
Ligands for SPECT and PET Imaging of Muscarinic-Cholinergic Receptors of the Heart and Brain


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ABSTRACT

Interest in the potential use of cerebral SPECT and PET imaging for determination of the density and activity of muscarinic-cholinergic receptors (mACHR) has been stimulated by the changes in these receptors which occur in many neurological diseases. In addition, the important involvement of mACHR in modulating negative inotropic cardiac activity suggests that such receptor ligands may have important applications in evaluation of changes which may occur in cardiac disease. In this paper, the properties of several key muscarinic receptor ligands being developed or which have been used for clinical SPECT and PET are discussed. In addition, the ORNL development of the new iodinated IQNP ligand based on QNB and the results of in vivo biodistribution studies in rats, in vitro competitive binding studies and ex vivo autoradiographic experiments are described. The use of radioiodinated IQNP may offer several advantages in comparison to IQNB because of its easy and high yield preparation and high brain uptake and the potential usefulness of the "partial" subtype selective IQNP isomers. We also describe the development of new IQNP-type analogues which offer the opportunity for radiolabeling with positron-emitting radioisotopes (carbon-11, fluorine-18 and bromine-76) for potential use with PET.

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INTRODUCTION

Recent advances in better understanding the involvement of neurotransmitter pathways and changes which occur in these pathways in various diseases have stimulated the development of radiolabeled ligands which freely cross the intact blood-brain barrier and exhibit high specific binding to neuroreceptors. Another important requirement is that only the unmetabolized ligand localizes in the receptor-rich tissue so that results of external imaging primarily represent ligand-receptor binding. The muscarinic acetylcholine receptor (mAChR) has been extensively studied and four distinct "subtypes" have been identified utilizing classical pharmacological techniques (M, - M,4) (1-2). While M, and M, are present in large amounts in the brain, M, is also found in the myocardium (pacemaker tissue) and M, is found in glandular tissue. More recently, the mAChR has been cloned and five subtypes (m, - m,5) have been identified (2-9). Although the mAChR literature is often confusing, the relationships between the different subtypes has been suggested, where M, = m, and M, = m,.

An evaluation of the anatomical distribution of the muscarinic subtypes has identified loss of cholinergic neurons in dementias, and autopsy studies of brains from patients with histologically proven Alzheimer's disease have shown degeneration of cholinergic neurons in the nucleus basalis of Meynert (2). In addition, receptor binding studies in brain homogenates from Alzheimer's patients have shown that the M, sites labeled by [H-3]-pirenzpine are increased in the striatum (10), while sites labeled with [H-3]-QNB are increased in the cortex (11). Studies have also shown that the high affinity component of agonist (pirenzpine) binding is reduced in the frontal cortex (12) and sites labeled with [H-3]-acetylcholine are decreased in the cortex (13). Collectively, these data suggest a loss of agonist binding sites and up-regulation of remaining antagonist binding sites in areas
known to be affected by the dementia. An important observation from post mortem studies which may have relevance to the development of radiolabeled ligands for imaging receptor density was the observation that presynaptic M₂ receptors degenerate in the cholinergic nerve projections of the nucleus basalis in the cortex and postsynaptic M₂ receptors may even increase by upregulation (2).

For potential cardiac imaging, radiolabeled ligands which bind to the mAChR may have applications in assessing physiological factors involved in myocardial infarction and "sudden death", since altered muscarinic receptor density may be involved in cardiac arrhythmias. In addition to heart muscle, both the sinoventricular and atrioventricular nodes also contain M₂ subtype of the mAChR receptor (14-15). Since bradycardia and the decrease in cardiac contractility are mediated by M₂ receptors, cardiac failure is associated by a dysfunction of cardiac muscarinic-cholinergic receptor activity (2). The pharmacological effects and physiology of muscarinic antagonists and agonists for both brain and heart have been described by Goyal (2). While a decrease in the cardiac rate is inhibited by low (nanomolar) concentrations of acetylcholine by inhibition of the hyperpolarization-activated current involved in generation of pacemaker activity, moderate concentrations have an inhibitory effect, and decrease the strength and rate of contraction. In contrast, high doses of the mAChR agonist carbachol increase the strength and rate of contraction both in vitro and in vivo. These effects are translated into the observed changes of ion channels by coupling with G proteins in modulating the activity of cyclic AMP levels.

In theory, muscarinic agonists and antagonists could play the same role as β-blockers, but their use is limited because of low pharmacological specificity which illicits other unwanted side effects. While release of catecholamines from sympathetic nerves are related to stimulation of β-adrenergic receptors which in turn affect a positive inotropic response, investigations suggest that
release of acetylcholine from parasympathetic nerve endings has a physiological role in depressing the contractile state (negative inotropic effect) enhanced by adrenergic stimulation (16-19). This regulatory effect is illustrated by the well known antagonism of the positive inotropic effect of either infused or neurally-released catecholamines by muscarinic agonists such as muscarine. In concert with these phenomena, the muscarinic receptors are found in regions of the cardiac pacemaker node (right ventricle) and the atrioventricular nodes.

The goals of this paper are to briefly review various radiolabeled ligands which bind to the muscarinic-cholinergic receptors in vivo and to discuss the properties of a new class of ligands based on the IQNP agents developed by McPherson, et al., which show promise for human studies with SPECT and PET (20-26).

**Halogenated Analogues of Dextetimide for SPECT and PET**

Because of its potent antagonist activity, dextetimide (27) was identified as a candidate for labeling with various radioisotopes for evaluation as candidates for SPECT or PET applications (Figure 1). An added advantage of using radiolabeled dextetimide analogues is that use of the radiolabeled biologically inactive isomer, levetimide, may permit background correction techniques for non-specific binding of radiolabeled dextetimide. Both isomers have been radiolabeled with carbon-11 (28), but due to the relatively short physical half-life of carbon-11 (20 minutes), a series of halogenated analogues was prepared and evaluated (29) for potential use with PET and SPECT. The results of these studies demonstrated that the 4-fluoro-, 2-fluoro, 4-bromo- and 4-iododextetimide analogues retain the binding affinity for mAChR exhibited the non-substituted dextetimide parent compound. The 4-bromine-76-labeled analogues of both dextetimide and levetimide have been
recently prepared by electrophilic bromodesilylation, and in vivo studies of mAChR with these labeled analogues are expected to be reported in the near future (30). The [F-18]-labeled 2- and 4-fluoro analogues have also been prepared (31) and evaluated in mice, demonstrating better in vivo stability compared to the 2-fluorodexetimide analogue. However, the low radiochemical yields and the long time period required for preparation of these fluorinated analogues require improvement before these analogues would be expected to be practical for routine use.

While both cerebral and peripheral uptake of [I-123]-iododexetimide is blocked by scopolamine pre-treatment, only peripheral uptake is blocked by pirenzepine pre-treatment, since this antagonist cannot pass through the intact blood/brain barrier (29). Pharmacokinetic studies suggested that although heart imaging with iododexetimide could be conducted within 15-60 minutes following intravenous administration, brain imaging would probably require an overnight waiting period to permit vascular clearance (32).

A series of radioiodinated analogues of iododexetimide were initially prepared and evaluated in mice by Wilson, et al. (29). From these studies 4-iododexetimide analogue was identified as the best candidate for potential SPECT imaging and in vivo and in vitro binding data demonstrated the high affinity of this analogue for m-AChR (IC$_{50}$ = 3.3 nM for muscarinic receptor). The results of these and other initial promising animal studies with iodine-123-labeled dexetimide have progressed to patient studies (32-34). In one recent study, the biodistribution of [I-123]-iododexetimide was evaluated for SPECT imaging of muscarinic receptors in the heart and brain of healthy volunteers (32). Both whole body scans and serial SPECT imaging with a three-headed camera permitted an evaluation of the biodistribution and pharmacokinetics of the radioiodinated dexetimide (32). Radioactivity in the myocardium reached a maximal value soon after injection and decreased slowly
with time. Approximately 0.6% of the injected dose remained in the myocardium after 5 hours, decreasing to 0.4% after 14 hours. Cerebral activity increased slowly following injection and reached a maximum value of 1.9% of injected dose, permitting high quality SPECT images. However, due to the high liver and lung uptake and non-specific binding, iododexetimide has not been considered a suitable candidate for imaging of cardiac mAChR (35). Another expected disadvantage for the routine use of iododexetimide to study receptor density is the apparent lack of receptor subtype specificity.

**Radioiodinated IQNB**

The preparation and evaluation of radioiodinated 3-quinuclidinyl 4-iodobenzilate (IQNB, Figure 2) permitted *in vivo* gamma camera imaging of muscarinic-cholinergic receptors (36-41). Various isomers of *[I-123]*-IQNB have also been evaluated in humans (38-39), but the literature data are sometimes contradictory. Some studies report a differentiation between normal controls and dementia patients, while other studies report no differences. These contrasting results could be due to the small number of patients studied, and differences in methodology and patient selection. Nonetheless, because of the potential importance of measuring differences in muscarinic receptor activity in dementias and other diseases, these types of studies should be expanded to include larger groups of patients of well defined selection criteria. In addition, the two asymmetric centers in IQNB result in the possibility of four different isomers which may have differential sub-type affinities. From an analysis of data in the literature, practical disadvantages for the routine use of *[I-123]*-R,R-IQNB include the relatively low radioiodination yields (42) reported for the triazene decomposition technique and modest cerebral uptake (< 1 per cent i.d.). In addition, vascular clearance for IQNB may be slower than that for IQNP since an overnight waiting period is usually
conducted before SPECT imaging is initiated in patients following intravenous administration of [I-123]-IQNB (36). Although the *in vitro* data suggest that both QNB and IQNB do not exhibit muscarinic subtype selectivity, detailed autoradiographic studies have demonstrated that $M_2$ selectivity is detected *in vivo* with QNB (43-45). These results illustrate the differences often observed and the caution in comparing *in vitro* and *in vivo* data. While the use of iodine-exchange techniques can substantially increase the radioiodination yields of IQNB, the specific activity is *a priori* reduced by this approach, which would be expected to reduce receptor-mediated localization because of competition with unlabeled IQNB. Probably the highest yields would be obtained by an electrophilic destannylation reaction, which would also produce high specific activity product. At the time of this writing, the later approach is being pursued and has been shown to be a useful alternative (K. S. Lee, V. K. Sood and B. Zeeberg, manuscript in preparation).

**Radioiodinated IQNP Analogues**

Other approaches have recently been initiated in attempts to simplify radiolabeling, increase radioiodination yields, increase global brain uptake, and decrease blood levels permitting SPECT imaging within a short time after injection. While radioiodine is attached in the *para*-position of one of the phenyl rings in IQNB, McPherson, *et al.* recently designed a similar analogue (IQNP) in which radioiodine is chemically attached as a terminal vinyl iodide (Figure 3) (20-24). The strategy for development of this new ligand was two-fold, since high radioiodination yields are usually obtained from iododestannylation of vinyl tributylstannanes (Figure 4), and the expected decrease in lipophilicity of the ligand thus allowing high cerebral uptake and a shorter time required between administration and imaging. The possibility of *cis/trans* isomerism in conjunction with isomerism at the two asymmetric centers would also provide the opportunity to evaluate the effects of isomerism
on the relative target/non target localization and possibility sub-type selectivity. The results of in vivo animal studies demonstrated that IQNP may have several advantages in comparison with IQNB (20-23). Because of the relatively high expense of iodine-123 free of iodine-124 produced by proton irradiation of enriched xenon-124 targets, it is important to have high radiochemical and chromatographic yields in a relatively short time frame. Following radiiodination, HPLC purification and formulation, radiiodinated IQNP is obtained in > 65 % yield, which is much higher than the traditional triazene decomposition route for preparation of IQNB, which is reported to proceed in about 15 % yield (42). It also appears that vascular clearance of IQNP is more rapid, and more importantly, that the global cerebral uptake of IQNP is about three times higher than that reported for IQNB. Confirmation of the results from these initial studies will require dual-label studies in which IQNB and IQNP are evaluated in the same animals.

Evaluation of the various isomers of IQNP by McPherson, et al., clearly demonstrated that a combination of structural features, including the absolute configuration of the two asymmetric centers in conjunction with isomerism of the vinyl iodide are important features which affect tissue uptake and retention, and possibly subtype affinity (Figures 5-8) (22-23). While the E-(R,R)-isomer, for instance, shows high uptake in the cortex and other cerebral regions (Figure 6), it also exhibits low uptake and rapid washout from the heart (Figure 5) and cerebellum (Figure 8). In contrast, in addition to high uptake in various cerebral regions, the Z-(R,R)-isomer also showed very high uptake in the myocardium and cerebellum (Figures 5 and 8). These data suggest that the [I-123]-E-(R,R)-IQNP isomer may have utility for brain imaging and that the [I-123]-Z-(R,R)-IQNP isomer may be useful for imaging the heart. The in vivo subtype selectivity is more clearly assessed by evaluation of autoradiographic studies in rats (Figure 10), which demonstrate that both the E- and Z-(R,R) isomers label the thalamic nuclei to about the same degree. While the E-(R,R) isomer appears to
label the pons to a lesser degree than the Z-(R,R) isomer, substantially less of the E-(R,R) isomer localizes in the colliculi in comparisons to Z-(R,R)-IQNP. These data suggest that Z-(R,R)-IQNP is probably "slightly" m2 selective or non-selective in vivo, and that E-(R,R)-IQNP is probably non-selective or very slightly m1/m4 selective in vivo. A slight in vivo m2 selectivity is also consistent with competitive studies with IQNB (unpublished data).

The results of in vitro binding studies correlate well with the in vivo biodistribution studies (Table 1) and show that the relative affinity of the Z-(R,R)-IQNP isomer is much higher for the M2-rich regions in comparison with the E-(R,R)-IQNP isomer. The potential significance of this "partial" subtype selectivity has not yet been determined and will require further studies, especially in primates, as a prelude to initial human evaluation. In other initial metabolic studies, analysis of lipid extracts from brain and other rat tissues demonstrated that E-(R,R)-IQNP is the only radioactive species found in brain extracts for up to 24 hours following intravenous administration of radioiodinated E-(R,R)-IQNP (20,24).

**Analogues of IQNB and IQNP for Potential PET Studies**

Several analogues of QNB and other related compounds (Figures 2 and 9) have been radiolabeled with positron-emitting radionuclides for PET studies (46-55). These include [\(^{11}\text{C}\)]-(+)-2α-tropanyl benzilate (\(^{11}\text{C}-\text{TRB}\)) (48) and [\(^{11}\text{C}\)]-methylscopolamine (49-51). The presence of the tertiary nitrogen atom of the heterocyclic quinuclidinol ring system in QNB and QNP also affords an opportunity for simple quaternization of the ring nitrogen with [\(^{11}\text{C}\)]-methyl iodide (Figures 2 and 9) and evaluation of the heart uptake of these analogues, since such charged species will not cross the blood-brain barrier. The good heart uptake of [C-11]-methiodide of QNB evaluated in humans by
PET (52-53) demonstrates that this agent has potential for cardiac PET. At least initial cardiac uptake may reflect the well established myocardial extraction of monovalent cations, with subsequent receptor binding. Preliminary studies performed with the methiodide of IQNP, however, did not demonstrate similar high cardiac uptake. This type of modification in the IQNP series thus appears to decreases receptor binding affinity.

The corresponding methyl QNP analogues (Figure 3) have not yet been prepared and evaluated, but may offer an opportunity to evaluate the effects of lipophilicity and bulk on receptor affinity of these analogues. The propyl analogue is shown in Figure 3 as an example, but introduction of shorter, longer or branched alkyl chains would represent a series of new compounds. However, because of widespread availability from production in medical cyclotrons and a long half-life, fluorine-18 would be expected to be the radioisotope of choice for PET studies of QNB and QNP analogues. Several para-fluoroalkyl-substituted analogues in the QNB series have been prepared and show receptor binding affinity in vitro (54-55), and presumably further studies with these new compounds will be pursued.

In addition to the vinyl iodide analogues, the vinylbromide and fluoroalkyl analogues of IQNP (Figure 3) have also been recently reported by Luo, et al. (25-26). In a similar manner as stabilization of radioiodide as a vinyl iodide, to increase stability and minimize possible facile in vivo loss, radiobromine is usually attached to radiopharmaceuticals as either a vinyl bromide or on a phenyl ring. Since the fluorine-carbon bond is stronger and vinyl fluorides are difficult to prepare, stabilization of fluorine as a vinyl fluoride is not required and for this reason the simple alkyl fluorides can be prepared. The racemic vinyl bromide analogue, BrQNP, has been prepared and its ability to block localization of radioiodinated IQNP has been evaluated in rats (25). These studies consist
of pre-treatment of animals with a dose of approximately 3 mg BrQNP/kg one hour prior to administration of radioiodinated IQNP. If the BrQNP has high affinity for the receptor sites, pretreatment should significantly reduce uptake of the radioiodinated ligand. The results of the such studies are shown in Table 1, and clearly demonstrate that BrQNP "blocks" uptake of the radioiodinated ligand (25). Bromine-76 is accelerator-produced and is one of the limited number of bromine radioisotopes practical for in vivo imaging. Bromine-76-labeled BrQNP has been prepared and is currently being evaluated in animals (Maziere, et al., personal communication).

Because of the opportunity for production of large amounts in medical cyclotrons, fluorine-18 is the radioisotope of choice for PET imaging of receptor activity and recent studies by Luo, et al. (26), have resulted in the synthesis, characterization and first blocking studies with "FQNE" and "FQNPE", which are two new fluorinated analogues of IQNP (Figures 11-12). Because of unexpected ring closure of the fluoropropyl- and fluorobutyl analogues by participation of the tertiary hydroxyl group to form the cyclic furan and pyran cyclic ethers, the fluoroethyl ("FQNE") and fluoropentyl ("FQNPe") analogues were identified as the target compounds. The synthesis of FQNPe is shown in Figure 12 and this is expected to be the best analogue amendable for fluorine-18-labeling. Both of this new analogues were also evaluated by pre-blocking prior to the intravenous administration of [I-125]-Z-(R,R)-IQNP to rats, and the data (Tables 2 and 3) clearly demonstrate significant blocking, as strong evidence of receptor affinity, and similar in vitro confirmed the results of the in vivo studies (Table 1). Pre-blocking studies at a concentration of about 3 mg/kg demonstrated that FQNPe blocked localization of [I-131]-Z-(R,R)-IQNP in muscarinic receptor-rich tissues, indicating that the [F-18]-labeled FQNPe analogue is an attractive candidate for further evaluation as a potential PET imaging agent. These data are illustrated in Figure 13.
SUMMARY

In this paper the development and use of radiolabeled ligands for in vivo evaluation of mAChR activity in the brain and heart have been briefly discussed. The potential use of M2-subtype selective ligands for the monitoring of muscarinic neuron activity in Alzheimer’s patients would be an important contribution. Agents with "partial" selectivity such as Z-(R,R)-IQNP should be further evaluated, however, since use of such agents may offer some important clinical capabilities for the evaluation of changes in muscarinic-cholinergic neuronal activity which changes in many diseases.

ACKNOWLEDGEMENTS

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Table 1. Mean *In Vitro* Binding Affinity Values of IQNP Analogues - $K_d$ (nM)

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<tr>
<td>m1</td>
<td>0.32</td>
<td>0.383</td>
<td>6.83</td>
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<td>0.23</td>
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<tr>
<td>m2</td>
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<td>0.60</td>
<td>12.575</td>
<td>62.8</td>
<td>3.53</td>
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Table 2. Regional Levels (Per Cent Injected Dose/Gm ± S.D.) of Radioactivity Three Hours Following Intravenous Administration of [I-131]-Z-(R,R)-IQNP in Control Rats and Rats Pretreated One Hour Earlier With Unlabeled FQNE (2-3 mg/kg).*

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Striatum</th>
<th>Hippocampus</th>
<th>Pons</th>
<th>Cerebellum</th>
<th>Heart</th>
<th>Blood</th>
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<tr>
<td>Control</td>
<td>1.20</td>
<td>0.73</td>
<td>0.67</td>
<td>0.70</td>
<td>0.43</td>
<td>1.98</td>
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<td></td>
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<td>±0.20</td>
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<td>FQNE</td>
<td>0.67</td>
<td>0.35</td>
<td>0.22</td>
<td>0.40</td>
<td>0.16</td>
<td>0.78</td>
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<tr>
<td></td>
<td>±0.15</td>
<td>±0.14</td>
<td>±0.19</td>
<td>±0.08</td>
<td>±0.09</td>
<td>±0.30</td>
<td>±0.02</td>
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</tbody>
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* Five female Fisher rats per group.
Table 3. Regional Levels (Per Cent Injected Dose/Gm ± S.D.) of Radioactivity Three Hours Following Intravenous Administration of [I-131]-Z-(R,R)-IQNP in Control Rats and Rats Pretreated One Hour Earlier With Unlabeled FQNPe (2-3 mg/kg).*

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Striatum</th>
<th>Hippocampus</th>
<th>Pons</th>
<th>Cerebellum</th>
<th>Heart</th>
<th>Blood</th>
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<tr>
<td>Control</td>
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<td>0.45</td>
<td>1.84</td>
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<tr>
<td></td>
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<td>±0.16</td>
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<td>FQNPe</td>
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<td>0.06</td>
<td>0.24</td>
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<td></td>
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<td>±0.03</td>
<td>±0.05</td>
<td>±0.07</td>
<td>±0.04</td>
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* Five female Fisher rats per group.
FIGURE LEGENDS

Figure 1. Examples of radiolabeled dexetimide analogues for imaging muscarinic-cholinergic receptors \textit{in vivo}.

Figure 2. Radiolabeled QNB Analogues

Figure 3. Examples of new radiolabeled IQNP analogues for SPECT and PET.

Figure 4. Chemical synthesis of substrate and radioiodination of INQP isomers.

Figure 5. Comparison of the heart uptake and retention of radioiodinated IQNP isomers.

Figure 6. Comparison of rat cortical uptake and retention of [I-125]-IQNP isomers.

Figure 7. Comparison of rat striatal uptake and retention of [I-125]-IQNP isomers.

Figure 8. Comparison of rat cerebellar uptake and retention of [I-125]-IQNP isomers.

Figure 9. Examples of other quaternized [\text{[\text{CH}_3]}]-labeled compounds for imaging muscarinic receptors.

Figure 10. Autoradiographs of cross sections of rat brains following intravenous administration of 200 \( \mu \text{Ci} \) of iodine-131-labeled E-(R,R)-IQNP (left panel) with sacrifice at 2 hours. In the right panel, are shown similar data following administration of 200 \( \mu \text{Ci} \) of the Z-(R,R)-IQNP isomer with a 4 hour sacrifice.

Figure 11. Chemical Synthesis of new FQNE analogue.

Figure 12. Chemical Synthesis of new FQNP\text{e} analogue.

Figure 13. Example of blocking of muscarinic receptor localization of [I-131]-Z-(R,R)-IQNP by pre-treatment of rats with FQNP\text{e} (appox. 3 mg/kg) one hour prior to administration of the radioiodinated ligand. The rats were sacrificed three hours later.
SPECT Ligands

$\text{4 - }^{123}\text{I} - \text{iododextimide}$

$\text{4 - }^{123}\text{I} - \text{iodolevetimide}$

PET Ligands

$\text{4 - }^{18}\text{F} - \text{Fluorodextimide}$

$\text{2 - }^{18}\text{F} - \text{Fluorodextimide}$

$\text{4 - }^{76}\text{Br} - \text{Dextimide}$

$\text{4 - }^{76}\text{Br} - \text{Levetimide}$

Figure 1. Examples of radiolabeled dextimide analogues for imaging muscarinic-cholinergic receptors in vivo.
SPECT Ligands

PET Ligands

IQNB Analogues
(R = methyl, ethyl or propyl)

Figure 2. Radiolabeled analogues of IQNB for SPECT and PET.
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Figure 8. Comparison of rat cerebellar uptake and retention of [I-125]-IQNP isomers.
Figure 8. Examples of other quaternized $^{11}$CH$_3$-labeled compounds for imaging muscarinic receptors.
Figure 10. Autoradiograph of cross section of rat brain following intravenous administration of iodine-131-labeled E-(R,R)-IQNP (left panel) and Z-(R,R)-IQNP (right panel). Each image was individually scaled for display purposes, although the relative radioactivity concentrations can be compared, the absolute per cent injected dose/gram of tissue values cannot be discerned. Coronal slices were taken through the anteroventral thalamic nucleus (Top Panels; Slice #24 from "The Rat Brain Stereotaxic Coordinates," G. Paxinos and C. Watson), hippocampus (Middle Panels; Slice #34) and pons (Lower Panels; Slice #47). Anatomical regions are identified as follows: RSG, retrosplenial granular cortex; RSA, retrosplenial agranular cortex; AVVL, Ventrolateral subnucleus of the anteroventral thalamic nucleus; AVDM, dorsomedial subnucleus of the anteroventral thalamic nucleus; Rt, reticular thalamic nucleus; VL, ventrolateral thalamic nucleus; AD, anterodorsal thalamic nucleus; AM, ateromedial thalamic nucleus; PVA, paraventricular thalamic nucleus, anterior; DG, dentate gyrus; CPU, caudate putamen; GP, globus pallidus; ic, internal capsule; CA1, field CA1 of Ammon's horn; CA2, field CA2 of Ammon's horn; CA3, field CA3 of Ammon's horn; CA4, field CA4 of Ammon's horn; Pn, Pontine nucleus.
Figure 10
Figure 11. Chemical Synthesis of new FQNE analogue.
Figure 12. Chemical Synthesis of new FQNPe analogue.
Figure 13.
Example of blocking of muscarinic receptor localization of [1-125]-Z-(R,R)-IQNP by pre-treatment of rats with FQNPc (approx. 3 mg/kg) one hour prior to administration of the radiolabeled ligand. The rats were sacrificed three hours later.