Lord, J. A. H., Waterfield, A. A., Hughes, J., Kosterlitz, H. W. (1977) Endogenous opioid peptides: multiple agonists and receptors. Nature (London) 267: 495–499

Martin, W. R., Eades, C. G., Thompson, J. A., Huppler, R. E., Gilber, P. E. (1976) The effects of morphine and nalorphine like drugs in the nondependent and morphine dependent chronic spinal dog. J. Pharmacol. Exp. Ther. 197: 517–532

Morley, J. S. (1980) Structure activity relationships of enkephalin-like peptides. Ann. Rev. Pharmacol. Toxicol. 20: 81–110

Nicolas, P., Hammonds, R. G., Li, C. H. (1984) β-Endorphin-induced analgesia is inhibited by synthetic analogs of β-endorphin. Proc. Natl. Acad. Sci. USA. 81: 3074–3077

Pert, C., Snyder, S. H. (1973) Opiate receptor: demonstration in nervous tissue. Science 179: 1011–1014

Portoghese, P. S. (1989) Bivalent ligands and the message-address concept in the design of selective opioid receptor antagonist. Trends Pharmacol. Sci. 10: 230–235

Portoghese, P. S., Lipkowski, A. W., Takemori, A. E. (1987) Binaltorphimine and norbinaltorphimine, a potent and selective κ-opioid receptor antagonist. Life Sci. 40: 1287–1292

Portoghese, P. S., Sultana, M., Takemori, A. E. (1988) Naltrindole, a highly selective and potent non-peptide delta opioid receptor antagonist. Eur. J. Pharmacol. 146: 185–186

Takemori, A. E., Naeseth, J. S., Portoghese, P. S. (1988) Norbinaltorphimine, a highly selective kappa-opioid antagonist in analgesic and receptor binding assays. J. Pharmacol. Exp. Ther. 245: 255–258

Takemori, A. E., Larson, D. L., Portoghese, P. S. (1981) The irreversible narcotic antagonist and reversible agonist properties of the fumarate methyl ester derivate of naltrexone. Eur. J. Pharmacol. 70: 445–453

Valenzuela, R., Li, C. H., Huidobro-Toro, J. P. (1989) Lack of mixed agonist-antagonist properties of [Gln^{8}-Gly^{31}]-βh-EP-Gly-Gly-NH_2 and [Arg^{9,19,24,28,29}]-βh-EP in the rat vas deferens neuroeffector junction: studies with naloxone, β-funaltrexamine and ICI 174,864. J. Pharm. Pharmacol. 41: 92–96

Yamashiro, D., Nicolas, P., Li, C. H. (1982) β-Endorphin: synthesis and properties of analogs modified in position 8 and 31. Int. J. Pept. Prot. Res. 20: 43–46

Zaoral, M., Yamashiro, D., Hammonds, R. G., Li, C. H. (1981) β-Endorphin: synthesis and radioreceptor binding activity of βh-EP 1–27 and its analogs. Ibid. 17: 292–296

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Permeability of the blood-brain barrier for atenolol studied by positron emission tomography

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Abstract—The permeability of the blood-brain barrier for atenolol, a hydrophilic β-adrenergic blocking agent, has been assessed in dogs, by studying the distribution of [^{11}C]atenolol in brain tissue with positron emission tomography. The passage of atenolol into the brain was very limited, but a measurable small net influx into the brain tissues did occur. Osmotic opening of the blood-brain barrier resulted in a marked increase of the atenolol concentrations in brain tissue. The approach described, with sequential non-invasive measurements in brain tissue, is applicable to pharmacokinetic studies of atenolol in man.

The β-adrenergic blocking agent atenolol is a hydrophilic compound which binds to only a limited extent to plasma proteins (Barber et al 1978). Both in dog and man, only 10 to 15% of the dose administered undergoes biotransformation (McAinsh 1977; Reeves et al 1978). After a single injection of atenolol, the drug is rapidly distributed to most tissues, but only a small fraction of the dose reaches the brain (Reeves et al 1978; Heel et al 1979). Higher concentrations were found in brain after chronic administration (Day et al 1977; Street et al 1979; Taylor et al 1981; Davies & McAinsh 1986). Treatment with atenolol was reported to result in a lower incidence of central nervous system side effects than with the more lipophilic compound propranolol. This was ascribed to the different physicochemical properties of the compounds and their different abilities to cross the blood-brain barrier (Cruickshank 1980; Fitzgerald 1980; Neil-Dwyer et al 1981; Westerlund 1983; Frcka & Lader 1988, McAinsh & Cruickshank 1990). With regard to the hypothesis of a central site of action for the antihypertensive effects of β-adrenoceptor blockers, the brain concentrations achieved are a point of discussion in the literature (Street et al 1979; Cruickshank et al 1980; Taylor et al 1981).

We have used positron emission tomography with [^{11}C]atenolol to assess, in anaesthetized dogs, the passage of the drug through the blood-brain barrier. This technique allows non-invasive measurements of drug levels at any desired organ site and is therefore particularly suited to study the early phenomena of drug distribution in brain tissue (Agon et al 1988a). Osmotic opening of the blood-brain barrier was used as an experimental model for the study of the distribution of atenolol in conditions with loss of integrity of the blood-brain barrier.

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Materials and methods

Animals and preparation. Adult mongrel dogs, 9·5–16 kg, were anaesthetized with intravenous sodium pentobarbitone (30 mg kg^{-1}). The dogs were ventilated after the administration of gallamine (2 mg kg^{-1}). Catheters were inserted in the right femoral artery for blood sampling, and in the left femoral vein for drug administration. In experiments where the distribution of atenolol in brain tissue was studied after blood-brain barrier disruption, an additional catheter was placed into the left internal carotid artery. The head of the dog was immobilized in a custom made headholder, with the orbito-meatal plane in a horizontal position.

Radiopharmaceuticals and positron emission tomography. [^{11}C]Atenolol, (2-[*p*-[2-hydroxy-3-([2-^{11}C]isopropylamino)propoxy]phenyl]acetamide), was synthesized according to a modified literature procedure (Antoni et al 1989) by alkylation of the corresponding desisopropyl compound with [2-^{11}C]isopropyl iodide (Goethals et al 1988) in *N,N*-dimethylformamide (DMF) at 120°C for 12 min. Purification was carried out by HPLC on a 10 μm RSil C18HL reversed-phase column with 0·02 M ammonium carbonate-methanol 1 : 1 as mobile phase. The [^{11}C]ateno-

lol-containing fraction (7·52–33·73 mCi, 0·28–1·25 GBq) was concentrated to a volume of 2 mL by evaporation and diluted with saline containing non-labelled atenolol, to a total dose of 1·25 or 0·125 mg kg^{-1}.

The NeuroECAT positron tomograph (ORTEC) was used to study the distribution of the drug. The slice studied was perpendicular to the orbito-meatal plane and 20 mm anterior to the stereotaxic zero. The slice thickness was 16 mm and the in plane resolution equals 8·5 mm in high resolution mode (Hoffman et al 1983). Sequential scans were performed with decay compensation. Radioactivity in arterial blood and plasma was measured in a well gamma-counter (Canberra model 1774). The gamma-counter and the positron camera were calibrated with the same standard solution of ^{68}Ge.

Experimental protocol. The dog was positioned with the head in the gantry of the positron tomograph. [^{11}C]Atenolol, 1·25 mg kg^{-1} (n = 3) or 0·125 mg kg^{-1} (n = 3), was administered over 15 s via the venous femoral catheter. Starting at end-injection time, 25 sequential scans of the same slice were performed over a period of 90 min and 12 arterial blood samples were collected in heparinized tubes at regular time intervals for blood and plasma radioactivity counting.

In experiments with osmotic opening of the blood-brain barrier, a hyperosmolar mannitol solution (25% w/v; n = 2), or a saline solution (control animals; n = 2), was infused into the left internal carotid artery over a period of 30 s at a rate of 2 mL s^{-1}. Five min later [^{11}C]atenolol (0·125 mg kg^{-1}) was injected i.v. and the positron emission tomography scanning procedure was started.

Data processing

Positron emission tomography. Positron emission tomography images of the scanned slice of the head were displayed in colour code form on a 100 × 100 pixel matrix. A region of interest was selected which corresponds to the brain hemispheres. An identical region of interest was analysed in the 25 consecutive scans; the nature of the tissue in the region of interest was checked on post-mortem dissection. Radioactivity concentrations are always expressed as normalized concentrations, i.e. μCi (mL tissue)$^{-1}$/μCi injected (g body weight)$^{-1}$ (Woodard et al 1975).

Modelling and fitting procedure. For a quantitative interpretation of the pattern of radioactivity concentrations in brain tissue, the general model approach, as described by Blasberg et al (1983), was used (Fig. 1). The fitting of the data was performed on a personal computer using the non-linear squares program MULTI (Yamaoka et al 1981). Goodness of fit for the considered model was supported by the values of the sum of squares of the residuals, and the Akaike Information Criteria (AIC), which takes into account the sum of squares of the residuals, the number of points and the number of parameters.

Arterial blood and plasma curves were fitted to a three-exponential equation. Plasma concentrations were used as input function in the differential equations to fit the radioactivity concentration in brain tissue. The radioactivity concentration in blood was used to calculate the radioactivity corresponding to labelled compound in the vascular compartment of the tissue. Indeed, the experimental values obtained correspond to the sum of the brain tissue radioactivity and the radioactivity present in the vascular compartment within the region of interest. The results obtained are the parameters describing the model, i.e. the transfer rate constants and the functional vascular volume.

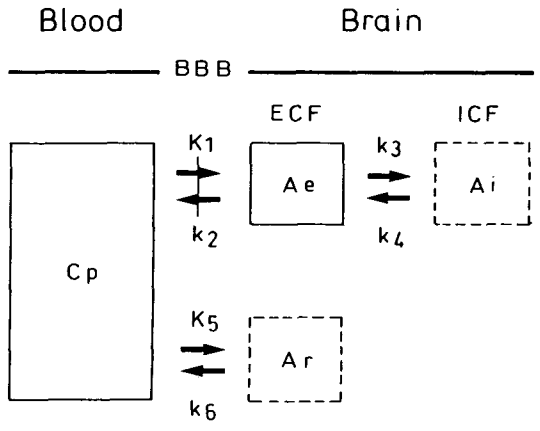

FIG. 1. General four compartment model, describing the exchange of drugs through the blood-brain barrier between plasma (p), brain extracellular fluid (ECF, e), brain intracellular fluid (ICF, i), and a parallel compartment (r). C_p represents concentration in plasma; A represents amount per unit mass tissue in the different compartments. The differential equations describing the model are: $dAe/dt = K_1Cp - (k_2 + k_3)Ae + k_4Ai$, $dAi/dt = k_3Ae - k_4Ai$ and $dAr/dt = K_5Cp - k_6Ar$, with upper case K's and lower case k's defined according to Blasberg et al (1983). K times the concentration of test substance and k times the amount of test substance, in the region from which transport occurs, are equal to the fluxes out of the respective regions (units are mL (g tissue)$^{-1}$ min^{-1} for K and min^{-1} for k). The amount measured equals $Ae + Ai + Ar + V_vCb$, with C_b the concentration in blood and V_v the functional vascular volume (mL (g tissue)$^{-1}$). In the two compartment model, exchange with ICF and parallel compartment are not considered.

Results

A representative experiment, in basal conditions without manipulation of the blood-brain barrier, is shown in Fig. 2A. Experimental values, for radioactivity concentrations in the brain region of interest vs time, are shown together with the data fitted to a two compartment model. The calculated values for the two transfer rate constants (K_1, k_2) and the functional vascular volume (V_v) are summarized for all experiments in Table 1. A four-compartment model did not describe the data better (data not shown). The transfer of [^{11}C]atenolol through the blood-brain barrier is limited, as indicated by the very low transfer rate constants and the low net brain concentrations, after correction for the vascular contribution. There was no apparent dose-effect.

A representative experiment with osmotic opening of the blood-brain barrier is depicted in Fig. 2B. The manipulation of the blood-brain barrier resulted in a clearly altered pattern of radioactivity distribution in the brain. A model with four compartments was necessary to describe the data adequately. Osmotic opening facilitates the passage of [^{11}C]atenolol through the blood-brain barrier as shown by the higher measured brain concentrations and the clearly higher values for the estimated transfer rate constants. In control animals, where the internal carotid perfusion was performed with saline solution, there were no indications of marked alterations of blood-brain barrier permeability for atenolol, and a two-compartment model described the data well.

Discussion

Our experiments show that after a single intravenous bolus injection of [^{11}C]atenolol, radioactivity concentrations achieved in brain tissue are very low. Considering the limited biotransfor-

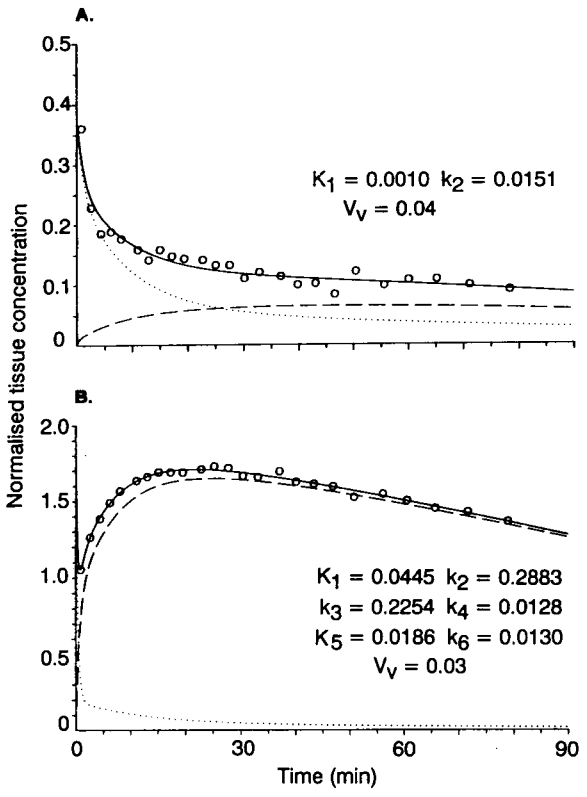

FIG. 2. Representative experiments after i.v. administration of [^{11}C]atenolol in (A) normal blood-brain barrier status and (B) altered blood-brain barrier, after infusion into the internal carotid artery of a hyperosmolar mannitol solution. Radioactivity concentrations vs time for brain region of interest (O) and fitted data for total radioactivity in the region of interest (———), vascular contribution (· · ·), and net brain tissue (– – –). Note the difference in concentration scale between A and B.

Table 1. Estimated transfer rate constants and functional vascular volume describing the passage of [^{11}C]atenolol through the blood-brain barrier in experiments with normal and altered blood-brain barrier*.

Intact blood-brain barrier				
Dose atenolol	Dog	K_1	k_2	V_v
1·25 mg kg^{-1}	227	0·0015	0·0097	0·07
	228	0·0008	0·0131	0·04
	229	0·0014	0·0081	0·06
0·125 mg kg^{-1}	231	0·0008	0·0070	0·06
	237	0·0007	0·0123	0·04
	244	0·0010	0·0151	0·04
Altered blood-brain barrier				
Mannitol infusion				
Dose atenolol	Dog	K_1	k_2	V_v
		k_3	k_4	
		K_5	k_6	
0·125 mg kg^{-1}	235	0·0445	0·2883	
		0·2254	0·0128	
		0·0186	0·0130	0·03
	247	0·0654	0·1494	
		0·3714	0·0183	
		0·0156	0·0105	0·04
Saline infusion (controls)				
Dose atenolol	Dog	K_1	k_2	V_v
0·125 mg kg^{-1}	236	0·0064	0·0119	0·07
	238	0·0062	0·0092	0·09

*Transfer rate constants K_n (mL (g tissue)$^{-1}$ min^{-1}) and k_n (min^{-1}); functional vascular volume V_v (mL (g tissue)$^{-1}$).

mation of atenolol (Reeves et al 1978) and the short observation period, it can be assumed that the measured radioactivity concentrations correspond almost entirely to unchanged atenolol. Calculations, based on distribution models which take into account the regional cerebral blood volume, indicate that passage of [^{11}C]atenolol through the blood-brain barrier, albeit slow, occurs with measurable net brain concentrations.

The transfer rate constant K_1, describing the passage from plasma to brain, is low. This is in accordance with the low lipophilicity (P_{HA} = 0·015, octanol/water pH 7·4, 37°C (Woods & Robinson 1981)) and the low fraction un-ionized at pH 7·4 (pKa = 9·50 (Taylor et al 1981)). The partition parameter P*, defined as the product of P_{HA} and the un-ionized fraction, (Rapoport 1976) is very low; P* = 0·0149.

In previous studies with acute administration of labelled atenolol, brain radioactivity was undetectable by autoradiography in rat and monkey (Reeves et al 1978; Berzin et al 1983) or low by direct tissue measurements in rat and man (Street et al 1979; Neil-Dwyer et al 1981). Low cerebrospinal fluid concentrations have been observed after acute administration of atenolol in cats, dogs and man (Van Zwieten & Timmermans 1979; Neil-Dwyer et al 1981; Taylor et al 1981; Abrahamsson et al 1989). Higher brain concentrations in rats and dogs (Street et al 1979; Davies & McAinsh 1986) and higher cerebrospinal fluid concentrations in dogs and man were found during chronic atenolol administration (Taylor et al 1981; Abrahamsson et al 1989). Our data and estimated model parameters, showing net brain influx, are compatible with these findings. However, due to the limitations inherent in the use of the short-lived radioisotope carbon-11 ($t_{\frac{1}{2}}$ = 20·4 min), study of the brain concentrations of atenolol during long term treatment was not possible.

In studies in man, measurements of atenolol in cerebrospinal fluid are usually used as an index for the passage of the drug into the brain. However, cerebrospinal fluid concentrations do not reliably reflect the actual atenolol concentrations in brain tissue (Neil-Dwyer et al 1981) and they vary according to the sampling site (Abrahamsson et al 1989). Moreover, interpretation of cerebrospinal fluid concentrations rely on the assumption of intact blood-brain and brain-cerebrospinal fluid barriers, which may not hold true in some pathological situations, such as in infections or malignancies affecting the central nervous system, in chronic hypertension and in hypertensive encephalopathy (Rapoport 1976).

As an experimental model for altered integrity of the blood-brain barrier, we used an intracarotid infusion of a hyperosmolar mannitol solution, which results in the widening of the tight junctions between the endothelial cells of the exposed cerebral capillary beds (Rapoport 1976). We have previously used positron emission tomography to demonstrate the modified pattern of distribution of drugs into the brain after such a manipulation (Agon et al 1988b). In the present study, osmotic opening of the blood-brain barrier resulted in markedly higher brain concentrations of atenolol, with markedly higher estimated transfer rate constants. The fact that a four-compartment model, rather than a two-compartment model, was necessary to describe the data after osmotic opening of the blood-brain barrier is an expected outcome in a situation with higher net drug transfer from plasma to brain. Indeed, the additional compartments do not contribute substantially to the model in situations with intact blood-brain barrier and low plasma to brain transfer (Agon & Kaufman 1989). According to the model proposed by Blasberg et al (1983), k_3 and k_4 describe the exchange between

the extracellular and intracellular compartment within brain tissue. The influx rate from the extracellular to the intracellular compartment is clearly higher than from plasma to the extracellular fluid. This is in accordance with the reported findings of a high distribution volume of atenolol in the dog (Fitzgerald 1980), which suggest that atenolol can cross cellular membranes. In our experiments we observed a clearly higher influx of [^{11}C]atenolol into muscle tissue (data not shown).

Increased passage of atenolol into the brain, in situations with altered integrity of the blood-brain barrier, could have clinical implications as far as central nervous system effects (Day & Roach 1974; Davy et al 1986) or side effects (Drayer 1987; McAinsh & Cruickshank 1990) are concerned.

Using positron emission tomography, we were able to study in a non-invasive manner the brain concentrations of atenolol in situations with intact and altered blood-brain barrier status. With this technique sequential data, needed to calculate transfer rate constants, are obtained in one animal, whereas in more conventional radiolabelled studies, each time point is represented by a different animal. Moreover, this approach is applicable to pharmacokinetic studies of atenolol in man in whom, due to evident constraints, it is usually not possible to assess directly drug concentrations in brain tissue.

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References

Abrahamsson, T., Lignell, E., Mikulski, A., Olovson, S.-G., Regardh, C. G. (1989) Central nervous system kinetics of atenolol and metoprolol in the dog during long term treatment. Drug Metab. Dispos. 17: 82–86

Agon, P., Kaufman, J. M. (1989) Modelling applied to PET-studies on blood-brain barrier transfer of ^{11}C-labelled drugs in the dog. In: Beckers, C., Goffinet, A., Bol, A. (eds) Positron Emission Tomography in Clinical Research and Clinical Diagnosis: Tracer Modelling and Radioreceptors. Kluwer Academic Publishers, pp 108–117

Agon, P., Braeckman, R., Van Haver, D., Denutte, H., Goethals, P., Donche, H., Vermeulen, F., Deman, J., Kaufman, J. M. (1988a) Drug distribution in dog brain studied by positron emission tomography. Biopharm. Drug Disp. 9: 567–577

Agon, P., Kaufman, J.-M., Goethals, P., Van Haver, D., Bogaert, M. G. (1988b) Study with positron emission tomography of the osmotic opening of the dog blood-brain barrier for quinidine and morphine. J. Pharm. Pharmacol. 40: 539–543

Antoni, G., Ulin, J., Långström, B. (1989) Synthesis of the ^{11}C-labelled β-adrenergic receptor ligands atenolol, metoprolol and propranolol. Appl. Radiat. Isot. 40: 561–564

Barber, H. E., Hawksworth, G. M., Kitteringham, N. R., Petersen, J., Petrie, J. C., Swann, J. M. (1978) Protein binding of atenolol and propranolol to human serum albumin and in human plasma. Br. J. Clin. Pharmacol. 6: 446P–447P

Berzin, B., Asseman, P. L., Desry, D., Vilarem, D., Thery, C. (1983) Atenolol in the central nervous system of monkeys. Drugs 25 (Suppl. 2): 278

Blasberg, R. G., Patlak, C. S., Fenstermacher, J. D. (1983) Selection of experimental conditions for the accurate determination of blood-brain transfer constants from single-time experiments: a theoretical analysis. J. Cereb. Blood Flow Metabol. 3: 215–225

Cruickshank, J. M. (1980) The clinical importance of cardioselectivity and lipophilicity in beta blockers. Am. Heart J. 100: 160–178

Cruickshank, J. M., Neil-Dwyer, G., Cameron, M. M., McAinsh, J. (1980) β-Adrenoreceptor-blocking agents and the blood-brain barrier. Clin. Sci. 59: 453s–455s

Davies, M. K., McAinsh, J. (1986) Tissue atenolol levels following chronic β-adrenoceptor blockade using oral atenolol in dogs. J. Pharm. Pharmacol. 38: 316–319

Davy, M., Midol-Monnett, M., Heimburger, M, Wepierre, J., Cohen, Y. (1986) Central action of β-adrenoceptor antagonists on blood pressure after acute administration in rats. J. Pharmacol. 17: 28–36

Day, M. D., Roach, A. G. (1974) Cardiovascular effects of β-adrenoreceptor blocking agents after intracerebroventricular administration in conscious normotensive cats. Clin. Exp. Pharmacol. Physiol. 1: 333–339

Day, M. D., Hemsworth, B. A., Street, J. A. (1977) The central uptake of β-adrenoceptor antagonists. J. Pharm. Pharmacol. 29 (Suppl.): 52P

Drayer, D. E. (1987) Lipophilicity, hydrophilicity, and the central nervous system side effects of beta blockers. Pharmacotherapy 7: 89–91

Fitzgerald, J. D. (1980) Atenolol. In: Scriabine, A. (ed.) Pharmacology of Antihypertensive Drugs. Raven Press, New York, pp 263–273

Frcka, G., Lader, M. (1988) Psychotropic effects of repeated doses of enalapril, propranolol and atenolol in normal subjects. Br. J. Clin. Pharmacol. 25: 67–73

Goethals, P., Sambre, J., Sleghers, G., Van Haver, D. (1988) Remote controlled unit for the production of [2-^{11}C]isopropyl iodide. J. Radioanal. Nucl. Chem. Letters 128: 85–92

Heel, R. C., Brogden, R. N., Speight, T. M., Avery, G. S. (1979) Atenolol: a review of its pharmacological properties and therapeutic efficacy in angina pectoris and hypertension. Drugs 17: 425–460

Hoffman, E. J., Phelps, M. E., Huang, S. C. (1983) Performance evaluation of a positron tomograph designed for brain imaging. J. Nucl. Med. 24: 245–257

McAinsh, J. (1977) Clinical pharmacokinetics of atenolol. Postgrad. Med. J. 53 (Suppl. 3): 74–78

McAinsh, J., Cruickshank, J. M. (1990) Beta-blockers and central nervous system side effects. Pharmacol. Ther. 46: 163–197

Neil-Dwyer, G., Bartlett, J., McAinsh, J., Cruickshank, J. M. (1981) β-Adrenoceptor blockers and the blood-brain barrier. Br. J. Clin. Pharmacol. 11: 549–553

Rapoport, S. I. (1976) Blood-brain Barrier in Physiology and Medicine. Raven Press, New York

Reeves, P. R., Barnfield, D. J., Longshaw, S., McIntosh, D. A., Winrow, M. J. (1978) Disposition and metabolism of atenolol in animals. Xenobiotica 8: 305–311

Street, J. A., Hemsworth, B. A., Roach, A. G., Day, M. D. (1979) Tissue levels of several radiolabelled β-adrenoceptor antagonists after intravenous administration in rats. Arch. Int. Pharmacodyn. Ther. 237: 180–190

Taylor, E. A., Jefferson, D., Carroll, J. D., Turner, P. (1981) Cerebrospinal fluid concentrations of propranolol, pindolol and atenolol in man: evidence for central actions of β-adrenoceptor antagonists. Br. J. Clin. Pharmacol. 12: 549–559

Van Zwieten, P. A., Timmermans, P. B. (1979) Comparison between the acute hemodynamic effects and brain penetration of atenolol and metoprolol. J. Cardiovasc. Pharmacol. 1: 85–96

Westerlund, A. (1983) A comparison of the central nervous system side effects caused by lipophilic and hydrophilic β-blockers. Drugs 25 (Suppl. 2): 280–281

Woodard, H. Q., Bigler, R. E., Freed, B., Russ, G. (1975) Expression of tissue isotope distribution. J. Nucl. Med. 16: 958–959

Woods, P.B., Robinson, M.L. (1981) An investigation of the comparative liposolubilities of β-adrenoceptor blocking agents. J. Pharm. Pharmacol. 33: 172–173

Yamaoka, K., Tanigawara, Y., Nakagawa, T., Uno, T. (1981) A pharmacokinetic analysis program (MULTI) for microcomputer. J. Pharmacobio-Dyn. 4: 879–885