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van Waarde, Aaren; Vaalburg, W.; Doze, Petra; Bosker, Fokko; Elsinga, P.H

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

Aren van Waarde*, Willem Vaalburg, Petra Doze, Fokko J.Bosker[1] and Philip H. Elsinga

PET Center and [1]Dept. Biological Psychiatry, Groningen University Hospital P.O.Box 30001, Hanzeplein 1 9700 RB Groningen The Netherlands

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 ^{11}C or ^{18}F and some of these are successful myocardial imaging agents, only two (*S*-1'-^{18}F-fluorocarazolol and *S*-1'-^{18}F-fluoroethylcarazolol) could actually visualize ß-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 ß-adenoceptor imaging. However, other imaging techniques could be examined. Cerebral ß-adrenoceptors might be labeled after temporary opening of the blood-brain barrier (BBB) and simultaneous administration of a hydrophilic ligand such as S-^{11}C-CGP12388. Another approach to target ß-adrenoceptor ligands to the CNS is esterification of a myocardial imaging agent (such as ^{11}C-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 α- and β-adrenoceptors [8]. The former induce activation of the uterus and vasoconstriction, the latter inhibition of the uterus and vasodilation. Later still, ß-adrenoceptors were classified in two different subtypes: $ß_1$ and $ß_2$ [136]. Beta-1 agonists stimulate cardiac contractility and lipolysis, whereas beta-2 agonists cause bronchodilation and vasodepression. Since then, $ß_1$-adrenoceptors involved in lipolysis have been reclassified as 'atypical' or $ß_3$-adrenoceptors [14]. A fourth subtype, the putative $ß_4$-adrenoceptor, has been suggested to exist in myocardial and adipose tissue [84, 127]. Blocking this subtype requires much higher concentrations of ß-adrenoceptor antagonists than those required to block $ß_1$- or $ß_2$-adrenoceptors.

Since responses to stressful situations occur all over the body, ß-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 ß-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

*Address correspondence to this author at the PET Center, Groningen University Hospital, P.O. Box 30001, Hanzeplein 1, 9700 RB Groningen, The Netherlands; Tel: +31-50-3613215; Fax: +31-50-3611687;
E-mail: a.van.waarde@pet.azg.nl

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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 ß-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 ß-adrenoceptors are involved in several physiological functions, such as respiratory [12, 81], cardiovascular [231] and renal [132] sympathetic nervous control. Furthermore, ß-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 ß-adrenoceptor density and/or ß-adrenoceptor signalling in particular brain areas.

Cerebral ß-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 ß-adrenoceptor density and of the activity of ß-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 ß-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 ß-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 ß-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 ß-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 ß-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 ß-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 ß-adrenoceptor densities and/or coupling of ß-adrenoceptors to the G_s protein. Low doses of lipophilic ß-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 ß-adrenoceptor function. In some patients with Parkinson's disease, an increased number of $ß_1$ 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 ß-adrenoceptor subpopulations (decrease of $ß_1$, increase of $ß_2$) [123, 247] and impaired ß-adrenoceptor coupling to adenylyl cyclase [47] in various regions of the brain. An almost complete loss of $ß_1$-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 $ß_2$-adrenoceptor density in the posterior putamen, probably as a result of gliosis [249]. Normal aging is accompanied by a slow decrease of $ß_1$-adrenoceptor densities in human brain [123, 202]. Apparently, this loss is accelerated in certain forms of neurodegeneration.

POSITRON EMISSION TOMOGRAPHY (PET) OF CEREBRAL ß-ADRENOCEPTORS

If a method could be developed to image and quantify ß-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 *ß-adrenoceptor availability* after administration of noradrenalin reuptake inhibitors could be assessed in the intact human brain, reduced ß-adrenoceptor availability indicating increased occupancy of the ß-adrenoceptor population by endogenous noradrenalin.

(c) The time course of *$ß_1$-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 ß-adrenergic sites [257], but glial cells possess $ß_2$-adrenoceptors [154]. Gliosis after neurodegeneration might therefore be visualized with a suitable $ß_2$-adrenoceptor ligand and PET. Proliferation of microglia results normally in increased $ß_2$-adrenoceptor densities in white matter, but astrocyte proliferation in multipe sclerosis is not accompanied by such increases because astrocytes in MS have lost their $ß_2$-adrenoceptors [52, 257].

Myocardial and pulmonary ß-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, respectively[1]), they do not cross the blood-brain barrier. Therefore, the Ciba-Geigy compounds are not suitable for visualization of ß-adrenoceptors in the central nervous system.

Some lipophilic ß-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 ß-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 ß-adrenoceptors in human brain, the following questions should be answered in this review:

(1) Do other lipophilic ß-blockers exist which could be labeled with ^{11}C or ^{18}F and tested as radiopharmaceuticals for cerebral ß-adrenoceptor imaging?

(2) Can a strategy be devised to increase the brain uptake of established ß-adrenoceptor ligands, so that they become suitable for visualisation of ß-adrenoceptors within the central nervous system?

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

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 ß-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 ß-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 ß-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].

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 ß-adrenoceptor imaging, since most ß-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 ß-adrenoceptors are widely distributed throughout the brain and low densities are only observed in white matter, pons and medulla [257]. Most ß-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 ß-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 (^{11}C only 20 minutes), this is a stringent requirement.

PREDICTIVE VALUE OF THE CRITERIA

The literature on ß-blockers usually provides only the following information: (i) chemical structure of the compound; (ii) some proof of its action (affinity to ß-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 ß-adrenoceptors?

To answer the first question, we plotted the uptake of sixteen ß-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 ß-blockers occurs at log P values between +2 and +3, just as has been described for other radiopharmaceuticals. Unfortunately, ß-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.

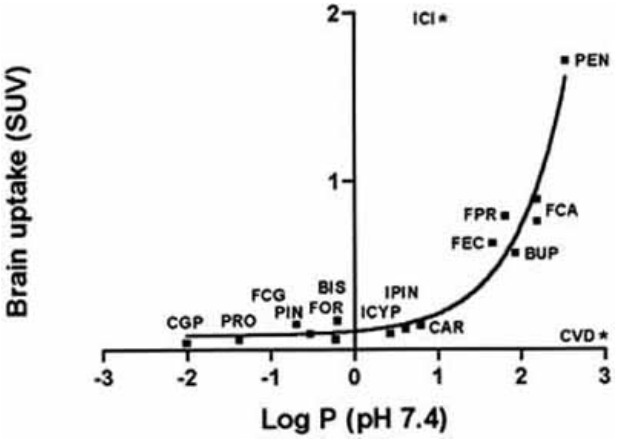


Fig. (1). Relationship between (calculated) log P and brain uptake of ß-adrenoceptor ligands. Brain uptake is plotted as the SUV in rat brain at 60 min post injection (with exception of formoterol and procaterol for which only data at 10 min post injection were available). Uptake data were from the following 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 ^{11}C-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 ß-blockers which are only weak substrates for this ATP-dependent drug efflux pump [174]. Another exception is ^{11}C-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 ß-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 ß-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 ß-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 ß-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 $ß_1$:$ß_2$ 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 ß-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 ($<= 10^{-10}$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-1 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 ß-adrenoceptors may have been overestimated. Estimations of the affinity of ß-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 ß-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 ß-adrenoceptor imaging.

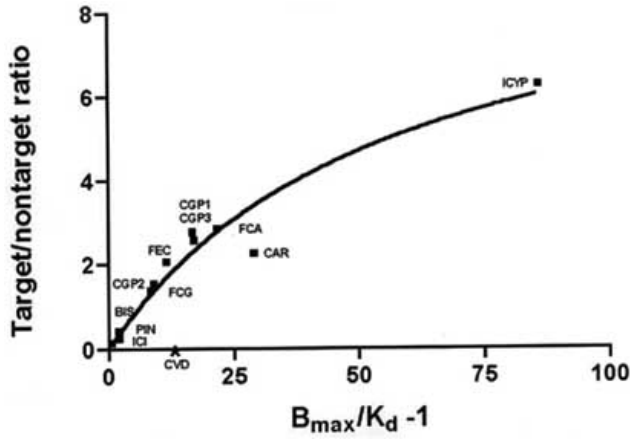


Fig. (2). Relationship between the *in vitro* affinities of ß-adrenoceptor ligands and their target/nontarget ratios observed in rat heart *in vivo*. Target/nontarget ratios were calculated from tissue uptake in the absence and presence of propranolol, at 60 min after injection (with exception of ICI118,551, 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 ß-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 ß-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 ß-adrenoceptor antagonists (K_d > 100 nM, Table **3**).

Of the 57 extremely potent ß-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 ß-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]Iodohydroxybenzylpindolol 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 ß-adrenoceptors and could be explored for

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

Compound	$ß_1$ affinity (nM)	$ß_2$ 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 *et al.,* compd 12	0.1 [77]	0.5 [77]	-1.19c
Erhardt *et al.,* 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 *et al.,* compd 4a	35 [129]	0.6 [129]	-2.80c
Kierstead *et al.,* compd 4d	650 [129]	< 0.1 [129]	-3.71c
Kierstead *et al.,* compd 4f	60 [129]	0.8 [129]	-3.38c
Kierstead *et al.,* compd 4v	55 [129]	< 0.1 [129]	-3.52c

(Table 1) contd….

Compound	ß$_1$ affinity (nM)	ß$_2$ 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 *et al.*, compd 3b	0.2 [156]	< 0.1 [156]	+0.91c
McClure *et al.*, compd 34	0.6 [158]	Not determined	+0.14c
McClure *et al.*, compd 40	0.7 [158]	Not determined	+0.86c
McClure *et al.*, compd 42	0.7 [158]	Not determined	+0.86c
(S,R) 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. ß-Adrenoceptor Antagonists with Affinities in the nM Range for at least one of the ß-Adrenoceptor Subtypes

Compound	ß$_1$ affinity (nM)	ß$_2$ 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 et al., compd 15a	Unknown	1.3 [37]	+0.04c
Carré et al., compd 15b	Unknown	1.3 [37]	+0.13c
Carré et al., compd 9b	Unknown	2.0 [37]	+1.41c
Compound A	Like MK-761 [207]	Like MK-761 [207]	+0.23c

(Table 2) contd….

Compound	ß$_1$ affinity (nM)	ß$_2$ 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
l-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 ß-Blockers

Compound	ß$_1$ affinity (nM)	ß$_2$ 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]

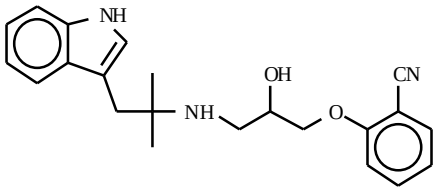
(Table 3) contd….

Compound	ß$_1$ affinity (nM)	ß$_2$ 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
exo 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

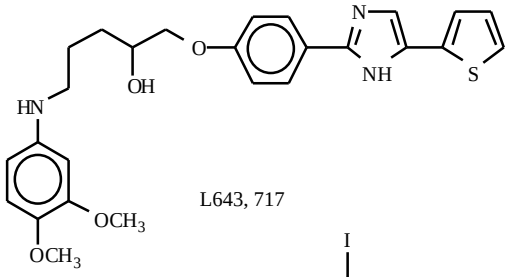
(Table 3) contd….

Compound	ß$_1$ affinity (nM)	ß$_2$ affinity (nM)	Log P (pH 7.4)
Affinity > 100 nM			
Landiolol	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

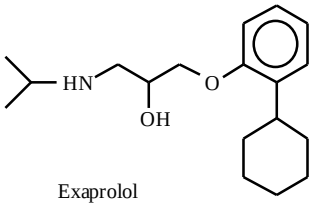
Abbreviations as in Table 1



Bucindolol



L643, 717



Exaprolol

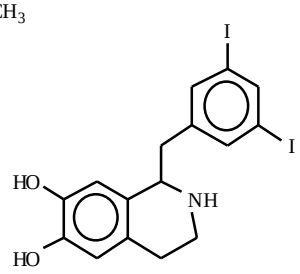


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Fig. (3). Chemical structures of some potent ß-blockers which have not yet been labeled with a positron emitter.

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 ß-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 ß-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 ß-adrenoceptor imaging. ^{11}C-Exaprolol and ^{11}C-L643,717 may be prepared, using the acetone and methyliodide methods.

ENHANCING LIGAND UPTAKE: BLOOD-BRAIN BARRIER OPENING

Since there are very few novel candidate ligands for ß-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 ß-adrenoceptor imaging.

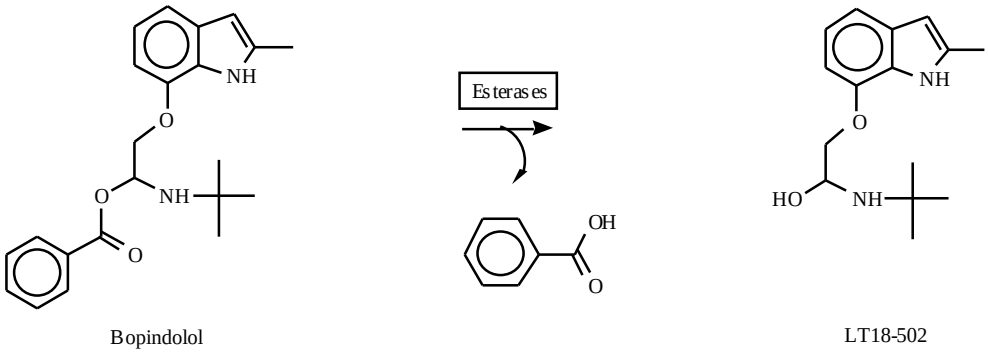
First, the barrier modifiers have to be infused through a vessel which supplies blood to the brain, preferably the arteria carotis. Intrafemoral infusion is not effective [34]. After infusion of the therapeutic agents, the blood-brain barrier is opened in one cerebral hemisphere only (the ipsilateral 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 $ß_1$ and $ß_2$ 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 $ß_1$-adrenoceptors (K_d 229 nM), but it is



Bopindolol LT18-502

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 ^{11}C-carvedilol. If the esterified ß-blockers are not actively expelled from the brain, visualisation of cerebral ß-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 beta-blockers, has been used to deliver beta-adrenoceptor antagonists to the iris-ciliary body of the eye [26].

Calculations show that the logP of several potent ß-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 ß-adrenoceptors.

CONCLUSION

The development of radioligands for visualisation of cerebral beta-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 beta-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 = Procaterol

SUV = Standardized Uptake Value

REFERENCES

References 259-261 are related articles recently published in Current Pharmaceutical Design.

[1] Aberg G, Adler G, Wikberg J. Inhibition and facilitation of lacrimal flow by beta-adrenergic drugs. Acta Ophthalmol 1979; 57: 225-235.

[2] Adam KR, Baird JR, Burges RA, Linnell J. The beta-blocking potency and cardioselectivity of tolamolol and its isomers in rodents. Eur J Pharmacol 1974; 25: 170-175.

[3] Adler S, Martinez J, Williams DS, Verbalis JG. Positive association between blood brain barrier disruption and osmotically-induced demyelination. Mult Scler 2000; 6: 24-31.

[4] Aellig WH, Nuesch E, Engel G, Grevel J, Niederberger W, Rosenthaler J. Relationship between plasma concentrations and cardiac beta- adrenoceptor blockade--a study with oral and intravenous bopindolol. Br J Clin Pharmacol 1986; 21: 45-51.

[5] Affolter H, Hertel C, Jaeggi K, Portenier M, Staehelin M. (-)-S-[^{3}H]CGP-12177 and its use to determine the rate constants of unlabeled beta-adrenergic antagonists. Proc Natl Acad Sci USA 1985; 82: 925-929.

[6] Agon P, Goethals P, Van Haver D, Kaufman JM. Permeability of the blood-brain barrier for atenolol studied by positron emission tomography. J Pharm Pharmacol 1991; 43: 597-600.

[7] Agon P, Kaufman JM, Goethals P, Van Haver D, Bogaert MG. Study with positron emission tomography of the osmotic opening of the dog blood-brain barrier for quinidine and morphine. J Pharm Pharmacol 1988; 40: 539-543.

[8] Ahlquist RP. A study of the adrenotropic receptors. Am J Physiol 1948; 153: 586-600.

[9] Ahren B Rerup C. Effects of beta-adrenoceptor agonists and antagonists on thyroid hormone secretion. Eur J Pharmacol 1983; 88: 383-387.

[10] Amerini S, Bini R, Cerbai E, Ledda F, Mantelli L, Mugelli A. *In vitro* evaluation of the beta-blocking and electrophysiological properties of mepindolol. Arch Int Pharmacodyn Ther 1986; 282: 276-287.

[11] Anand A Charney DS. Norepinephrine dysfunction in depression. J Clin Psychiatry 2000; 61 Suppl 10: 16-24.

[12] Annane D. Beta-adrenergic mediation of the central control of respiration: myth or reality. J Toxicol Clin Exp 1991; 11: 325-336.

[13] Arango V, Underwood MD, Mann JJ. Alterations in monoamine receptors in the brain of suicide victims. J Clin Psychopharmacol 1992; 12: 8S-12S.

[14] Arch JR, Ainsworth AT, Cawthorne MA, Piercy V, Sennitt MV, Thody VE, et al. Atypical beta-adrenoceptor on brown adipocytes as target for anti-obesity drugs. Nature 1984; 309: 163-165.

[15] Bailly D. The role of ß-adrenoceptor blockers in the treatment of psychiatric disorders. CNS Drugs 1996; 5: 115-136.

[16] Barnes PJ. Beta-adrenergic receptors and their regulation. Am J Respir Crit Care Med 1995; 152: 838-860.

[17] Barnett FH, Rainov NG, Ikeda K, Schuback DE, Elliott P, Kramm CM, et al. Selective delivery of herpes virus vectors to experimental brain tumors using RMP-7. Cancer Gene Ther 1999; 6: 14-20.

[18] Baum T, Rowles G, Shropshire AT, Gluckman MI. Beta adrenergic blocking and cardiovascular properties of two new substances, Ko 1313 and Ko 1366. J Pharmacol Exp Ther 1971; 176: 339-349.

[19] Berger G, Mazière M, Prenant C, Sastre J, Syrota A, Comar D. Synthesis of ^{11}C-propranolol. J Radioanal Chem 1982; 74: 301-304.

[20] Berman DE, Dudai Y. Memory extinction, learning anew, and learning the new: dissociations in the molecular machinery of learning in cortex. Science 2001; 291: 2417-2419.

[21] Berridge MS, Cassidy EH, Terris AH, Vesselle JM. Preparation and *in vivo* binding of [^{11}C]carazolol, a radiotracer for the beta-adrenergic receptor. Nucl Med Biol 1992; 19: 563-569.

[22] Bhattacharjee, AK, Nagashima T, Kondoh T, Tamaki N. Quantification of early blood-brain barrier disruption by in situ brain perfusion technique. Brain Res Brain Res Protoc 2001; 8: 126-131.

[23] Biegon A, Israeli M. Regionally selective increases in beta-adrenergic receptor density in the brains of suicide victims. Brain Res 1988; 442: 199-203.

[24] Bilski AJ, Hadfield SE, Wale JL. The pharmacology of epanolol (ICI 141292)--a new beta 1-selective adrenoceptor partial agonist. J Cardiovasc Pharmacol 1988; 12: 227-232.

[25] Bilski AJ, Halliday SE, Fitzgerald JD, Wale JL. The pharmacology of a beta 2-selective adrenoceptor antagonist (ICI 118,551). J Cardiovasc Pharmacol 1983; 5: 430-437.

[26] Bodor N, el-Koussi A, Kano M, Nakamura T. Improved delivery through biological membranes. 26. Design, synthesis, and pharmacological activity of a novel chemical delivery system for beta-adrenergic blocking agents. J Med Chem 1988; 31: 100-106.

[27] Bonomi L, Perfetti S, Noya E, Bellucci R, Massa F. Comparison of the effects of nine beta-adrenergic blocking agents on intraocular pressure in rabbits. Albrecht Von Graefes Arch Klin Exp Ophthalmol 1979; 210: 1-8.

[28] Bouzoubaa M, Leclerc G, Rakhit S, Andermann G. New chiral and isomeric cyclopropyl ketoxime propanolamine derivatives with potent beta-adrenergic blocking properties. J Med Chem 1985; 28: 896-900.

[29] Brannan SK, Miller A, Jones DJ, Kramer GL, Petty F. Beta-adrenergic receptor changes in learned helplessness may depend on stress and test parameters. Pharmacol Biochem Behav 1995; 51: 553-556.

[30] Brasch H, Dominiak P. Beta-adrenoceptor blocking effects of two bopindolol metabolites in isolated guinea-pig atria. Arzneimittelforschung 1992; 42: 97-100.

[31] Brixius K, Bundkirchen A, Bolck B, Mehlhorn U, Schwinger RH. Nebivolol, bucindolol, metoprolol and carvedilol are devoid of intrinsic sympathomimetic activity in human myocardium. Br J Pharmacol 2001; 133: 1330-1338.

[32] Brodde OE. The functional importance of beta 1 and beta 2 adrenoceptors in the human heart. Am J Cardiol 1988; 62: 24C-29C.

[33] Brodde OE, Karad K, Zerkowski HR, Rohm N, Reidemeister JC. Coexistence of beta 1- and beta 2-adrenoceptors in human right atrium. Direct identification by (+/-)-[^{125}I]iodocyanopindolol binding. Circ Res 1983; 53: 752-758.

[34] Bullard DE, Bigner DD. Blood-brain barrier disruption in immature Fischer 344 rats. J Neurosurg 1984; 60: 743-750.

[35] Bylund DB, Charness ME, Snyder SH. Beta adrenergic receptor labeling in intact animals with ^{125}I- hydroxybenzylpindolol. J Pharmacol Exp Ther 1977; 201: 644-653.

[36] Cahill L, Prins B, Weber M, McGaugh JL. Beta-adrenergic activation and memory for emotional events. Nature 1994; 371: 702-704.

[37] Carre MC, Youlassani A, Caubere P, Saint-Aubin-Floch A, Blanc M, Advenier C. Synthesis of a novel series of (aryloxy) propanolamines: new selective beta 2-blocking agents. J Med Chem 1984; 27: 792-799.

[38] Cash R, Ruberg M, Raisman R, Agid Y. Adrenergic receptors in Parkinson's disease. Brain Res 1984; 322: 269-275.

[39] Chen IJ, Liou SJ, Liou SS, Lin CN. Xanthonolol: a calcium channel and beta-adrenoceptor blocker with vasodilating properties. Gen Pharmacol 1993; 24: 1425-1433.

[40] Chen IJ, Yeh JL, Lo YC, Sheu SH, Lin YT. Capsinolol: the first beta-adrenoceptor blocker with an associated calcitonin gene-related peptide releasing activity in the heart. Br J Pharmacol 1996; 119: 7-14.

[41] Cheng HC, Reavis OK, Grisar JM, Claxton GP, Weiner DL, Woodward JK. Antihypertensive and adrenergic receptor blocking properties of the enantiomers of medroxalol. Life Sci 1980; 27: 2529-2534.

[42] Chin WP, Sun HT, Kawada T, Imai S. Beta-blocking actions and the partial agonist activity of bopindolol, a new beta-adrenoceptor antagonist, and its two metabolites. Nippon Yakurigaku Zasshi 1989; 94: 27-33.

[43] Clark BJ, Saameli K, Troxler F. Proceedings: Pharmacological studies with LL 21-945, a new beta- adrenoceptor blocking agent with a long duration of action. Br J Pharmacol 1974; 52: 123P.

[44] Clifton JE, Collins I, Hallett P, Hartley D, Lunts LH, Wicks PD. Arylethanolamines derived from salicylamide with alpha- and beta-adrenoceptor blocking activities. Preparation of labetalol, its enantiomers, and related salicylamides. J Med Chem 1982; 25: 670-679.

[45] Conway PG, Tejani-Butt S, Brunswick DJ. Interaction of beta adrenergic agonists and antagonists with brain beta adrenergic receptors *in vivo*. J Pharmacol Exp Ther 1987; 241: 755-762.

[46] Correa FM, Innis RB, Rouot B, Pasternak GW, Snyder SH. Fluorescent probes of alpha- and beta-adrenergic and opiate receptors: biochemical and histochemical evaluation. Neurosci Lett 1980; 16: 47-53.

[47] Cowburn RF, Vestling M, Fowler CJ, Ravid R, Winblad B, O'Neill C. Disrupted beta 1-adrenoceptor-G protein coupling in the temporal cortex of patients with Alzheimer's disease. Neurosci Lett 1993; 155: 163-166.

[48] Crow TJ, Cross AJ, Cooper SJ, Deakin JF, Ferrier IN, Johnson JA, et al. Neurotransmitter receptors and monoamine metabolites in the brains of patients with Alzheimer-type dementia and depression, and suicides. Neuropharmacology 1984; 23: 1561-1569.

[49] Daemmgen JW, Diederen W, Kadatz R, Pelzer H. Pharmacology of H-I 42, a novel long-acting and highly selective ß$_1$-adrenoceptor blocking agent. Naunyn Schmiedebergs Arch Pharmacol 1982; 321: R20.

[50] Daemmgen JW, Engelhardt G, Pelzer H. Pharmacological properties of an extremely selective beta 1- adrenoceptor antagonist, 2-[4-[3-(tert-Butylamino)-2-hydroxypropoxy] phenyl]-3-methyl-6-methoxy-4(3H)-quinazolinone [+/-)HX-CH 44 BS). Arzneimittelforschung 1985; 35: 383-390.

[51] Dale HH. On some physiological actions of ergot. J Physiol 1906; 34: 163-206.

[52] De Keyser J, Wilczak N, Leta R, Streetland C. Astrocytes in multiple sclerosis lack beta-2 adrenergic receptors. Neurology 1999; 53: 1628-1633.

[53] de Mey C, Schroeter V, Butzer R, Jahn P, Weisser K, Wetterich U, et al. Dose-effect and kinetic-dynamic relationships of the beta-adrenoceptor blocking properties of various doses of talinolol in healthy humans. J Cardiovasc Pharmacol 1995; 26: 879-8.

[54] De Paermentier F, Cheetham SC, Crompton MR, Katona CL, Horton RW. Lower cortical beta-adrenoceptor binding sites in post-mortem samples from depressed suicide victims. Br J Pharmacol 1989; 98 Suppl: 818P.

[55] De Paermentier F, Cheetham SC, Crompton MR, Katona CL, Horton RW. Brain beta-adrenoceptor binding sites in antidepressant-free depressed suicide victims. Brain Res 1990; 525: 71-77.

[56] De Paermentier F, Cheetham SC, Crompton MR, Katona CL, Horton RW. Brain beta-adrenoceptor binding sites in depressed suicide victims: effects of antidepressant treatment. Psychopharmacology 1991; 105: 283-288.

[57] Deli MA, Dehouck MP, Cecchelli R, Abraham CS, Joo F. Histamine induces a selective albumin permeation through the blood- brain barrier *in vitro*. Inflamm Res 1995; 44 Suppl 1: S56-S57.

[58] Dickinson KE, Nahorski SR. Atypical characteristics of frog and chick erythrocyte beta- adrenoceptors. Eur J Pharmacol 1981; 74: 43-52.

[59] Dishino DD, Welch MJ, Kilbourn MR, Raichle ME. Relationship between lipophilicity and brain extraction of C-11-labeled radiopharmaceuticals. J Nucl Med 1983; 24: 1030-1038.

[60] Doggrell SA. Effects of (+)- and (-)-amosulalol on the rat isolated right ventricle. J Cardiovasc Pharmacol 1987; 9: 213-218.

[61] Dooley DJ, Bittiger H, Reymann NC. CGP 20712 A: a useful tool for quantitating beta 1- and beta 2- adrenoceptors. Eur J Pharmacol 1986; 130: 137-139.

[62] Doze P, Elsinga PH, de Vries EF, Van Waarde A, Vaalburg W. Mutagenic activity of a fluorinated analog of the beta-adrenoceptor ligand carazolol in the Ames test. Nucl Med Biol 2000; 27: 315-319.

[63] Doze P, Elsinga PH, Maas B, Van Waarde A, Wegman T, Vaalburg W. Synthesis and evaluation of radiolabeled antagonists for imaging of beta-adrenoceptors in the brain with PET. Neurochem Int 2002; 40: 145-155.

[64] Doze P, Elsinga PH, Van Waarde A, Pieterman RM, Pruim J, Vaalburg W, et al. Quantification of beta-adrenoceptor density in the human heart with (S)-[^{11}C]CGP 12388 and a tracer kinetic model. Eur J Nucl Med 2002; 29: 295-304.

[65] Doze P, van-Waarde A, Elsinga PH, Hendrikse NH, Vaalburg W. Enhanced cerebral uptake of receptor ligands by modulation of P-glycoprotein function in the blood-brain barrier. Synapse 2000; 36: 66-74.

[66] Doze P, Van Waarde A, Elsinga PH, Van Loenen-Weemaes AMA, Willemsen ATM, Vaalburg W. Validation of S-1'-[^{18}F]fluorocarazolol for *in vivo* imaging and quantification of cerebral ß-adrenoceptors. Eur J Pharmacol 1998; 353: 215-226.

[67] Doze P, Van Waarde A, Tewson TJ, Vaalburg W, Elsinga PH. Synthesis and evaluation of (S)-[^{18}F]-fluoroethylcarazolol for *in vivo* beta-adrenoceptor imaging in the brain. Neurochem Int 2002; 41: 17-27.

[68] Dreyer AC, Offermeier J. *In vitro* assessment of the selectivities of various beta-adrenergic blocking agents. Life Sci 1980; 27: 2087-2092.

[69] Eckelman WC. Sensitivity of new radiopharmaceuticals. Nucl Med Biol 1998; 25: 169-173.

[70] Eckelman WC, Gibson RE. The design of site-directed radiopharmaceuticals for use in drug discovery. In: Burns HD, Gibson RE, Dannals RF, Siegl PK Ed. Nuclear Imaging in Drug Discovery, Development and Approval. Boston, Birkhäuser 1992; 113-134.

[71] Ek BA, Nahorski SR. Beta-adrenergic control of motility in the rat colon. II. Proportions of beta 1- and beta 2-adrenoceptors identified with ^{125}I-(-)pindolol binding. Gastroenterology 1986; 90: 408-413.

[72] Elsinga PH, Doze P, Van Waarde A, Pieterman RM, Blanksma PK, Willemsen AT, et al. Imaging of beta-adrenoceptors in the human thorax using (S)-[^{11}C]CGP12388 and positron emission tomography. Eur J Pharmacol 2001; 433: 173-176.

[73] Elsinga PH, Van Waarde A, Visser GM, Vaalburg W. Synthesis and preliminary evaluation of (R,S)-1-[2-((carbamoyl-4-hydroxy) phenoxy)-ethylamino]-3-[4-(1-[^{11}C]-methyl-4-trifluorometh yl-2-imidazolyl)phenoxy]-2-propanol ([11C]CGP 20712A) as a selective ß$_1$-adrenoceptor ligand for PET. Nucl Med Biol 1994; 21: 211-217.

[74] Emerich DF, Snodgrass P, Pink M, Bloom F, Bartus RT. Central analgesic actions of loperamide following transient permeation of the blood brain barrier with Cereport (RMP-7). Brain Res 1998; 801: 259-266.

[75] Emilien G, Maloteaux JM. Current therapeutic uses and potential of beta-adrenoceptor agonists and antagonists. Eur J Clin Pharmacol 1998; 53: 389-404.

[76] Erdlenbruch B, Jendrossek V, Eibl H, Lakomek M. Transient and controllable opening of the blood-brain barrier to cytostatic and antibiotic agents by alkylglycerols in rats. Exp Brain Res 2000; 135: 417-422.

[77] Erhardt PW, Woo CM, Matier WL, Gorczynski RJ, Anderson WG. Ultra-short-acting beta-adrenergic receptor blocking agents. 3. Ethylenediamine derivatives of (aryloxy)propanolamines having esters on the aryl function. J Med Chem 1983; 26: 1109-1112.

[78] Fekete MI, Elekes I, Kurti M, Borvendeg J. Pharmacology of GYKI-41 099 (chlorpropanol, Tobanum) a new potent beta-adrenergic antagonist. Arch Int Pharmacodyn Ther 1980; 248: 190-202.

[79] Femmer K, Poppe H. Pharmacology of the optically active isomers of talinolol (cordanum) 2. Pharmazie 1982; 37: 505-508.

[80] Flugge G, Ahrens O, Fuchs E. Beta-adrenoceptors in the tree shrew brain. II. Time-dependent effects of chronic psychosocial stress on [^{125}I]iodocyanopindolol bindings sites. Cell Mol Neurobiol 1997; 17: 417-432.

[81] Folgering H. Central beta-adrenergic effects on the control of ventilation in cats. Respiration 1980; 39: 131-138.

[82] Friebe M, Suda K, Spies H, Syhre R, Berger R, Johannsen B, et al. Permeation studies *in vitro* and *in vivo* of potential radiopharmaceuticals with affinity to neuroreceptors. Pharm Res 2000; 17: 754-760.

[83] Fujita H, Tanaka J, Maeda N, Sakanaka M. Adrenergic agonists suppress the proliferation of microglia through beta 2-adrenergic receptor. Neurosci Lett 1998; 242: 37-40.

[84] Galitzky J, Langin D, Verwaerde P, Montastruc JL, Lafontan M, Berlan M. Lipolytic effects of conventional beta 3-adrenoceptor agonists and of CGP 12,177 in rat and human fat cells: preliminary pharmacological evidence for a putative beta 4-adrenoceptor. Br J Pharmacol 1997; 122: 1244-1250.

[85] Gharami K, Das S. Thyroid hormone-induced morphological differentiation and maturation of astrocytes are mediated through the beta-adrenergic receptor. J Neurochem 2000; 75: 1962-1969.

[86] Gibson RE, Eckelman WC, Rzeszotarski WJ, Jiang VW, Mazaitis A, Paik C, et al. Radiotracer localization by ligand-receptor interactions. In: Colombetti LG Ed. Principles of Radiopharmacology, Volume 2. West Palm Beach, CRC Press 1979; 17-40.

[87] Gobbi M, Mennini T, Ratti E. Biochemical characterization of a new highly cardioselective beta- adrenoceptor antagonist. J Pharm Pharmacol 1988; 40: 243-246.

[88] Goodenough DJ, Atkins F. Theoretical limitations of tumor imaging. In: Srivastava S Ed. Radiolabeled Monoclonal Antibodies for Imaging and Therapy. New York, Plenum Press 1988; 495-512.

[89] Gorczynski RJ Vuong A. Cardiovascular pharmacology of ACC-9089--a novel, ultra-short-acting, beta-adrenergic receptor antagonist. J Cardiovasc Pharmacol 1984; 6: 555-564.

[90] Graafsma SJ, van Tits LJ, Rodrigues de Miranda JF, Thien T. Kinetics of (-)^{125}iodocyanopindolol binding to intact human mononuclear cells. J Recept Res 1988; 8: 773-785.

[91] Greven J, van Eys B, Jacobs W. Stimulation of glucose release of the rat kidney *in vivo* by epinephrine and isoprenaline. Pharmacology 1975; 13: 265-271.

[92] Gries J, Unger L, Einig H, Friedrich L, Hofmann HP, Kreiskott H, et al. Pharmacological characterization of the new highly potent beta-adrenergic receptor blocker soquinolol. Arzneimittelforschung 1988; 38: 1271-1279.

[93] Gurguis GN, Kramer G, Petty F. Indices of brain beta-adrenergic receptor signal transduction in the learned helplessness animal model of depression. J Psychiatr Res 1996; 30: 135-146.

[94] Gurguis GN, Turkka J, Laruelle M, Kleinman J, Linnoila M. Coupling efficiency of brain beta-adrenergic receptors to Gs protein in suicide, alcoholism and control subjects. Psychopharmacology 1999; 145: 31-38.

[95] Gurguis GN, Yonkers KA, Blakeley JE, Phan SP, Williams A, Rush AJ. Adrenergic receptors in premenstrual dysphoric disorder. II. Neutrophil beta2-adrenergic receptors: G_s protein coupling, phase of menstrual cycle and prediction of luteal phase symptom severity. Psychiatry Res 1998; 79: 31-42.

[96] Haspel T. Beta-blockers and the treatment of aggression. Harv Rev Psychiatry 1995; 2: 274-281.

[97] Hauck RW, Schulz C, Emslander HP, Bohm M. Pharmacological actions of the selective and non-selective beta- adrenoceptor antagonists celiprolol, bisoprolol and propranolol on human bronchi. Br J Pharmacol 1994; 113: 1043-1049.

[98] Hayes MJ, Qing F, Rhodes CG, Rahman SU, Ind PW, Sriskandan S, et al. *In vivo* quantification of human pulmonary beta-adrenoceptors: effect of beta-agonist therapy. Am J Respir Crit Care Med 1996; 154: 1277-1283.

[99] Härtfelder G, Lessenich H, Schmitt K. Penbutolol (Hoe 893 d), ein neues, stark wirksames ß-Sympatholytikum mit langer Wirkungsdauer. Arzneimittelforschung 1972; 22: 930-932.

[100] Hellriegel ET, D'Mello AP. The effect of acute, chronic and chronic intermittent stress on the central noradrenergic system. Pharmacol Biochem Behav 1997; 57: 207-214.

[101] Hendrikse NH. Monitoring Interactions at ATP-Dependent Drug Efflux Pumps. Curr Pharm Des 2000; 6: 1653-1668.

[102] Heron C, Gould TJ, Bickford P. Acquisition of a runway motor learning task is impaired by a beta adrenergic antagonist in F344 rats. Behav Brain Res 1996; 78: 235-241.

[103] Hipolide DC, Tufik S, Raymond R, Nobrega JN. Heterogeneous effects of rapid eye movement sleep deprivation on binding to alpha- and beta-adrenergic receptor subtypes in rat brain. Neuroscience 1998; 86: 977-987.

[104] Hodges-Savola C, Rogers SD, Ghilardi JR, Timm DR, Mantyh PW. Beta-adrenergic receptors regulate astrogliosis and cell proliferation in the central nervous system *in vivo*. Glia 1996; 17: 52-62.

[105] Hoey AJ, Jackson CM, Pegg GG, Sillence MN. Characteristics of cyanopindolol analogues active at the beta 3- adrenoceptor in rat ileum. Br J Pharmacol 1996; 119: 564-568.

[106] Horii D, Kawada T, Takeda K, Imai S. Comparison of beta-adrenergic blocking activities of propranolol, isopropylmethoxamine, sotalol, practolol, alprenolol, pindolol, oxprenolol and D-32

in the atria and trachea of the guinea-pig. Arzneimittelforschung 1974; 24: 1275-1277.

[107] Horner HC, Barbu K, Bard F, Hall D, Janatpour M, Manning K, et al. Permeation of the blood-brain barrier for drug delivery to the brain. NIDA Res Monogr 1992; 120: 218-229.

[108] Hosohata Y, Sasaki K, Suzuki M, Karakisawa Y, Maruyama K, Tsuchihashi H, et al. Alpha-1 and beta-adrenergic receptor blocking potencies of bopindolol and its two metabolites (18-502 and 20-785) as assessed by radioligand binding assay methods. Gen Pharmacol 1995; 26: 743-747.

[109] Hosohata Y, Suzuki M, Karakisawa Y, Maruyama K, Nagatomo T. The affinity of bopindolol and its two metabolites for a beta 2-adrenoceptor in the bovine mesenteric artery. Biol Pharm Bull 1994; 17: 1296-1298.

[110] Hughes B, Kane KA, McDonald FM, Parratt JR. Aspects of the cardiovascular pharmacology of exaprolol. J Pharm Pharmacol 1984; 36: 597-601.

[111] Hugues FC, Julien D, Bors V, Mougeot G, Marche J. Determination in man of the beta blocking properties and the pharmacological half of pargolol. Therapie 1980; 35: 475-481.

[112] Ichiyama M, Sada S, Takahashi Y, Sada H, Ban T. Effects of bucumolol, nadolol and nifenalol on maximum upstroke velocity of action potential in guinea pig papillary muscles. Naunyn Schmiedebergs Arch Pharmacol 1986; 332: 297-304.

[113] Iguchi S, Iwamura H, Nishizaki M, Hayashi A, Senokuchi K, Kobayashi K, et al. Development of a highly cardioselective ultra short-acting beta- blocker, ONO-1101. Chem Pharm Bull 1992; 40: 1462-1469.

[114] Ijzerman AP, Aue GH, Bultsma T, Linschoten MR, Timmerman H. Quantitative evaluation of the beta 2-adrenoceptor affinity of phenoxypropanolamines and phenylethanolamines. J Med Chem 1985; 28: 1328-1334.

[115] Ijzerman AP, Bultsma T, Timmerman H, Zaagsma J. The relation between ionization and affinity of beta-adrenoceptor ligands. Naunyn Schmiedebergs Arch Pharmacol 1984; 327: 293-298.

[116] Imura T, Shimohama S, Sato M, Nishikawa H, Madono K, Akaike A, et al. Differential expression of small heat shock proteins in reactive astrocytes after focal ischemia: possible role of beta-adrenergic receptor. J Neurosci 1999; 19: 9768-9779.

[117] Innis RB, Correa FM, Synder SH. Carazolol, an extremely potent beta-adrenergic blocker: binding to beta- receptors in brain membranes. Life Sci 1979; 24: 2255-2264.

[118] Inui J, Imamura H. Beta-adrenoceptor blocking and electrophysiological effects of bufetolol in the guinea pig atria. Eur J Pharmacol 1977; 41: 251-260.

[119] Jiao S, Miller PJ, Lapchak PA. Enhanced delivery of [^{125}I]glial cell line-derived neurotrophic factor to the rat CNS following osmotic blood-brain barrier modification. Neurosci Lett 1996; 220: 187-190.

[120] Johansson B. Effects of atenolol, metroprolol, and pamatolol on cardiac and vascular beta-adrenoceptors in the rat. J Cardiovasc Pharmacol 1979; 1: 287-298.

[121] Joyce JN, Lexow N, Kim SJ, Artymyshyn R, Senzon S, Lawrence D, et al. Distribution of beta-adrenergic receptor subtypes in human post-mortem brain: alterations in limbic regions of schizophrenics. Synapse 1992; 10: 228-246.

[122] Kafka MS, Benedito MA, Blendy JA, Tokola NS. Circadian rhythms in neurotransmitter receptors in discrete rat brain regions. Chronobiol Int 1986; 3: 91-100.

[123] Kalaria RN, Andorn AC, Tabaton M, Whitehouse PJ, Harik SI, Unnerstall JR. Adrenergic receptors in aging and Alzheimer's disease: increased beta 2- receptors in prefrontal cortex and hippocampus. J Neurochem 1989; 53: 1772-1781.

[124] Kam ST, Matier WL, Mai KX, Barcelon-Yang C, Borgman RJ, O'Donnell JP et al. [(Arylcarbonyl)oxy]propanolamines. 1. Novel beta-blockers with ultrashort duration of action. J Med Chem 1984; 27: 1007-1016.

[125] Katz MS, Dax EM, Gregerman RI. Beta adrenergic regulation of rat liver glycogenolysis during aging. Exp Gerontol 1993; 28: 329-340.

[126] Kau ST, Howe BB, Li JH, Smith LH, Keddie JR, Barlow JJ, et al. ICI 147,798: a novel diuretic agent with beta adrenoceptor blocking activity. J Pharmacol Exp Ther 1987; 242: 818-826.

[127] Kaumann AJ. Four beta-adrenoceptor subtypes in the mammalian heart. Trends Pharmacol Sci 1997; 18: 70-76.

[128] Kaumann AJ, Lemoine H. Direct labelling of myocardial beta 1-adrenoceptors. Comparison of binding affinity of ^{3}H-(-)-bisoprolol with its blocking potency. Naunyn Schmiedebergs Arch Pharmacol 1985; 331: 27-39.

[129] Kierstead RW, Faraone A, Mennona F, Mullin J, Guthrie RW, Crowley H, et al. beta 1-selective adrenoceptor antagonists. 1. Synthesis and beta- adrenergic blocking activity of a series of binary (aryloxy)propanolamines. J Med Chem 1983; 26: 1561-1569.

[130] Klimek V, Rajkowska G, Luker SN, Dilley G, Meltzer HY, Overholser JC, et al. Brain noradrenergic receptors in major depression and schizophrenia. Neuropsychopharmacology 1999; 21: 69-81.

[131] Knezl V, Magna D, Sotnikova R, Drimal J. Effect of the new beta-adrenolytic compound propyl-3-acetyl-4-[(2- hydroxy-3-isopropylamino) propoxy]carbanylate hydrochloride on isolated heart muscle. Arzneimittelforschung 1994; 44: 7-12.

[132] Koepke JP, Jones S, DiBona GF. Hypothalamic beta 2-adrenoceptor control of renal sympathetic nerve activity and urinary sodium excretion in conscious, spontaneously hypertensive rats. Circ Res 1986; 58: 241-248.

[133] Koike K, Horinouchi T, Takayanagi I. Comparison of interactions of R(+)- and S(-)-isomers of beta-adrenergic partial agonists, befunolol and carteolol, with high affinity site of beta-adrenoceptors in the microsomal fractions from guinea-pig ciliary body, right atria and trachea. Gen Pharmacol 1994; 25: 1477-1481.

[134] Kroll RA, Neuwelt EA. Outwitting the blood-brain barrier for therapeutic purposes: osmotic opening and other means. Neurosurgery 1998; 42: 1083-1099.

[135] Lacey RJ, Berrow NS, Scarpello JH, Morgan NG. Selective stimulation of glucagon secretion by beta 2-adrenoceptors in isolated islets of Langerhans of the rat. Br J Pharmacol 1991; 103: 1824-1828.

[136] Lands AM, Arnold A, McAuliff JP, Ludvena FP, Brown RG. Differentiation of receptor systems activated by sympathomimetic amines. Nature 1967; 214: 597-598.

[137] Law MP. Demonstration of the suitability of CGP 12177 for *in vivo* studies of ß-adrenoceptors. Br J Pharmacol 1993; 109: 1101-1109.

[138] Le Fur G, Canton T, Malgouris C, Paillard JJ, Hardy JC, Gueremy C, et al. Stereospecificity of the *in vitro* and *in vivo* blockade of beta- receptors by FM 24, a slowly reversible ligand. Life Sci 1981; 29: 2481-2489.

[139] Lefroy DC, De Silva R, Choudhury L, Uren NG, Crake T, Rhodes CG, et al. Diffuse reduction of myocardial beta-adrenoceptors in hypertrophic cardiomyopathy: a study with positron emission tomography. J Am Coll Cardiol 1993; 22: 1653-1660.

[140] Lekieffre J, Carre A. Evaluation of the acute hemodynamic effects of butofilolol in the arterial hypertensive patient. Comparison with propranolol and atenolol. Ann Cardiol Angeiol 1984; 33: 339-343.

[141] Lemmer B, Neumann G. Circadian phase dependency of the effects of different beta-receptor blocking drugs on motor activity of rats. Importance of drug lipophilicity. Arzneimittelforschung 1987; 37: 321-325.

[142] Lemoine H. Beta-adrenoceptor ligands: Characterization and quantification of drug effects. Quant Struct Act Relat 1992; 11: 211-218.

[143] Lemoine H, Ehle B, Kaumann AJ. Direct labelling of beta 2-adrenoceptors. Comparison of binding potency of ^{3}H-ICI 118,551 and blocking potency of ICI 118,551. Naunyn Schmiedebergs Arch Pharmacol 1985; 331: 40-51.

[144] Lemoine H, Kaumann AJ. A novel analysis of concentration-dependence of partial agonism Ring- demethylation of bupranolol results in a high affinity partial agonist (K 105) for myocardial and tracheal beta-adrenoceptors. Naunyn Schmiedebergs Arch Pharmacol 1982; 320: 130-144.

[145] Leon M. Catecholaminergic contributions to early learning. Adv Pharmacol 1998; 42: 961-964.

[146] Levin BE, Dunn-Meynell A. Noradrenergic innervation does not affect chronic regulation of [^{125}I]pindolol receptors in fetal rat brain transplants or host neocortex. Brain Res 1989; 494: 325-338.

[147] Levin VA. Relationship of octanol/water partition coefficient and molecular weight to rat brain capillary permeability. J Med Chem 1980; 23: 682-684.

[148] Lin YT, Wu BN, Horng CF, Huang YC, Hong SJ, Lo YC, et al. Isoeugenolol: a selective beta1-adrenergic antagonist with tracheal

and vascular smooth muscle relaxant properties. Jpn J Pharmacol 1999; 80: 127-136.

[149] Little KY, Clark TB, Ranc J, Duncan GE. Beta-adrenergic receptor binding in frontal cortex from suicide victims. Biol Psychiatry 1993; 34: 596-605.

[150] Los Angeles JE, Nikulin VI, Shams G, Konkar AA, Mehta R, Feller DR, et al. Iodinated analogs of trimetoquinol as highly potent and selective beta 2-adrenoceptor ligands. J Med Chem 1996; 39: 3701-3711.

[151] Maj J, Klimek V, Lewandowska A, Zazula M. Central beta- and alpha-adrenolytic activities of adimolol. Pol J Pharmacol Pharm 1987; 39: 81-90.

[152] Malta E, Mian MA, Raper C. The *in vitro* pharmacology of xamoterol (ICI 118,587). Br J Pharmacol 1985; 85: 179-187.

[153] Mano K, Akbarzadeh A, Townley RG. Effect of hydrocortisone on beta-adrenergic receptors in lung membranes. Life Sci 1979; 25: 1925-1930.

[154] Mantyh PW, Rogers SD, Allen CJ, Catton MD, Ghilardi JR, Levin LA, et al. Beta 2-adrenergic receptors are expressed by glia *in vivo* in the normal and injured central nervous system in the rat, rabbit, and human. J Neurosci 1995; 15: 152-164.

[155] Mattsson H, Andersson T, Carlsson E, Hedberg A, Lundgren B, Olsson T. beta 1-and beta 2-adrenoceptor stimulatory effects of prenalterol. Naunyn Schmiedebergs Arch Pharmacol 1982; 321: 302-308.

[156] Mauleon D, Pujol MD, Rosell G. Synthesis and beta-adrenergic antagonism of 2-(aryloxy)-1-(2- piperidyl)ethanols. J Med Chem 1988; 31: 2122-2126.

[157] McCaffrey PM, Riddell JG, Shanks RG. An assessment of the partial agonist activity of Ro 31-1118, flusoxolol and pindolol in man. Br J Clin Pharmacol 1987; 24: 571-580.

[158] McClure DE, Baldwin JJ, Randall WC, Lyon TF, Mensler K, Lundell GF, et al. Antihypertensive beta-adrenergic blocking agents: N-aralkyl analogues of 2-[3-(tert-butylamino)-2-hydroxypropoxy]-3-cyanopyridine. J Med Chem 1983; 26: 649-657.

[159] McGaugh JL. Memory--a century of consolidation. Science 2000; 287: 248-251.

[160] Melamed E, Lahav M, Atlas D. Direct localisation of beta-adrenoceptor sites in rat cerebellum by a new fluorescent analogue of propranolol. Nature 1976; 261: 420-422.

[161] Merlet P, Delforge J, Syrota A, Angevin E, Maziere B, Crouzel C, et al. Positron emission tomography with 11C CGP-12177 to assess beta- adrenergic receptor concentration in idiopathic dilated cardiomyopathy. Circulation 1993; 87: 1169-1178.

[162] Meyerson LR, Wennogle LP, Abel MS, Coupet J, Lippa AS, Rauh CE, et al. Human brain receptor alterations in suicide victims. Pharmacol Biochem Behav 1982; 17: 159-163.

[163] Milavec-Krizman M, Evenou JP, Wagner H, Berthold R, Stoll AP. Characterization of beta-adrenoceptor subtypes in rat kidney with new highly selective beta 1 blockers and their role in renin release. Biochem Pharmacol 1985; 34: 3951-3957.

[164] Minneman KP, Hegstrand LR, Molinoff PB. Simultaneous determination of beta-1 and beta-2 adrenergic receptors in tissues containing both receptor subtypes. Mol Pharmacol 1979; 16: 34-46.

[165] Moerlein SM, Laufer P, Stocklin G. Effect of lipophilicity on the *in vivo* localization of radiolabelled spiperone analogues. Nucl Med Biol 1985; 12: 353-356.

[166] Monopoli A, Forlani A, Bevilacqua M, Vago T, Norbiato G, Bertora P, et al. Interaction of selected vasodilating beta-blockers with adrenergic receptors in human cardiovascular tissues. J Cardiovasc Pharmacol 1989; 14: 114-120.

[167] Moore RY, Bloom FE. Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems. Annu Rev Neurosci 1979; 2: 113-168.

[168] Moresco RM, Matarrese M, Soloviev D, Simonelli P, Rigamonti M, Gobbo C, et al. Synthesis and *in vivo* evaluation of [^{11}C]ICI 118551 as a putative subtype selective beta2-adrenergic radioligand. Int J Pharm 2000; 204: 101-109.

[169] Mostaghim R, Maddox YT, Ramwell PW. Endothelial potentiation of relaxation response to beta adrenoceptor blocking agents. J Pharmacol Exp Ther 1986; 239: 797-801.

[170] Muguruma K, Imamura K, Morii H, Watanabe Y. Down-regulation of beta-adrenergic receptor following long-term monocular deprivation in cat visual cortex. Brain Res 1996; 740: 131-140.

[171] Murphy VA, Johanson CE. Adrenergic-induced enhancement of brain barrier system permeability to small nonelectrolytes: choroid plexus versus cerebral capillaries. J Cereb Blood Flow Metab 1985; 5: 401-412.

[172] Nakagawa Y, Sugai T, Chin WP, Shibuya T, Hashimoto K, Imai S. Pharmacological profile of a new beta-adrenoceptor blocker, 4-[3-(tert- butylamino)-2-hydroxypropoxy]-N-methylisocarbostyril hydrochloride (N- 696). Arzneimittelforschung 1984; 34: 194-199.

[173] Nanoff C, Freissmuth M, Schutz W. The role of a low beta 1-adrenoceptor selectivity of [^{3}H]CGP-12177 for resolving subtype-selectivity of competitive ligands. Naunyn Schmiedebergs Arch Pharmacol 1987; 336: 519-525.

[174] Neuhoff S, Langguth P, Dressler C, Andersson TB, Regardh CG, Spahn-Langguth H. Affinities at the verapamil binding site of MDR1-encoded P- glycoprotein: drugs and analogs, stereoisomers and metabolites. Int J Clin Pharmacol Ther 2000; 38: 168-179.

[175] Nichols AJ, Sulpizio AC, Ashton DJ, Hieble JP, Ruffolo RR. The interaction of the enantiomers of carvedilol with alpha 1- and beta 1-adrenoceptors. Chirality 1989; 1: 265-270.

[176] Ohnishi T, Aida K, Awazu S. Enhancement of blood-brain barrier permeability by sodium caprate. J Pharm Pharmacol 1999; 51: 1015-1018.

[177] Okuhira M, Nakazawa M, Kameda H, Hara K, Kawada T, Imai S. Beta-blocking action of bopindolol, a new beta-blocker, and its active metabolites in open chest dogs. Arch Int Pharmacodyn Ther 1993; 323: 5-15.

[178] Oldendorf WH, Stoller BE, Tishler TA, Williams JL, Oldendorf SZ. Transient blood-brain barrier passage of polar compounds at low pH. Am J Physiol 1994; 267: H2229-H2236.

[179] Pandey SC, Ren X, Sagen J, Pandey GN. Beta-adrenergic receptor subtypes in stress-induced behavioral depression. Pharmacol Biochem Behav 1995; 51: 339-344.

[180] Pazos A, Probst A, Palacios JM. Beta-adrenoceptor subtypes in the human brain: autoradiographic localization. Brain Res 1985; 358: 324-328.

[181] Pitha J, Zjawiony J, Nasrin N, Lefkowitz RJ, Caron MG. Potent beta-adrenergic antagonist possessing chemically reactive group. Life Sci 1980; 27: 1791-1798.

[182] Pleschka K, Nurnberger F. Beta-adrenergic signal transduction in the hypothalamus of the European hamster: relation with the seasonal hibernation cycle and the diurnal activity cycle. Biol Cell 1997; 89: 525-529.

[183] Porciatti F, Cerbai E, Masini I, Mugelli A. Electrophysiological evaluation of the beta-blocking properties and direct membrane effects of l-moprolol and its enantiomer d-moprolol. Arch Int Pharmacodyn Ther 1989; 299: 200-209.

[184] Prenant C, Sastre J, Crouzel C, Syrota A. Synthesis of ^{11}C-pindolol. J Label Comp Radiopharm 1987; 24: 227-232.

[185] Qing F, Hayes MJ, Rhodes CG, Krausz T, Fountain SW, Burke MM, et al. Reduced ß- adrenoceptor density *in vivo* in human lung tumours: a preliminary study with positron emission tomography. Thorax 1996; 51: 727-732.

[186] Qing F, Rhodes CG, Hayes MJ, Krausz T, Fountain SW, Jones T, et al. *In vivo* quantification of human pulmonary beta-adrenoceptor density using PET: Comparison with *in vitro* radioligand binding. J Nucl Med 1996; 37: 1275-1281.

[187] Quast U, Vollmer KO. Binding of beta-adrenoceptor antagonists to rat and rabbit lung: special reference to levobunolol. Arzneimittel-forschung 1984; 34: 579-584.

[188] Rajakumar G, Koller MM, Scarpace PJ. Beta-adrenergic receptors and salivary gland secretion during aging. Growth Dev Aging 1992; 56: 215-223.

[189] Rapoport SI. Microinfarction: osmotic BBB opening or micro-crystals in infusate? J Neurosurg 1991; 74: 685.

[190] Rapoport SI. Advances in osmotic opening of the blood-brain barrier to enhance CNS chemotherapy. Expert Opin Investig Drugs 2001; 10: 1809-1818.

[191] Rashidbaigi A, Ruoho AE. Synthesis and characterization of iodoazidobenzylpindolol. J Pharm Sci 1982; 71: 305-307.

[192] Recanatini M. Partition and distribution coefficients of aryloxypro-panolamine beta- adrenoceptor antagonists. J Pharm Pharmacol 1992; 44: 68-70.

[193] Regardh CG, Lundborg P, Gabrielsson M, Heggelund A, Kylberg-Hanssen K. Pharmacokinetics of a single intravenous and oral dose of pafenolol--a beta 1-adrenoceptor antagonist with atypical absorption and disposition properties--in man. Pharm Res 1990; 7: 1222-1227.

[194] Reynolds RD, Gorczynski RJ, Quon CY. Pharmacology and pharmacokinetics of esmolol. J Clin Pharmacol 1986; 26 Suppl A: A3-A14.

[195] Rimele TJ, Henry DE, Giesa FR, Buckley SK, Geiger G, Heaslip RJ, et al. Comparison of the beta-adrenoceptor affinity and selectivity of cetamolol, atenolol, betaxolol, and ICI-118,551. J Cardiovasc Pharmacol 1988; 12: 208-217.

[196] Rogausch H, del Rey A, Oertel J, Besedovsky HO. Norepinephrine stimulates lymphoid cell mobilization from the perfused rat spleen via beta-adrenergic receptors. Am J Physiol 1999; 276: R724-R730.

[197] Roman-Goldstein S, Clunie DA, Stevens J, Hogan R, Monard J, Ramsey F, et al. Osmotic blood-brain barrier disruption: CT and radionuclide imaging. AJNR Am J Neuroradiol 1994; 15: 581-590.

[198] Roth BL, Ernsberger P, Steinberg SA, Rao S, Rauser L, Savage J, et al. The *in vitro* pharmacology of the beta-adrenergic receptor pet ligand (S)-fluorocarazolol reveals high affinity for cloned beta-adrenergic receptors and moderate affinity for the human 5-HT_{1A} receptor. Psychopharmacology 2001; 157: 111-114.

[199] Saija A, Princi P, Trombetta D, Lanza M, De Pasquale A. Changes in the permeability of the blood-brain barrier following sodium dodecyl sulphate administration in the rat. Exp Brain Res 1997; 115: 546-551.

[200] Sakuma N, Tsuchihashi H, Hosohata Y, Akashi H, Kinami J, Nagatomo T. Beta-blocking potency and selectivity of bopindolol and its two metabolites for beta 1- and beta 2-adrenergic receptors as assessed by radioligand binding assay. J Pharmacobiodyn 1991; 14: 250-255.

[201] Saltvedt E, Fauchald P. Effect of single and twice daily doses of primidolol (UK-11,443) in hypertension. Curr Med Res Opin 1980; 6: 528-533.

[202] Sastre M, Guimon J, Garcia-Sevilla JA. Relationships between beta- and alpha2-adrenoceptors and G coupling proteins in the human brain: effects of age and suicide. Brain Res 2001; 898: 242-255.

[203] Sato S, Kawase T, Harada S, Takayama H, Suga S. Effect of hyperosmotic solutions on human brain tumour vasculature. Acta Neurochir 1998; 140: 1135-1141.

[204] Satoh E, Narimatsu A, Hosohata Y, Tsuchihashi H, Nagatomo T. The affinity of betaxolol, a beta 1-adrenoceptor-selective blocking agent, for beta-adrenoceptors in the bovine trachea and heart. Br J Pharmacol 1993; 108: 484-489.

[205] Scatchard G. The attractions of proteins for small molecules and ions. Ann N Y Acad Sci 1949; 51: 660-672.

[206] Schäfers M, Dutka D, Rhodes CG, Lammertsma AA, Hermansen F, Schober O, et al. Myocardial presynaptic and postsynaptic autonomic dysfunction in hypertrophic cardiomyopathy. Circ Res 1998; 82: 57-62.

[207] Scriabine A, Ludden CT, Morgan G, Baldwin JJ. Antihypertensive and cardiac effects of two novel beta-adrenoceptor blocking drugs. Experientia 1979; 35: 1634-1637.

[208] Shah MV, Audus KL, Borchardt RT. The application of bovine brain microvessel endothelial-cell monolayers grown onto polycarbonate membranes *in vitro* to estimate the potential permeability of solutes through the blood-brain barrier. Pharm Res 1989; 6: 624-627.

[209] Shimohama S, Taniguchi T, Fujiwara M, Kameyama M. Changes in beta-adrenergic receptor subtypes in Alzheimer-type dementia. J Neurochem 1987; 48: 1215-1221.

[210] Shin SH, Barton RE. Activation of the adrenergic beta-receptor stimulates prolactin release from primary cultured pituitary cells. Neuroendocrinology 1993; 57: 670-677.

[211] Shiratsuchi M, Kawamura K, Akashi T, Ishihama H, Nakamura M, Takenaka F. Synthesis and activity of optical isomers of nipradilol. Chem Pharm Bull 1987; 35: 3691-3698.

[212] Siegal T, Rubinstein R, Bokstein F, Schwartz A, Lossos A, Shalom E, et al. *In vivo* assessment of the window of barrier opening after osmotic blood- brain barrier disruption in humans. J Neurosurg 2000; 92: 599-605.

[213] Silke B, Verma SP, Sharma SK, Frais MA, Reynolds G, Taylor SH. Comparative effects of atenolol and cicloprolol on cardiac performance in coronary heart disease. J Cardiovasc Pharmacol 1989; 13: 155-161.

[214] Singh KP. Influence of beta-adrenoceptor antagonists on spontaneous rate and on force of contraction of isolated rabbit atria. Indian J Physiol Pharmacol 1983; 27: 311-316.

[215] Soloviev DV, Matarrese M, Moresco RM, Todde S, Bonasera TA, Sudati F, et al. Asymmetric synthesis and preliminary evaluation of (R)- and (S)- [^{11}C]bisoprolol, a putative $beta_1$-selective adrenoceptor radioligand. Neurochem Int 2001; 38: 169-180.

[216] Somani P. Study on some selective ß-adrenoreceptor blocking effects of 1-(4-nitrophenyl)-1-hydroxy-2-methyl isopropylamino-ethane (alpha-methyl INPEA). Br J Pharmacol 1969; 37: 609-617.

[217] Sood S, Dhawan JK, Ramesh V, John J, Gopinath G, Kumar VM. Role of medial preoptic area beta adrenoceptors in the regulation of sleep-wakefulness. Pharmacol Biochem Behav 1997; 57: 1-5.

[218] Spellerberg B, Prasad S, Cabellos C, Burroughs M, Cahill P, Tuomanen E. Penetration of the blood-brain barrier: enhancement of drug delivery and imaging by bacterial glycopeptides. J Exp Med 1995; 182: 1037-1043.

[219] Spigelman MK, Zappulla RA, Malis LI, Holland JF, Goldsmith SJ, Goldberg JD. Intracarotid dehydrocholate infusion: a new method for prolonged reversible blood-brain barrier disruption. Neurosurgery 1983; 12: 606-612.

[220] Staehelin M, Simons P, Jaeggi K, Wigger N. CGP-12177. A hydrophilic beta-adrenergic receptor radioligand reveals high affinity binding of agonists to intact cells. J Biol Chem 1983; 258: 3496-3502.

[221] Stockmeier CA, Meltzer HY. Beta-adrenergic receptor binding in frontal cortex of suicide victims. Biol Psychiatry 1991; 29: 183-191.

[222] Suarez EC, Sherwood A, Hinderliter AL. Hostility and adrenergic receptor responsiveness: evidence of reduced beta-receptor responsiveness in high hostile men. J Psychosom Res 1998; 44: 261-267.

[223] Sugrue MF, Armstrong JM, Gautheron P, Mallorga P, Viader MP. A study on the ocular and extraocular pharmacology of metipranolol. Graefes Arch Clin Exp Ophthalmol 1985; 222: 123-127.

[224] Sutin J, Griffith R. Beta-adrenergic receptor blockade suppresses glial scar formation. Exp Neurol 1993; 120: 214-222.

[225] Suzuki M, Iwasaki Y, Yamamoto T, Konno H, Kudo H. Sequelae of the osmotic blood-brain barrier opening in rats. J Neurosurg 1988; 69: 421-428.

[226] Sybertz EJ, Baum T, Pula KK, Nelson S, Eynon E, Sabin C. Studies on the mechanism of the acute antihypertensive and vasodilator actions of several beta-adrenoceptor antagonists. J Cardiovasc Pharmacol 1982; 4: 749-758.

[227] Sztriha L, Betz AL. Oleic acid reversibly opens the blood-brain barrier. Brain Res 1991; 550: 257-262.

[228] Takayanagi I, Koike K, Nakagoshi A. Interactions of some partial agonists with high and low affinity binding sites in beta-adrenoceptors. Can J Physiol Pharmacol 1987; 65: 18-22.

[229] Takenaka T, Tachikawa S. Beta-adrenergic blocking and cardiovascular properties of a new compound, 1- (7-indenyloxy)-3-isopropylaminopropan-2-ol-hydrochloride (YB-2). Arzneimittelforschung 1972; 22: 1864-1869.

[230] Takita M, Kigoshi S, Muramatsu I. Selectivity of bevantolol hydrochloride towards alpha- and beta- adrenoceptor subtypes in rat cerebral cortex. Jpn J Pharmacol 1992; 58: 193-196.

[231] Tan N, Morimoto A, Morimoto K, Sone R, Nishiyasu T, Watanabe T, et al. Involvement of central beta-adrenoceptors in the tachycardia induced by water immersion stress in rats. Physiol Behav 2000; 68: 291-297.

[232] Tarasiuk A, Sofer S. Effects of adrenergic-receptor blockade and ligation of spleen vessels on the hemodynamics of dogs injected with scorpion venom. Crit Care Med 1999; 27: 365-372.

[233] Taylor EM, Eden RJ, Fielden R, Owen DA. Studies on the autonomic nervous system with SK&F 92657, a new antihypertensive agent causing direct arterial vasodilatation and beta- adrenoceptor blockade. J Cardiovasc Pharmacol 1981; 3: 355-368.

[234] Tewson TJ, Stekhova S, Kinsey B, Chen L, Wiens L, Barber R. Synthesis and biodistribution of R- and S-isomers of [F-18]-fluoropropranolol, a lipophilic ligand for the beta-adrenergic receptor. Nucl Med Biol 1999; 26: 891-896.

[235] Tomiwa K, Hazama F, Mikawa H. Reversible osmotic opening of the blood-brain barrier. Prevention of tissue damage with filtration of the perfusate. Acta Pathol Jpn 1982; 32: 427-435.

[236] Tondo L, Conway PG, Brunswick DJ. Labeling *in vivo* of beta adrenergic receptors in the central nervous system of the rat after

administration of [^{125}I] iodopindolol. J Pharmacol Exp Ther 1985; 235: 1-9.

[237] Tsuchihashi H, Nakashima Y, Kinami J, Nagatomo T. Characteristics of ^{125}I-iodocyanopindolol binding to beta-adrenergic and serotonin-1B receptors of rat brain: selectivity of beta-adrenergic agents. Jpn J Pharmacol 1990; 52: 195-200.

[238] Tumer N, Bender J, Roberts J. Absence of age-related changes in the binding of the beta adrenergic antagonist 125I-iodohydroxybenzylpindolol in rat heart. Proc Soc Exp Biol Med 1987; 186: 118-122.

[239] Ueki J, Rhodes CG, Hughes JMB, De Silva R, Lefroy DC, Ind PW, et al. *In vivo* quantification of pulmonary ß-adrenoceptor density in humans with (S)-[^{11}C]CGP-12177 and PET. J Appl Physiol 1993; 75: 559-565.

[240] Van Waarde A, Elsinga PH, Brodde OE, Visser GM, Vaalburg W. Myocardial and pulmonary uptake of S-1'-[^{18}F]fluorocarazolol in intact rats reflects radioligand binding to ß-adrenoceptors. Eur J Pharmacol 1995; 272: 159-168.

[241] Van Waarde A, Elsinga PH, Doze P, Heldoorn M, Jaeggi KA, Vaalburg W. A novel beta-adrenoceptor ligand for positron emission tomography: Evaluation in experimental animals. Eur J Pharmacol 1998; 343: 289-296.

[242] Van Waarde A, Meeder JG, Blanksma PK, Brodde OE, Visser GM, Elsinga PH, et al. Uptake of radioligands by rat heart and lung *in vivo*: CGP12177 does and CGP26505 does not reflect binding to ß-adrenoceptors. Eur J Pharmacol 1992; 222: 107-112.

[243] Van Waarde A, Visser TJ, Elsinga PH, De Jong BM, van der Mark TW, Kraan J, et al. Imaging beta-adrenoceptors in the human brain with (S)-1'-[^{18}F]fluorocarazolol. J Nucl Med 1997; 38: 934-939.

[244] Verbeuren TJ, Laekeman G, Majchrowicz BB, Jordaens FH, Zonnekeyn LL, Herman AG. Effects of tertatolol on post- and prejunctional beta adrenoceptors. J Pharmacol Exp Ther 1985; 233: 801-809.

[245] Visser TJ, Van der Wouden EA, Van Waarde A, Doze P, Elsinga PH, Vaalburg W. Synthesis and biodistribution of [^{11}C]procaterol, a $ß_2$-adrenoceptor agonist for positron emission tomography. Appl Radiat Isotop 2000; 52: 857-863.

[246] Visser TJ, Van Waarde A, Doze P, Elsinga PH, van der Mark TW, Kraan J, et al. Characterisation of $ß_2$-adrenoceptors, using the agonist [^{11}C]formoterol and positron emission tomography. Eur J Pharmacol 1998; 361: 35-41.

[247] Vogt BA, Crino PB, Volicer L. Laminar alterations in gamma-aminobutyric acidA, muscarinic, and beta adrenoceptors and neuron degeneration in cingulate cortex in Alzheimer's disease. J Neurochem 1991; 57: 282-290.

[248] Vorbrodt AW, Dobrogowska DH, Tarnawski M, Lossinsky AS. A quantitative immunocytochemical study of the osmotic opening of the blood-brain barrier to endogenous albumin. J Neurocytol 1994; 23: 792-800.

[249] Waeber C, Rigo M, Chinaglia G, Probst A, Palacios JM. Beta-adrenergic receptor subtypes in the basal ganglia of patients with Huntington's chorea and Parkinson's disease. Synapse 1991; 8: 270-280.

[250] Warembourg H, Ducloux G. Clinical study of a new anti-arrhythmia agent: nadoxolol. Lille Med 1976; 21: 386-388.

[251] Weiland NG Wise PM. Diurnal rhythmicity of beta-1- and beta-2-adrenergic receptors in ovariectomized, ovariectomized estradiol-treated and proestrous rats. Neuroendocrinology 1989; 50: 655-662.

[252] Wu BN, Ho WC, Chiang LC, Chen IJ. Zingeronolol: A newly developed ß-adrenergic blocking agent derived from zingerone, a pungent principle of ginger. Asia Pacific J Pharmacol 1996; 11: 5-12.

[253] Wu BN, Shen KP, Lin RJ, Huang YC, Chiang LC, Lo YC, et al. Lipid solubility of vasodilatory vanilloid-type beta-blockers on the functional and binding activities of beta-adrenoceptor subtypes. Gen Pharmacol 2000; 34: 321-328.

[254] Wuppermann D, Zimmermann F, Friedrich L. Comparative study on the effects of alprenolol, bunitrolol, ethaverine, oxprenolol, papaverine, practolol, pindolol, pronethalol, propranolol, toliprolol and verapamil on cardiac and bronchial beta- receptors. Arzneimittelforschung 1978; 28: 794-798.

[255] Yeh JL, Liou SF, Liang JC, Huang YC, Chiang LC, Wu JR, et al. Vanidipinedilol: a vanilloid-based beta-adrenoceptor blocker displaying calcium entry blocking and vasorelaxant activities. J Cardiovasc Pharmacol 2000; 35: 51-63.

[256] Yu BH, Dimsdale JE, Mills PJ. Psychological states and lymphocyte beta-adrenergic receptor responsiveness. Neuropsycho-pharmacology 1999; 21: 147-152.

[257] Zeinstra E, Wilczak N, De Keyser J. [^{3}H]dihydroalprenolol binding to beta adrenergic receptors in multiple sclerosis brain. Neurosci Lett 2000; 289: 75-77.

[258] Zheng LB, Berridge MS, Ernsberger P. Synthesis, binding properties, and ^{18}F labeling of fluorocarazolol, a high-affinity ß-adrenergic receptor antagonist. J Med Chem 1994; 37: 3219-3230.

[259] de Paulis T. The discovery of epidepride and its analogs as high-affinity radioligands for imaging extrastriatal dopamine D(2) receptors in human brain. Curr Pharm Design 2003; 9(8): 673-96.

[260] Knox AJ. The scientific rationale of combining inhaled gluco-corticoids and long acting beta 2 adrenoceptor agonists. Curr Pharm Design 2002; 8(20): 1863-9.

[261] Schechter LE, Dawson LA, Harder JA. The potential utility of 5-HT1A receptor antagonists in the treatment of cognitive dysfunction associated with Alzheimer s disease. Curr Pharm Design 2002; 8(2): 139-45.