGP12388 [64, 72]. Since the lipophilicity of these radiopharmaceuticals is very low (calculated log P at pH 7.4 -2.07 and -2.01, respectively¹), they do not cross the blood-brain barrier. Therefore, the Ciba-Geigy compounds are not suitable for visualization of β -adrenoceptors in the central nervous system.

Some lipophilic β -adrenoceptor antagonists have also been labeled with a positron emitter. These include: S- ^{11}C -bisoprolol (logP -0.20, [215]), S- ^{11}C -carazolol (logP +0.80, [21]), ^{11}C -carvedilol (logP +2.97, [63]), S- ^{18}F -fluorocarazolol (logP +2.19, [258]), S- ^{18}F -fluoroethylcarazolol (logP +1.66, [67]), ^{18}F -fluoroisopropylbupranolol (logP +1.93, [63]), ^{18}F -fluoroisopropylpenbutolol (logP +2.53, [63]), ^{18}F -fluoropropranolol (logP +1.81, [234]), ^{11}C -ICI 118,551 (logP +1.07, [168]), ^{11}C -pindolol (logP -0.53, [184]), ^{11}C -propranolol (logP +0.43, [19]) and ^{11}C -toliprolol (logP -0.22, [63]). Only two out of these twelve radiopharmaceuticals displayed specific binding in rodent brain: ^{18}F -fluorocarazolol and ^{18}F -fluoroethylcarazolol. A pilot study with non-carrier-added ^{18}F -fluorocarazolol indicated specific binding of this radioligand also in the human brain [243]. Unfortunately, in later more extensive screening, both fluorinated carazolol analogs showed a positive Ames (i.e., mutagenicity) test ([62], Doze unpublished). Therefore, these radioligands can no longer be employed for human studies.

Radioiodinated analogs of pindolol (ICYP and IPIN) display some specific binding within the CNS *in vivo* [236, 63], but the brain uptake of these compounds is low, resulting in very poor signal-to-noise ratios. Moreover, ICYP binds not only to β -adrenoceptors, but also to several subtypes of the serotonin (5-HT) receptor within the brain [63].

Since no other radiopharmaceuticals are available for PET imaging of β -adrenoceptors in human brain, the following questions should be answered in this review:

- (1) Do other lipophilic β -blockers exist which could be labeled with ^{11}C or ^{18}F and tested as radiopharmaceuticals for cerebral β -adrenoceptor imaging?
- (2) Can a strategy be devised to increase the brain uptake of established β -adrenoceptor ligands, so that they become suitable for visualisation of β -adrenoceptors within the central nervous system?

CRITERIA FOR THE SELECTION OF LIGAND CANDIDATES

1. Affinity

Receptor imaging requires a specific signal above background radioactivity. To predict if a radioligand will provide a specific signal that can be detected externally, the bound/free ratio (B/F) is often estimated from the Scatchard equation [205]:

$$B/F = B_{\max}/K_d - B/K_d$$

Since the specific activity of positron-emitting radioligands is very high (i.e., B is very small), the term B/K_d can be neglected and B/F is approximately equal to B_{\max}/K_d . This ratio, originating from equilibrium binding equations developed for *in vitro* binding assays, describes target/nontarget binding in the ideal case. The actual ratio of bound/free radioactivity observed *in vivo* is often much lower because of metabolism, protein binding and non-specific uptake of the radioligand [86]. For receptor visualisation, a B/F ratio 10 is required in planar imaging and 4 in PET [88, 70].

Estimations of β -adrenoceptor density (B_{\max}) in human brain vary over a fairly wide range depending on the laboratory of assay, the radioligand employed, the method used to obtain a membrane fraction and the age and personal history of the subjects. In frontal cortex, the lowest value reported was 18 fmol/mg protein [38] and the highest value was 147 fmol/mg protein [209]. If we assume an average protein content of tissue of 10%, these values correspond to 1.8-14.7 pmol/g wet weight. Thus, the affinity of a radioligand to visualize β -adrenoceptors in the frontal cortex should be < 0.45-3.7 nM for PET ($B_{\max}/K_d > 4$) and < 0.18-1.47 nM for planar imaging ($B_{\max}/K_d > 10$). In reality, the affinity should be even higher because there is always some metabolism, protein and non-specific binding.

2. Lipophilicity

Imaging of neuroreceptors within the CNS is only possible when the radiopharmaceutical is transported across the blood-brain barrier (BBB). The cerebral endothelium acts as a lipophilic physical barrier by which the passive entry of hydrophilic compounds into the brain is restricted. Optimal diffusion across the blood-brain barrier occurs if the drug has an octanol/water partition coefficient (log P) of +2 to +3, the maximum of the parabola describing the relationship between lipophilicity and brain uptake [59, 147, 165, 208]. Reduced lipophilicity results in little transport of the test drug across phospholipid bilayers, and increased lipophilicity promotes nonspecific binding of the compound to blood cells and plasma proteins, which reduces delivery to the brain.

3. Lack of Affinity to P-Glycoprotein

Although successful CNS radioligands possess logP values between +0.5 and +3, this does not imply that all compounds with that lipophilicity will show good brain uptake. Many β -blockers are substrates for P-glycoprotein (Pgp) [174]. This protein is expressed in endothelial cells of the blood-brain barrier and it promotes active efflux of drugs from the CNS. Cerebral uptake of Pgp-substrates is therefore much lower than would be expected on the basis of their lipophilicity [101].

¹ Calculated logP values were determined with the computer program Pallas. All values mentioned in this article refer to pH 7.40.

4. Optimal Molecular Size and Charge

Besides lipophilicity, the distribution of charge within a molecule seems to affect its brain uptake. Higher uptake (0.8-4.8% ID/g) has been observed for compounds with electron withdrawing substituents in beta-position to the amine group (pK_a values 7.4 to 8.3) than for those with more basic amine groups (pK_a values > 8.9, < 0.4% ID/g), even though both classes of compounds had similar octanol/water partition coefficients at pH 7.4 [82].

Passive diffusion across the blood-brain barrier is also dependent on molecular volume, larger volumes resulting in reduced transport. It has been claimed that for optimal brain uptake, a drug should have a molecular weight smaller than 600 Da [69]. The criterion of molecular size is not relevant to β -adrenoceptor imaging, since most β -adrenoceptor (ant) agonists have molecular weights between 200 and 350 Da.

5. Specificity for the Target

The ideal radioligand should bind to a single receptor population only. Changes in binding parameters can then be attributed to one clearly-defined subtype. Truly specific compounds are rare. If the anatomic localization of receptor populations within the human brain is sufficiently distinct, a single ligand with affinity to all sites of interest can be employed. However, visualisation of the noradrenergic system requires highly specific ligands, since β -adrenoceptors are widely distributed throughout the brain and low densities are only observed in white matter, pons and medulla [257]. Most β -adrenoceptor antagonists display significant affinity towards serotonin 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors. Affinity of the radioligand to these serotonergic sites should be at least 2 (preferably even 3) orders of magnitude less than that to β -adrenoceptors for successful PET imaging [198].

6. Resistance to Metabolism

An ideal radioligand should either show negligible metabolism within a PET time scale (i.e., 2 h) or it should be metabolized to hydrophilic radioactive products with negligible brain uptake. In that case, bound radioactivity within the CNS will reflect mainly parent compound which greatly facilitates tracer-kinetic modeling.

7. Amenable to Labeling

Candidate radiopharmaceuticals should possess molecular groups that can be labeled using rapid synthetic procedures. Because of the short half-lives of positron emitters (¹¹C only 20 minutes), this is a stringent requirement.

PREDICTIVE VALUE OF THE CRITERIA

The literature on β -blockers usually provides only the following information: (i) chemical structure of the compound; (ii) some proof of its action (affinity to β -adrenoceptors, or data on functional antagonism); (iii) in some cases, also a measured octanol/water partition coefficient. If candidate radiopharmaceuticals should be selected based on literature data, the following questions may arise:

1. Can the brain uptake of radioligands be predicted on the basis of (measured or calculated) octanol/water partition coefficients?
2. Can the magnitude of the specific binding (i.e., the signal-to-noise ratio in PET images) of radioligands in target organs such as the brain be predicted on the basis of their *in vitro* affinities to β -adrenoceptors?

To answer the first question, we plotted the uptake of sixteen β -adrenoceptor ligands within rat CNS against their (calculated) log P value at pH 7.4 (Fig. 1). This plot suggests that optimal brain uptake of β -blockers occurs at log P values between +2 and +3, just as has been described for other radiopharmaceuticals. Unfortunately, β -blockers with log P values > 3 have not yet been labeled with a positron emitter and evaluated for PET imaging. Therefore, no data points are available for the right half of the parabola. The fitted curve (a Boltzmann sigmoidal) has a good correlation coefficient ($r = 0.97$) and the relationship between log P and brain uptake is highly significant ($p = 0.0003$). However, two compounds were not included in the fit since they did not obey the general trend. In figure 1, these ligands are indicated by asterisks.

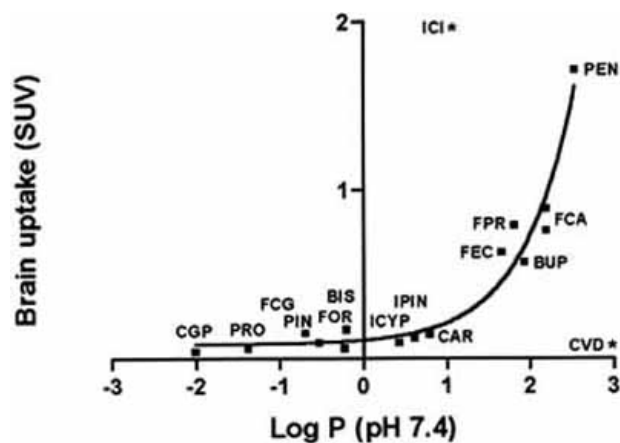


Fig. (1). Relationship between (calculated) log P and brain uptake of β -adrenoceptor ligands. Brain uptake is plotted as the SUV in rat brain at 60 min post injection (with exception of formoterol and procaterol for which only data at 10 min post injection were available). Uptake data were from the following publications: CGP [241], PRO [245], FCG [241], PIN [63], FOR [246], BIS [215], ICYP [63], IPIN [236], CAR [65], FEC [67], FPR [234], BUP [63], FCA [240, 66], PEN [63], ICI [168], CVD [63].

The most noteworthy exception is ¹¹C-carvedilol (CVD). This drug is quite lipophilic (calculated log P + 2.97 at pH 7.4), but its brain uptake is negligible (SUV = 0.08 at 60 min post injection, [63]). The exceptionally low brain uptake is probably due to the fact that carvedilol is a high-affinity substrate for P-glycoprotein and actively expelled from the CNS, in contrast to other β -blockers which are only weak substrates for this ATP-dependent drug efflux pump [174]. Another exception is ¹¹C-ICI 118,551 (ICI). Brain uptake of this compound is much higher than predicted on the basis of the curve fit. This finding is hard to explain - perhaps the

ligand is metabolized to a lipophilic radioactive product which can more easily cross the blood brain barrier. Unfortunately, the literature does not provide information on radiolabeled species arising from ^{11}C -ICI 118,551.

Figure 1 suggests that candidate radioligands should possess log P values greater than +1.5 in order to have adequate brain uptake. Apparently, octanol/water partition coefficients can predict uptake of β -adrenoceptor (ant) agonists within the CNS, although there are a few (2 out of 16) exceptions to the general rule.

To answer the question if the β -adrenoceptor affinity of a ligand can predict the magnitude of its specific signal in PET images, we plotted the measured ratio of specific/nonspecific binding (signal-to-noise ratio) for various β -blockers in rat heart *in vivo* against their binding potentials (B_{max} divided by K_d determined *in vitro*, see Figure 2). A similar figure cannot be prepared for rat brain, since only four β -adrenoceptor ligands (FEC, FCA, ICYP and IPIN) have shown specific binding within the CNS. To calculate B_{max}/K_d in rat heart, we assumed a B_{max} of 6 pmol/g wet weight of tissue [137] and a ratio of the $\beta_1:\beta_2$ subtypes of 83:17 [164].

The data from eleven compounds were well fitted by a hyperbola ($r = 0.97$, $p < 0.0001$). That the relationship between *in vitro* affinity and target/non-target ratio in PET imaging is curvilinear rather than linear is not surprising. Binding of potent β -adrenoceptor antagonists approaches equilibrium slowly, i.e. true equilibrium is reached only after several hours. It is thus possible that an interval of 60 min post injection is too short to acquire an optimal ratio of specific/nonspecific binding for potent radioligands, such as CAR and ICYP. Moreover, if K_d is very small ($\leq 10^{-10}\text{M}$), the expression B/K_d in the Scatchard equation will no longer be negligible, especially in the case of ligands labeled with carbon-11. Target-nontarget ratios (B/F) will in such cases be smaller than B_{max}/K_d .

Apparently, values for radioligand affinity determined *in vitro* can be used to predict the results of myocardial imaging. However, one compound deviated from the general pattern shown in Fig. 2, [^{11}C]carvedilol (CVD). According to *in vitro* assays, B_{max}/K_d of S-carvedilol in rat heart is 11.5 to 14 [175], but ^{11}C -carvedilol did not show any specific binding in rat heart *in vivo* [63]. The reason for the failure of [^{11}C]carvedilol as a myocardial imaging agent is not clear. The affinity of carvedilol to β -adrenoceptors may have been overestimated. Estimations of the affinity of β -adrenoceptor antagonists can vary by a factor of 10, depending on the tissue preparation and the laboratory of assay. The affinity of carvedilol was determined in guinea pig atrium rather than rat ventricle. If there is a species difference between rat and guinea pig and if the affinity of carvedilol was indeed overestimated, carvedilol data may in fact fit the plotted curve.

Figure 2 suggests that for an acceptable signal-to-noise ratio, the binding potential (B_{max}/K_d based on *in vitro* assays of B_{max} and K_d) of a radiolabeled β -blocker should be greater than 10. Based on the data presented in Fig. 1 and 2, we may predict that ligand candidates should have (calculated) log P values $> +1.5$ and affinities < 1.5 nM for successful β -adrenoceptor imaging.

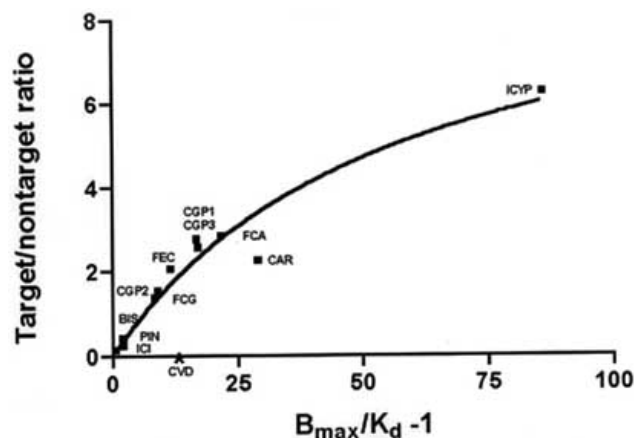


Fig. (2). Relationship between the *in vitro* affinities of β -adrenoceptor ligands and their target/nontarget ratios observed in rat heart *in vivo*. Target/nontarget ratios were calculated from tissue uptake in the absence and presence of propranolol, at 60 min after injection (with exception of ICI118,551, bisoprolol and CGP20712A, for which only data at 30 min were available). Uptake data were from the following publications: ICI [168], PIN [63], BIS [215], FCG [241], CGP2 [73], FEC [67], CGP1 [242], CGP3 [241], FCA [66], CAR [65], ICYP [63], CVD [63].

UNEXPLORED CANDIDATES

Are there still any β -blockers with moderate lipophilicity ($\log P +1.5$ -3) and high affinity which could be labeled with a positron emitter? In order to answer this question, we performed an extensive literature search and classified β -adrenoceptor antagonists into four different groups: (i) Extremely potent compounds ($K_d < 1$ nM, Table 1), (ii) Potent compounds (K_d 1-10 nM, Table 2), (iii) Beta-blockers with moderate affinities (K_d 10-100 nM, Table 3) and (iv) Weak β -adrenoceptor antagonists ($K_d > 100$ nM, Table 3).

Of the 57 extremely potent β -blockers listed in Table 1, only 10 are sufficiently lipophilic: bucindolol, carvedilol, CGP20712A, exaprolol, fluorocarazolol, fluoroethylcarazolol, iodoazidobenzylpindolol, iodohydroxybenzylpindolol, L643,717, and compound 21a. Carvedilol and CGP20712A have already been labeled and found to be unsuitable for cerebral β -adrenoceptor imaging [63, 242]. Fluorocarazolol and fluoroethylcarazolol are successful ligands, but they cannot be employed for human studies because of a positive Ames test [62]. Iodoazidobenzylpindolol is a photoaffinity label which cannot be used for PET imaging. [^{125}I]Iodo-hydroxybenzylpindolol shows very poor target/nontarget ratios *in vivo* [35]. Radioactive bucindolol, exaprolol, L643, 717, and compound 21a have not yet been prepared (see Figure 3 and [105] for chemical structures). Unfortunately, bucindolol and compound 21a are not amenable to labeling with a positron emitter. However, exaprolol can be labeled by reaction of a desisopropyl precursor with ^{11}C -acetone, and L643,717 by reaction of a hydroxy precursor with ^{11}C -methyl iodide.

Analogs of pindolol (not listed in Table 1) may show high affinities to β -adrenoceptors and could be explored for

Table 1. β -Adrenoceptor Antagonists with Affinities in the sub-nM Range for at least one of the β -Adrenoceptor Subtypes

Compound	β_1 affinity (nM)	β_2 affinity (nM)	Log P (pH 7.4)
(-) Alprenolol	Not determined	0.6 [58]	+0.35c +0.80m [5]
AlpM	Not determined	0.2 [181]	-1.77c -1.58c (2 isomers)
Arotinolol	0.2 [237]	0.5 [237]	-0.34c
(-) Befunolol	1 [133]	0.9 [133]	-0.62c -0.12m [192]
BFE61	Not determined	0.2 [228]	-0.11c
Bucindolol	1.7 [31]	0.8 [31]	+ 1.66c
Bucumolol	0.8 [112]	Not determined	-0.60c +0.93m [112]
Bunitrolol	0.7 [158]	Not determined	-0.92c -0.36m [192]
(-) Bupranolol	1.6 [143]	0.3 [143]	+0.29c +0.57m [141]
Butylpindolol	0.7 [45]	0.7 [45]	-0.16m [45]
Carazolol	0.15 [117]	Not determined	+0.80c +1.36m [220]
(-) Carteolol	0.1 [133]	0.1 [133]	-1.55c
(-) Carvedilol	0.4 [175]	Not determined	+2.97c
CGP 12177	0.3 [173]	0.9 [173]	-2.07c -0.49m [5]
CGP 12388	Like CGP 12177 [241]	Like CGP 12177 [241]	-2.01c
(-) CGP 20712A	0.5 [61]	4200 [61]	+1.78c
Chloranolol	Sub-nM [78]	Not determined	+0.47c
(-) Dihydroalprenolol	0.6 [58]	0.4 [58]	+0.69c +1.00m [220]
Erhardt <i>et al.</i> , compd 12	0.1 [77]	0.5 [77]	-1.19c
Erhardt <i>et al.</i> , compd 14	0.2 [77]	1 [77]	-1.25c
Exaprolol	0.2 [110]	Not determined	+1.61c
Fluorocarazolol	0.4 [243]	0.1 [243]	+2.19c
Fluoroethylcarazolol	0.5 [67]	0.4 [67]	+1.66c
ICI 89,406	0.3 [180]	100 [180]	-1.05c
ICI 118,551	68 [25]	0.5 [25]	+1.07c +1.33m [45]
ICI 147,798	0.8 [126]	1.6 [126]	-0.11c
Indenolol	Like propranolol [229]	Not determined	-0.05c
Iodoazidobenzylpindolol	Unknown	0.5-0.7 [191]	+4.16c
Iodocyanopindolol	< 0.1 [33]	< 0.01 [90]	+0.43c +1.26m [220]
Iodohydroxybenzylpindolol	< 0.2 [238]	0.2 [153]	+2.68c
Iodopindolol	0.2 [146]	Not determined	+0.62c
IPS 339	13 [155]	0.8 [155]	+0.98c
K 105	Like bupranolol [144]	Like bupranolol [144]	-0.24c
Kierstead <i>et al.</i> , compd 4a	35 [129]	0.6 [129]	-2.80c
Kierstead <i>et al.</i> , compd 4d	650 [129]	< 0.1 [129]	-3.71c
Kierstead <i>et al.</i> , compd 4f	60 [129]	0.8 [129]	-3.38c
Kierstead <i>et al.</i> , compd 4v	55 [129]	< 0.1 [129]	-3.52c

(Table 1) contd....

Compound	β_1 affinity (nM)	β_2 affinity (nM)	Log P (pH 7.4)
Kö-1313	< propranolol [18]	22 [114]	-0.83c
Kö-1366	< propranolol [18]	Like propranolol [18]	-0.92c
L 643,717	0.8 [169]	7413 [169]	+3.36c
Los Angeles, compd 21a	182 [150]	0.3 [150]	+3.76c
LT 18-502	0.7 [108]	0.4 [108]	-0.29c
Mauléon <i>et al.</i> , compd 3b	0.2 [156]	< 0.1 [156]	+0.91c
McClure <i>et al.</i> , compd 34	0.6 [158]	Not determined	+0.14c
McClure <i>et al.</i> , compd 40	0.7 [158]	Not determined	+0.86c
McClure <i>et al.</i> , compd 42	0.7 [158]	Not determined	+0.86c
(<i>S,R</i>) Nipradilol	0.3 [211]	0.7 [211]	-0.75c
(-) Penbutolol	< propranolol [99]	Not determined	+1.17c +1.97m [192]
(-) Pindolol	0.9 [106]	1.2 [106]	-0.53c -0.33m [45]
Procinolol	< alprenolol [214]	Not determined	+0.84m [192]
(-) Propranolol	0.6 [58]	0.7 [58]	+0.43 +1.20m [45]
Soquinolol	3.3 [92]	0.8 [92]	-1.78c
Spirendalol	12 [169]	< 0.1 [169]	+0.67c
Tertatolol	0.4 [244]	1.5 [244]	-0.09c
(-) Timolol	0.8 [58]	0.5 [58]	-2.14c
Toliprolol	Like bupranolol [254]	44 [114]	-0.22c

Symbols: compd = compound; c = calculated, m = measured log P.

Table 2. β -Adrenoceptor Antagonists with Affinities in the nM Range for at least one of the β -Adrenoceptor Subtypes

Compound	β_1 affinity (nM)	β_2 affinity (nM)	Log P (pH 7.4)
Adimolol	1.2 [151]	Not determined	+1.87c
BFE37	Not determined	2.3 [228]	+0.56c
Bisoprolol	1.6 [128]	100 [128]	-0.20c
BL 343 Ac	3.2 [131]	Not determined	-0.51c
Bopindolol	229 [108]	4.3 [108]	+2.45c
Bufetolol	2.2 [118]	Not determined	-0.53c
Bufuralol	2.5 [166]	Not determined	+0.73c
Bunolol	See levobunolol	See levobunolol	-0.53c
Capsinolol	6.9 [40]	9.1 [40]	+1.50c
Carré <i>et al.</i> , compd 15a	Unknown	1.3 [37]	+0.04c
Carré <i>et al.</i> , compd 15b	Unknown	1.3 [37]	+0.13c
Carré <i>et al.</i> , compd 9b	Unknown	2.0 [37]	+1.41c
Compound A	Like MK-761 [207]	Like MK-761 [207]	+0.23c

(Table 2) contd....

Compound	β_1 affinity (nM)	β_2 affinity (nM)	Log P (pH 7.4)
Compound 10	6.8 [28]	2.1 [28]	-0.53c
Dilevalol	6.3 [166]	Not determined	+0.65c
Epanolol	3.8 [24]	468 [24]	-0.75c +0.92m [24]
Eugenolol	5.2 [253]	6.6 [253]	+0.29c
Falintolol	23 [28]	6.9 [28]	-0.86c
Ferulidilol	9.1 [253]	31 [253]	+2.21c
Flestolol	9.8 [89]	6.9 [89]	-0.93c
Flusoxolol	>= pindolol [157]	Not determined	+1.19c
HX-CH 44 BS	5-10 [50]	7493-10000 [50]	-4.21c
Kam 96	2.5 [124]	6.3 [124]	-0.32c
Labetalol	4.9 [44]	7.9 [44]	+0.65c
Levobunolol	Not determined	2.1 [187]	-0.53c
LK 203-939	4.5 [163]	9332 [163]	-0.55c
LK 204-545	3.2 [163]	10965 [163]	+0.81c
LL 21-945	2.5 [43]	Not determined	Unknown
(-) Medroxalol	4 [41]	Not determined	+0.50c
Mepindolol	1.6 [10]	5 [10]	-0.39c +0.05m [192]
Metipranolol	5 [223]	4 [223]	+0.08c +0.43m [192]
MK 761	1.5 [169]	Not determined	-1.78c
<i>l</i> -Moprolol	1.2 [183]	5.8 [183]	-0.77c -0.64m [192]
Nebivolol	7.6 [31]	310 [31]	+2.22c
Oxprenolol	2.1 [106]	6.2 [106]	-0.18c
(-) P0160	3 [87]	340 [87]	Unknown
S 2395.1	1259 [68]	4 [68]	Unknown
Sulfinalol	As MK761 [226]	Not determined	-0.30c
Tilisolol	55 [172]	2.8 [172]	-2.00c
(-) Tolamolol	2.8 [2]	36 [2]	+0.81c
Xibenolol	2.9 [106]	1.7 [106]	+0.19c

Abbreviations as in Table 1

Table 3. Low-Affinity β -Blockers

Compound	β_1 affinity (nM)	β_2 affinity (nM)	Log P (pH 7.4)
Affinity 10-100 nM			
(-) Amosulalol	13 [60]	Not determined	+0.55c
9-Amino-Acridine Propranolol	20 [160]	30 [46]	+1.72c
(-) Betaxolol	19 [142]	151 [142]	+0.24c +0.55m [192]

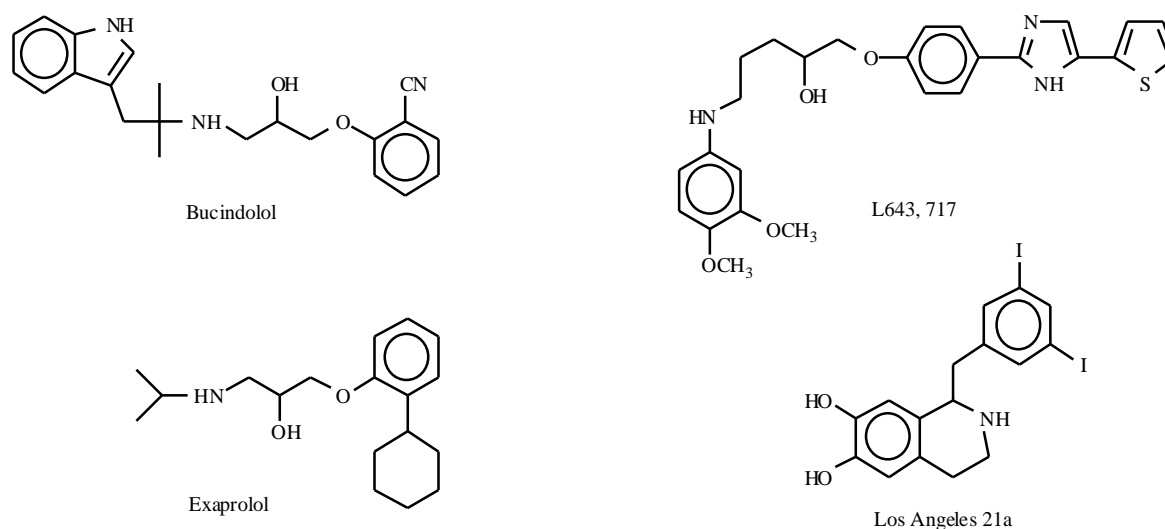
(Table 3) contd....

Compound	β_1 affinity (nM)	β_2 affinity (nM)	Log P (pH 7.4)
Affinity 10-100 nM			
Bevantolol	15 [230]	589 [230]	+2.22c
BFE-55	Not determined	20 [228]	-0.11c
<i>exo</i> Bornaprolol	25 [138]	Not determined	+1.44c +2.53m [192]
Cetamolol	20 [195]	50 [195]	-1.93c -1.03m [192]
Cicloprolol	15 [213]	Not determined	-0.15c
Dehydrozingeronolol	31 [253]	141 [253]	-0.52c
Eugenodilol	13 [253]	47 [253]	+2.44c
H-I 42 BS	14 [49]	3000 [49]	-0.76c
Isoeugenolol	13 [148]	759 [148]	+0.32c
LK 203-030	17 [163]	16596 [163]	-1.09c
LK 204-155	28 [163]	60256 [163]	-0.02c
Nadolol	13 [68]	32 [68]	+1.29c
Nadoxolol	Moderate [250]	Not determined	+1.85c
Pafenolol	28 [71]	2240 [71]	-0.69c +0.30m [193]
Pamatolol	28 [120]	2884 [120]	-1.05c
Pargolol	Moderate [111]	Not determined	-0.19m [192]
Primidolol	Moderate [201]	Not determined	Unknown
Prizidolol	69 [233]	93 [233]	-1.14c
Talinolol	Moderate [53, 79]	Not determined	-0.12c
Trimetoquinol	324 [150]	44 [150]	+1.44c
Vanidilol	21 [253]	22 [253]	-1.12c
Vanidipinedilol	81 [255]	229 [255]	Unknown
Vaninolol	21 [253]	174 [253]	-0.65c
Vasomolol	39 [253]	1549 [253]	-0.23c
Xamoterol	56 [152]	5754 [152]	-2.73c
Zingeronolol	30 [252]	155 [252]	-0.64c
Affinity > 100 nM			
Acebutolol	646 [142]	4169 [142]	-0.77c
(-) Atenolol	603 [142]	4266 [142]	-2.07c -2.24m [142]
Butidrine	Like atenolol [27]	Like atenolol [27]	+1.11c
Butofilolol	Like atenolol [140]	Like atenolol [140]	+0.11c
Butoxamine	15136 [204]	3715 [204]	-0.64c
Celiprolol	350 [97]	2800 [97]	-1.13c
DAPN	300 [46]	Not determined	?
Esmolol	110 [194]	4677 [194]	-0.44c
Ferulinolol	103 [253]	2412 [253]	-0.13c

(Table 3) contd....

Compound	β_1 affinity (nM)	β_2 affinity (nM)	Log P (pH 7.4)
Affinity > 100 nM			
Landirolol	257 [113]	66069 [113]	-2.11c
LT 20-785	1175 [108]	214 [108]	-1.92c
(-) Metoprolol	141 [142]	631 [142]	-0.56c
Nifenalol	126 [216]	Not determined	-0.59c
(-) Practolol	1175 [142]	128825 [142]	-1.74c -1.49m [106]
Pronethalol	Not determined	160 [115]	-0.10c
Sotalol	603 [106]	148 [106]	-1.15c
Xanthonolol	50000 [39]	Not determined	+2.15c

Abbreviations as in Table 1

**Fig. (3).** Chemical structures of some potent β -blockers which have not yet been labeled with a positron emitter.

imaging purposes. These include: benzylcyanopindolol, butylcyanopindolol, cyanopindolol, cyclohexylcyanopindolol, ethylesterpindolol, iodoallyl-cyanopindolol, iodobutylcyanopindolol, iodocyclohexylcyanopindolol, iodoethylesterpindolol, and isopropylcyanopindolol [105]. However, we do not expect these compounds to be suitable for cerebral beta-adrenoceptor imaging as: (i) they are not very lipophilic (calculated log P values $< +1.5$ with exception of iodocyclohexylcyanopindolol), so they will probably have low brain uptake and (ii) they probably bind not only to β -adrenoceptors but also to 5-HT_{1A} and 5-HT_{1B} receptors within mammalian brain [63].

Of the 41 potent compounds listed in Table 2, only one has a $K_d < 1.5$ nM and a log P $> +1.5$, namely adimolol. Unfortunately, adimolol has a chemical structure which is not amenable to labeling with either ^{11}C or ^{18}F .

Although some of the 46 β -blockers listed in Table 3 have been labeled with ^{11}C or ^{18}F and evaluated for imaging purposes, no specific binding was ever observed *in vivo*. This

result was to be expected, since for these antagonists, $B_{\max}/K_d < 1$. Therefore, they cannot accumulate in target tissues above plasma levels due to ligand-receptor interaction.

Thus, extensive screening of the pharmacological literature yields very few novel drugs which can still be labeled with a positron emitter and be evaluated as radiopharmaceuticals for cerebral β -adrenoceptor imaging. ^{11}C -Exaprolol and ^{11}C -L643,717 may be prepared, using the acetone and methyl iodide methods.

ENHANCING LIGAND UPTAKE: BLOOD-BRAIN BARRIER OPENING

Since there are very few novel candidate ligands for β -adrenoceptor imaging in the CNS, we considered the possibility of enhancing the brain uptake of existing radioligands (e.g. ^{11}C -CGP 12388 or ^{11}C -CGP12177) by temporary opening of the blood-brain barrier. Various strategies for BBB opening have been proposed to deliver therapeutic agents (cytostatic drugs, antisense oligonucleotides, immune

proteins and growth factors) to human brain for the treatment of intracerebral tumors and other diseases [107, 190, 134].

Permeability of the BBB can be increased by the following techniques:

Osmotic Shock

If a hypertonic solution of mannitol, arabinose or urea is administered for 30 s through a vessel which supplies blood to the brain, the endothelial cells in the cerebral vessels contract, both via passive shrinking and because of calcium-induced contraction of the cytoskeleton. This leads to transient opening of the blood-brain barrier, for a period of 10 min to about 2 h [22, 134, 212, 248].

Receptor-Mediated Permeability Increase

The cytoskeleton of endothelial cells can also be forced to contract by administration of bradykinin or histamine H_2 receptor agonists. The synthetic peptide RMP-7 (Cereport^R, labradimil) is used for this purpose in clinical trials [17, 57, 74].

Inducing Endothelial Leakiness

The endothelium lining the cerebral blood vessels can be made leaky by transient infusion of various compounds, such as short-chain alkylglycerols, sodium dodecylsulfate, dehydrocholate and oleic acid. Such compounds induce large pores in the vessel wall which allow the transport of therapeutic drugs with molecular weights up to 70 kD [76, 176, 199, 219, 227].

Acute Acidosis

Infusion of an acidic buffer (40 mM malonic acid pH 2.5) induces transient (60 s) opening of the tight junctions in the cerebral endothelium, resulting in significant brain uptake of polar test substances [178]. A similar effect is observed after provoking acute hypertension by infusion of epinephrine or phenylephrine [171].

Infusion of Bacterial Glycopeptides

Causes a time- and dose-dependent increase of the permeability of the blood-brain barrier for substances with molecular weight smaller than 20 kD [218].

Although such strategies have shown to be effective and will certainly result in increased uptake of polar radiopharmaceuticals within the CNS [6, 7, 119], they cannot be used for cerebral β -adrenoceptor imaging.

First, the barrier modifiers have to be infused through a vessel which supplies blood to the brain, preferably the arteria carotis. Intrafemoral infusion is not effective [34]. After infusion of the therapeutic agents, the blood-brain barrier is opened in one cerebral hemisphere only (the ipsilateral hemisphere). Cannulation of the carotis followed by osmotic opening of the blood-brain barrier is a surgical manipulation which cannot be performed in healthy volunteers. It requires general anesthesia [203] and is only allowed in patients when the benefits of the treatment outweigh its risks.

Second, osmotic opening of the blood-brain barrier appears to be relatively dangerous. Development of microinfarction is possible [225], although this risk can be minimized by administration of the mannitol solution via a Millipore filter to prevent infusion of microcrystals [235, 189]. Seizures were noticed in 2 out of 45 cancer patients upon infusion of mannitol [197]. Finally, there is the possibility of subsequent demyelination and development of multiple sclerosis [3].

This combination of factors makes opening of the BBB a last resort for the treatment of cancer, but not a viable option for the study of neuroreceptors within the human CNS.

ENHANCING LIGAND UPTAKE: PRODRUG APPROACH

Another approach to enhance the brain uptake of established radioligands is esterification of the OH-group in the aryloxy part of the molecule, resulting in a lipophilic prodrug which can be converted to the active compound by cerebral esterases. An example of this targeting strategy is the registered drug bopindolol (Sandonorm^R, see Fig. 4). Bopindolol is the benzoyl ester of the beta-blocker LT18-502. The active drug (LT18-502) has a high affinity to the β_1 and β_2 subtypes of adrenoceptors (K_d 0.7 and 0.4 nM), but its lipophilicity is low (calculated logP -0.29 at pH 7.4) which results in a relatively low bioavailability after oral dosing. The prodrug (bopindolol) is much more lipophilic (calculated logP +2.45 at pH 7.4) and easily taken up from the intestine. In contrast to its active metabolite, bopindolol has a rather low affinity to β_1 -adrenoceptors (K_d 229 nM), but it is

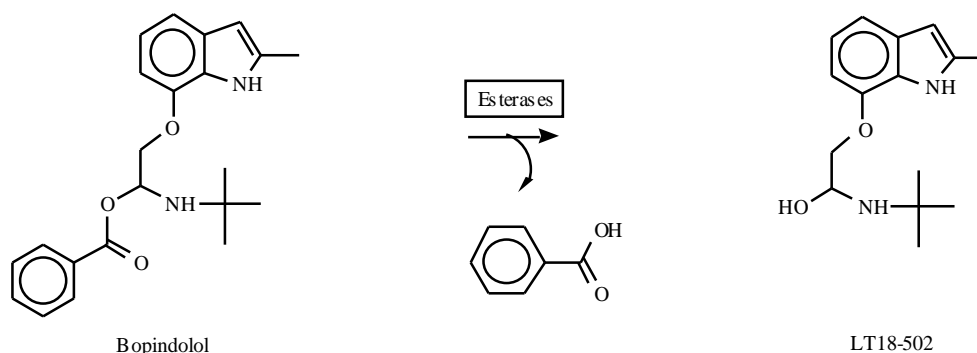


Fig. (4). Conversion of bopindolol to its active metabolite by esterases.

rapidly converted to LT18-502 *in vivo*, since the benzoyl ester bond is hydrolyzed [30, 42, 108, 109, 177, 200].

A similar targeting strategy could be employed to increase the delivery of hydrophilic ligands to the brain of intact animals or man. A calculated logP of +2.45 (as displayed by bopindolol) is about optimal for passive diffusion of a radiolabeled compound across the blood-brain barrier upon intravenous injection [147, 59, 165, 208]. Hopefully, the benzoyl esters are not substrates for P-glycoprotein, for this would result in very low brain uptake, as was observed for ¹¹C-carvedilol. If the esterified β -blockers are not actively expelled from the brain, visualisation of cerebral β -adrenoceptors will be critically dependent on rapid conversion of the prodrugs to the active compounds. The half-life of the benzoyl ester of LT18-502 in humans upon oral dosing is 18 min [4], i.e. within a PET time scale, but the half-life of the ester bond within the CNS is unknown. If the hydrolysis of benzoyl esters within the CNS is not rapid enough, other chemical structures (e.g. acetyl- and butyl esters) could be tried. A comparable targeting strategy, i.e. synthesis of ketoxime analogs of known β -blockers, has been used to deliver β -adrenoceptor antagonists to the iris-ciliary body of the eye [26].

Calculations show that the logP of several potent β -blockers can be changed to the optimal value of +2...+3 by the addition of a benzoyl group. Thus, this approach may hold promise for the development of novel radioligands for the visualisation of cerebral β -adrenoceptors.

CONCLUSION

The development of radioligands for visualisation of cerebral β -adrenoceptors has proven to be unusually difficult. Future work in this area should perhaps be focused on chemical modification of myocardial imaging agents to increase their lipophilicity (i.e., a prodrug approach to target the tracer to the CNS) rather than on labeling of β -blockers which are used as drugs.

ABBREVIATIONS

BIS	=	Bisoprolol
BUP	=	Fluoroisopropyl analog of bupranolol
CAR	=	Carazolol
CGP	=	CGP12177 and/or CGP12388
CGP1	=	CGP12177
CGP2	=	CGP20712A
CGP3	=	CGP12388
CVD	=	Carvedilol
FCA	=	Fluorocarazolol
FCG	=	Fluoroisopropyl analog of CGP12388
FEC	=	Fluoroethylcarazolol
FOR	=	Formoterol
FPR	=	Fluoropropranolol
ICI	=	ICI 118,551

ICYP	=	Iodocyanopindolol
IPIN	=	Iodopindolol
PEN	=	Penbutolol
PIN	=	Pindolol
PRO	=	Procateterol
SUV	=	Standardized Uptake Value

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