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Rabbit Corneal and Conjunctival Permeability of the Novel Aldose Reductase Inhibitors: *N*-{[4-(Benzoylamino)phenyl] sulphonyl}glycines and *N*-Benzoyl-*N*-phenylglycines

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Abstract

Corneal and conjunctival permeability has been investigated for novel aldose reductase inhibitors (ARIs) of the *N*{[4-(benzoylamino)phenyl]sulphonyl}glycine (benzoylaminophenylsulphonylglycine) and *N*-benzoyl-*N*-phenylglycine (benzoylphenylglycine) series, compounds developed for prevention of cataract formation in diabetic subjects.

Six benzoylaminophenylsulphonylglycines were synthesized with modifications either of the phenyl group or of the glycine structure and three benzoylphenylglycines were synthesized with modification in the phenyl group of the benzoyl moiety. Transport of ARIs in the mucosal to serosal direction was evaluated across rabbit cornea and conjunctiva bathed in glutathione–bicarbonate Ringer's solution maintained at pH 7·4 and 37°C. The permeability coefficients of the novel ARIs across cornea and conjunctiva ranged from 1·87 to $8{\cdot}95 \times 10^{-6}\,\mathrm{cm\,s^{-1}}$ and from 4·6 to $19{\cdot}15 \times 10^{-6}\,\mathrm{cm\,s^{-1}}$, respectively. The ratio of corneal to conjunctival permeability ranged from 0·12 to 0·79. The calculated log partition coefficient (log P) values for the ARIs were in the range 0·84 to 2·78. The log distribution coefficients (log D) were in the range −2·87 to −0·89. There was no apparent relationship between log P or log D and the permeability coefficients of the ARIs for either tissue. Cornea was more resistant to ARI transport than was conjunctiva. Substitution of a phenyl group for hydrogen in the glycine methylene group reduced the permeability coefficient. Permeability coefficients were different for different stereoisomers. Compared with the permeability coefficient of benzoylaminophenylsulphonylglycine, that of 4-fluorobenzoylaminophenylsulphonylglycine was lower in the cornea but similar in the conjunctiva. In both tissues, the permeability coefficient of 2-nitrobenzoylaminophenylsulphonylglycine was less than that of 4-nitrobenzoylaminophenylsulphonylglycine. There was no significant difference between the permeability coefficients of 3-nitro- and 4-nitrobenzoylphenylglycines through either tissue and the permeability coefficients of these compounds were greater than that of the more lipophilic 4-methylbenzoylphenylglycine.

The lack of dependence of the permeability coefficients on log P or log D and the different permeabilities of stereoisomers imply the existence of specialized transport processes for the ARIs tested in this study.

Although intensive insulin treatment in combination with an appropriate diet delays the onset and progression of long-term diabetic complications in subjects with insulin-dependent diabetes mellitus (Diabetes Control and Complications Trial Research Group 1993), even with the best clinical management, it is impossible to maintain normoglycaemia throughout a diabetic individual's life. Under hyperglycaemic conditions, there is a high risk of biochemical, structural and functional alterations in certain tissues of diabetic subjects. Biochemical changes include polyol accumulation, myoinositol depletion, endoneural Na^+ accumulation, and Na^+/K^+-ATPase impairment (Green &

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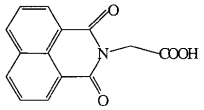
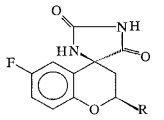
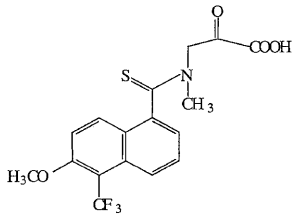
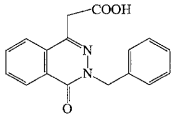
Mackway 1986; Green et al 1987). Structural changes include thickening of the basement membrane (Ljubimov et al 1996). Functional changes include changes in vascular permeability, corneal re-epithelialization (Datiles et al 1983), axonal transport, and glomerular filtration (Beyer-Mears et al 1984). Such biochemical, structural and functional changes can lead to severe late-diabetic complications, for example cataract, retinopathy, renal glomerulosclerosis, distal symmetric neuropathy, autonomic neuropathy, neural mono-neuropathy and increased risk of coronary heart disease and stroke (Clemments & Bell 1985).

In 1959, Van Heyningen (1959) proposed a hypothesis linking the accumulation of sorbitol and fructose in the lens of diabetic rats with the development of diabetic cataracts. Subsequently, Kinoshita (1965) related the accumulation of dulcitol in the lenses of galactosaemic rats with galactosaemic cataracts. Polyols such as sorbitol and dulcitol are formed by metabolic conversion of sugars by the enzyme aldose reductase (alditol : NADP oxidoreductase; ALR2; EC 1.1.1.21). Although the aetiology of sugar cataract formation might be multifactorial, the involvement of aldose reductase seems to be an important factor. Aldose reductase is located in the epithelium and cortical fibres of the lens (Akagi et al 1984).

Aldose reductase catalyses NADPH-dependent reduction of glucose to sorbitol in a variety of tissues in man. Increased activity of aldose reductase in tissues is a major biochemical event in a sequence of events leading to several late diabetic complications. Transgenic mice expressing high levels of aldose reductase have recently been shown to develop cataracts, a process which was accelerated in mice with sorbitol dehydrogenase deficiency, suggesting a role of aldose reductase and sorbitol in the formation of sugar cataract (Lee et al 1995). Inhibition of aldose reductase has been shown to reverse these biochemical changes and has proven effective in delaying and even preventing several diabetic complications (Yabe-Nishimura 1998). During the last three decades, a variety of structurally diverse compounds have been reported to have aldose reductase inhibitory activity in-vitro against rat or bovine lens aldose reductases; these include flavonoids (Varma 1986), hydantoin derivatives (Varma & Kinoshita 1976), oxazoline-1-acetic acid derivatives (Inagaki et al 1982), pyrimidine acetic acid derivatives (DeRuiter et al 1986), quinazoline acetic acid derivatives (Ellingboe et al 1990) and extracts of natural products (Goodwin et al 1984; Terashima et al 1990; Malamas & Miller 1991). Table 1 lists some aldose reductase inhibitors (ARIs) that have been tested in clinical trials; none is being marketed either because of side-effects (Spielberg et al 1991) or because of the lack of appreciable clinical effect (Engerman & Kern 1993).

Table 1. Examples of some clinically tested aldose reductase inhibitors.

Name	
Alrestatin	
Sorbinil	
Tolrestat (AY-27773)	
Statil (ICI 126 436)	

To obtain a potent ARI, Mayfield & DeRuiter (1987) synthesized a series of compounds including substituted glycine derivatives. Among these glycine derivatives, *N*-{[4-(benzoylamino)phenyl] sulphonyl}glycines (benzoylaminophenylsulphonylglycines) and *N*-benzoyl-*N*-phenylglycines (benzoylphenylglycines) had good in-vitro activity. Benzoylaminophenylsulphonylglycines are compounds with basic pharmacophoric groups present in aldose reductase inhibitors, for example *N*-substituted glycines, as in alrestatin and tolrestat (Table 1), and the sulphonyl group, as in 1-(4-bromophenylsulphonyl)hydantoin (De Ruiter et al 1987). Structure–activity studies of the benzoylaminophenylsulphonylglycine series suggested that the aromatic ring and the ring substitution, and the sulphonamide and carboxylate groups, all contribute to inhibitory potency by direct interaction with complementary binding sites present on aldose reductase (Mayfield & DeRuiter 1987). Of all the *N*-{[(substituted amino)phenyl]sulphonyl}glycines synthesized and tested for aldose reductase inhibition, the 4-benzoylamino derivative was found to be the most potent (DeRuiter et al 1991). This was

also true for benzoylphenylglycines. In this study, several molecules with good IC50 values (concentrations inhibiting activity by 50%) against rat aldose reductase were selected from the benzoylaminophenylsulphonylglycine and benzoylphenylglycine series.

The goal of ARI therapy for cataract treatment is to attain optimum drug levels in the lens for maximum duration. Topical administration is likely to achieve significant drug levels in the lens (Ohashi et al 1989; Brazzell et al 1990) and can minimize the side-effects associated with systemic administration (Crabbe et al 1985). To reach the lens, a drug molecule must cross the extraocular epithelial tissues including the cornea and the conjunctiva. The objective of this study was to determine the in-vitro permeability coefficients of the selected ARIs across the cornea and conjunctiva. The findings of this study will facilitate the development of potent and permeable molecules for the treatment of diabetic cataracts.

Materials and Methods

All materials were obtained from Sigma (St Louis, MO) and used as received.

Solutions for in-vitro transport

All experiments were conducted using glutathione–bicarbonate Ringer's (GBR) solution maintained at 37°C and pH 7·4. The GBR contained 111·55 mM NaCl, 4·82 mM KCl, 0·86 mM NaH_2PO_4, 29·2 mM $NaHCO_3$, 1·04 mM $CaCl_2{\cdot}2H_2O$, 0·74 mM $MgCl_2.6H_2O$, 5 mM D-glucose, and 0·3 mM reduced glutathione.

Drug synthesis

Benzoylaminophenylsulphonylglycines and benzoylphenylglycines were synthesized, purified and characterized by procedures described elsewhere (DeRuiter et al 1987, 1989a, b; Mayfield & DeRuiter 1987). The aldose reductase inhibitory activity of these compounds was also reported in the earlier studies.

In-vitro transport

New Zealand white female rabbits were killed by injecting sodium pentobarbital (125 mg kg^{-1}) into the right marginal ear vein. The cornea and conjunctiva were isolated and mounted according to the procedure reported by Kompella et al (1992, 1993). After mounting of the cornea or conjunctiva in modified Ussing chambers (Navicyte, Reno, NV), the tissues were exposed to GBR containing the drug (1 mg mL^{-1}) on the mucosal side and neat GBR on the serosal side. The fluids were maintained at 37°C and at pH 7·4 under 95% air-5% CO_2 aeration. Samples (750 μL) were collected from the serosal side after 0, 30, 60, 120, 180 and 240 min and the volume removed was replaced with GBR solution previously pre-equilibrated at 37°C.

Sample analysis

The amount of drug transported into the receiver compartment was measured by means of a microcomputer-controlled double-beam recording UV spectrophotometer (UV-160 recording spectrophotometer; Shimadzu, Kyoto, Japan). For all ARIs, standard graphs were generated between 0·3 and 25 μg mL^{-1} in the GBR solution at the λ_{max} of the respective compounds.

Data analysis

Log partition coefficient (log P) values of all the ARIs were calculated, by use of Rekker's approach, with Pallas software (Version 2.0; CompuDrug International, Budapest, Hungary). Log distribution coefficient (log D) and pK_a values for the ARIs were also estimated by use of Pallas software. The amounts (%) of ionized and un-ionized drug were calculated by use of the Henderson–Hasselbalch equation for weak acids at the pH of the Ringer's solution (7·4), which approximates tear pH. The apparent permeability coefficient (P_{app}) of the ARIs was calculated by normalizing the slope (μg s^{-1}) of the linear portion of the plot of cumulative amount of drug transported against time to the initial donor concentration (μg cm^{-3}) and the exposed surface area (cm^2) of the tissue. All P_{app} values in this manuscript are expressed as mean ± s.e.m. of results from 3 or 4 tissues obtained from different rabbits. The statistical significance of differences between the means of the data was evaluated by means of the unpaired Student's *t*-test. Differences were considered statistically significant when the *t*-value corresponded to a probability of less than 0·05.

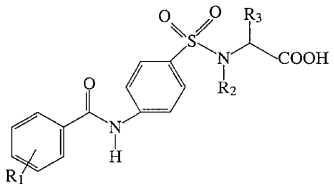
Results and Discussion

Several drugs intended for ocular therapy are administered as a drop in the precorneal region. To be effective at the intraocular targets, these drugs must cross extraocular barriers including the cornea and conjunctiva. In diabetic cataract treatment with

ARIs, the molecule should pass through these barriers and reach the target tissue, the lens, at concentrations sufficient to inhibit aldose reductase. The permeability properties of a drug across epithelial tissues such as the cornea and conjunctiva are governed by the chemical structure of the drug. To understand the influence of the structural properties of ARIs on corneal and conjunctival transport, two series of novel ARIs with good IC50 values were evaluated.

The IC50 values for rat lens aldose reductase have previously been reported for the ARIs evaluated in this study (DeRuiter et al 1987, 1989a, b; Mayfield & DeRuiter 1987). The partition coefficients, distribution coefficients (at pH 7·4) and pK_a values of these compounds were calculated by use of the Pallas software. Chemical structures, molecular weights, IC50, log P, log D, and pK_a are shown in Tables 2 and 3 for benzoylaminophenylsulphonylglycines and benzoylphenylglycines, respectively. The pK_a values of the ARIs ranged from 2·88–3·37. At the pH of the transport studies, the ARIs were ≥99·99% ionized. The amount of un-ionized drug was estimated at pH 7·4 and was 0·009% for ARIs 1, 4, 5 and 6 and 0·003% for ARIs 2 and 3. The amount un-ionized for ARIs 7, 8 and 9 was estimated to be 0·008, 0·008 and 0·009%, respectively. Topical administration of benzoylaminophenylsulphonylglycines to rabbits did not lead to visible signs of irritation or tissue damage, suggesting that these compounds are well-tolerated (data not shown).

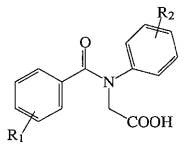
Table 2. Structures and properties of different analogues of benzoylaminophenylsulphonylglycine.



No.	R_1	R_2	R_3	Config.	MW	IC50	log P	log D	pK_a
ARI 1	H	H	H	–	334·35	0·4	1·09	−2·63	3·35
ARI 2	H	H	C_6H_5	*R*	410·44	140·0	2·77	−1·20	2·88
ARI 3	H	H	C_6H_5	*S*	410·44	0·6	2·77	−1·20	2·88
ARI 4	4-NO_2	H	H	–	379·34	0·7	0·97	−2·75	3·35
ARI 5	2-NO_2	H	H	–	379·34	0·3	0·84	−2·87	3·35
ARI 6	4-F	H	H	–	352·34	1·6	1·45	−0·89	3·35

MW, molecular weight; IC50, concentrations resulting in 50% inhibition of rat aldose reductase; log P, log partition coefficient; log D, log distribution coefficient. IC50 (μM) values were estimated using rat lens aldose reductase as previously reported (DeRuiter et al 1989a). Log P, log D and pK_a were calculated using Pallas 2.0 software.

Table 3. Structures and properties of different benzoylphenylglycines.



No.	R_1	R_2	MW	IC50	log P	log D	pK_a
ARI 7	3-NO_2	H	300·27	0·86	2·03	−1·75	3·30
ARI 8	4-NO_2	H	300·27	0·25	2·01	−1·77	3·30
ARI 9	4-CH_3	H	269·30	0·98	2·78	−0·98	3·37

MW, molecular weight; IC50, concentrations resulting in 50% inhibition of rat aldose reductase; log P, log partition coefficient; log D, log distribution coefficient. IC50 (μM) values were estimated using rat lens aldose reductase as previously reported (DeRuiter et al 1989b). Log P, log D and pK_a were calculated using Pallas 2.0 software.

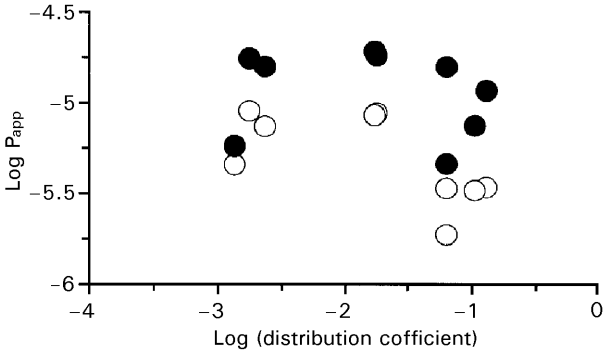


Figure 1. Correlation of the corneal and conjunctival permeability coefficients of aldose reductase inhibitors with their distribution coefficients. Permeability coefficients were determined in the mucosal-to-serosal direction: ○ cornea, ● conjunctiva.

For benzoylaminophenylsulphonylglycines the corneal P_{app} was in the range $1{\cdot}87–7{\cdot}44 \times 10^{-6}\,cm\,s^{-1}$ and the conjunctival P_{app} was in the range $5{\cdot}76–15{\cdot}84 \times 10^{-6}\,cm\,s^{-1}$ (Table 4). The P_{app} values of benzoylphenylglycines were $3{\cdot}27–8{\cdot}75 \times 10^{-6}\,cm\,s^{-1}$ in the cornea and $7{\cdot}45–19{\cdot}15 \times 10^{-6}\,cm\,s^{-1}$ in the conjunctiva. The log P_{app} values of all these molecules were compared with their calculated log D values (Figure 1). The lower P_{app} across the cornea compared with the conjunctiva is consistent with the greater resistance of the cornea (Marshall & Klyce 1983) compared with the conjunctiva (Kompella et al 1993).

For both tissues, log P_{app} was linearly regressed against the logarithm of the molecular weight, log P, log D, pK_a and the amount (%) of drug in the unionized form (from 0·003 to 0·009%). The respective correlation coefficients (r) obtained were −0·39, −0·56, −0·63, 0·61 and 0·57, respectively, for the cornea and −0·26, −0·20, −0·17, 0·25 and 0·22, again respectively, for the conjunctiva. Thus, there was no significant linear relationship between the permeability coefficient across either tissue and any of the parameters tested. Conjunctival permeability was less predictable (lower correlation coefficients) than corneal permeability. Lack of dependence of permeability coefficients on molecular weight, pK_a, log P or log D suggests that a mechanism other than simple diffusion might be transporting these molecules across the cornea and conjunctiva.

Of the benzoylaminophenylsulphonylglycine series of compounds, the unsubstituted benzoylaminophenylsulphonylglycine permeated most across both tissues. In the benzoylaminophenylsulphonylglycine series, replacement of hydrogen with phenyl at R_3 (Table 2) produced two stereoisomers with lower tissue permeability. Corneal transport of the *R* isomer (ARI 2) was significantly lower than that of benzoylaminophenylsulphonylglycine whereas conjunctival transport was similar. The permeability coefficient of the S isomer (ARI 3) across both cornea and conjunctiva was much lower than that of the unsubstituted benzoylaminophenylsulphonylglycine ($P < 0{\cdot}05$). The permeability coefficients of the two isomers across the conjunctiva were significantly different, indicating the possibility of specialized transport processes for these molecules. The substitution of a 4-nitro group in benzoylaminophenylsulphonylglycine (ARI 4) did not affect the permeability coefficient across either tissue. Substitution of a 2-nitro group (ARI 5), on the other hand, markedly reduced transport across both tissues and the difference between the two tissues was not statistically significant. Substitution of a fluorine (ARI 6) significantly reduced the permeability coefficient across the cornea but not across the conjunctiva.

Table 4. Permeability coefficients of benzoylaminophenylsulphonylglycines and benzoylphenylglycines.

No.	Cornea	Conjunctiva	C/J	OE	SE
ARI 1	7·44 ± 1·49	15·79 ± 0·27	0·47	0·19	0·39
ARI 2	1·87 ± 0·29	15·84 ± 1·36	0·12	0·00[a]	0·00[a]
ARI 3	3·37 ± 0·84	4·60 ± 0·93	0·73	0·06	0·08
ARI 4	8·95 ± 1·00	17·61 ± 3·23	0·51	0·13	0·25
ARI 5	4·55 ± 1·46	5·76 ± 0·40	0·79	0·15	0·19
ARI 6	3·43 ± 0·98	11·72 ± 3·54	0·29	0·02	0·07
ARI 7	8·75 ± 0·20	18·36 ± 2·36	0·48	0·10	0·21
ARI 8	8·59 ± 0·98	19·15 ± 2·34	0·45	0·34	0·77
ARI 9	3·27 ± 1·14	7·45 ± 1·40	0·44	0·03	0·08
Sorbinil	10·24 ± 3·42	16·03 ± 3·49	0·64	0·16	0·25

Permeability coefficients ($10^{-6}\,cm\,s^{-1}$) are means ± s.e.m. of results from 3 or 4 experiments. C/J is the ratio of the permeability coefficients in the cornea and conjunctiva. OE is an empirical indicator of ocular effectiveness of ARIs and is estimated as the ratio of the corneal permeability coefficient ($\mu m\,s^{-1}$) to the IC50 (μM). SE is an empirical indicator of systemic effectiveness of ARIs and is estimated as the ratio of the conjunctival permeability coefficient ($\mu m\,s^{-1}$) to the IC50 (μM). The permeability values for sorbinil were determined in this study and the IC50 value was reported previously (DeRuiter et al 1989b). [a]The OE and SE were 0·0001 and 0·0011, respectively.

The transport experiments with the benzoylphenylglycine series revealed that the permeabilities of 3-nitrobenzoylphenylglycine (ARI 7) and 4-nitrobenzoylphenylglycine (ARI 8) were similar to that of the unsubstituted benzoylaminophenylsulphonylglycine. An increase in lipophilicity as a result of 4-methyl-substitution significantly reduced the permeability coefficient across both tissues compared with ARI 7 or ARI 8. Thus, the permeability coefficient of benzoylphenylglycines seems to depend on modifications in position 4. A lack of enhancement in transport with increased lipophilicity also suggests the possibility of specialized transport mechanisms for this series of compounds. Because all the ARIs tested in this study are anionic, we speculate that anion transporters in the membrane might be responsible for the transport of some of the ARIs tested. The cornea / conjunctiva permeability ratios (Table 4) for the ARIs tested ranged from 0·12 (ARI 2) to 0·79 (ARI 5), i.e. whereas ARI 2 is more likely to enter systemic circulation through the conjunctiva, ARI 5 is more likely to enter the ocular tissues than the systemic circulation.

The long-term goal of our research is to develop prodrugs for ARIs with optimum in-vitro permeability coefficients and IC50 values. To identify compounds with these optimum properties, empirical indicators of ''ocular effectiveness'' and ''systemic effectiveness'' have been determined. With increasing corneal permeability of an ARI, the drug availability in the aqueous humour and lens can be expected to increase, i.e. the effectiveness of an ARI can be related positively to its permeability coefficient. On the other hand, the IC50 value is inversely related to the effectiveness of an ARI—the benefit is greater for compounds with lower IC50 values. If these relationships between effectiveness and both IC50 and permeability coefficient are assumed to be linear, then the ratio P_{app}/IC50 will be proportional to effectiveness. This effectiveness ratio, utilizing corneal P_{app}, is the ocular effectiveness indicator. When the conjunctival permeability coefficient is used in the ratio, the indicator is denoted as the systemic effectiveness indicator. This is because drug crossing the conjunctival epithelium is readily available to the underlying vasculature and the systemic circulation. These indicators are empirical, because they do not account for other disposition characteristics of the ARIs including possibly different precorneal residence, metabolism and excretion. The empirical indicators, ocular effectiveness and systemic effectiveness, are shown in Table 4 for the various ARIs tested in this study. On the basis of these indicators, it is evident that ARI 1 from the benzoylaminophenylsulphonylglycine series and ARI 8 from the benzoylphenylglycine series are likely to offer optimum ocular and systemic effectiveness. It is also apparent that the effectiveness indicators of these ARIs are higher than that of sorbinil, a well-studied aldose reductase inhibitor.

Acknowledgements

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