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Review Article

The Polyol Pathway as a Mechanism for Diabetic Retinopathy: Attractive, Elusive, and Resilient

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The polyol pathway is a two-step metabolic pathway in which glucose is reduced to sorbitol, which is then converted to fructose. It is one of the most attractive candidate mechanisms to explain, at least in part, the cellular toxicity of diabetic hyperglycemia because (i) it becomes active when intracellular glucose concentrations are elevated, (ii) the two enzymes are present in human tissues and organs that are sites of diabetic complications, and (iii) the products of the pathway and the altered balance of cofactors generate the types of cellular stress that occur at the sites of diabetic complications. Inhibition (or ablation) of aldose reductase, the first and rate-limiting enzyme in the pathway, reproducibly prevents diabetic retinopathy in diabetic rodent models, but the results of a major clinical trial have been disappointing. Since then, it has become evident that truly informative indicators of polyol pathway activity and/or inhibition are elusive, but are likely to be other than sorbitol levels if meant to predict accurately tissue consequences. The spectrum of abnormalities known to occur in human diabetic retinopathy has enlarged to include glial and neuronal abnormalities, which in experimental animals are mediated by the polyol pathway. The endothelial cells of human retinal vessels have been noted to have aldose reductase. Specific polymorphisms in the promoter region of the aldose reductase gene have been found associated with susceptibility or progression of diabetic retinopathy. This new knowledge has rekindled interest in a possible role of the polyol pathway in diabetic retinopathy and in methodological investigation that may prepare new clinical trials. Only new drugs that inhibit aldose reductase with higher efficacy and safety than older drugs will make possible to learn if the resilience of the polyol pathway means that it has a role in human diabetic retinopathy that should not have gone undiscovered.

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1. INTRODUCTION

The question of whether the minor pathway of glucose metabolism, called the polyol pathway, is an important player in retinopathy and other complications of human diabetes has been asked for over three decades [1], and the answer is not yet in. Such state of things begets two questions: why do we not have an answer yet? and perhaps more pointedly, why is the question still alive?

The answer to the first question begins as direct and practical, but becomes interlocutory. We have not had probes to address rigorously the question of whether the polyol pathway has a pathogenic role in human diabetic retinopathy. In practical terms, we have not had available drugs with a high therapeutic index in humans, that is, effective and well tolerated at the same time, so as to make possible their usage at doses documented to inhibit the pathway fully and predictably in the tissues of interest. But do we know which is the gold standard by which to measure “inhibition of the polyol pathway”? We are becoming aware that such knowledge is pivotal, and not easy to acquire. The answer to why we are still courting and querying the polyol pathway has to do with both the current treatment of diabetes and the polyol pathway itself. Intensive glycemic control is clearly effective in reducing the incidence and progression of diabetic retinopathy [2, 3], but with the means available today even the best efforts do not achieve normal glucose homeostasis, and retinopathy and other complications continue to develop and progress to clinically important stages also among well-controlled patients [2–4]. We are not yet able to offer adjunct treatments that can preempt the damaging effects of the residual hyperglycemia. The polyol pathway is by all criteria an enormously attractive target for adjunct treatment. The polyol pathway is also enormously resilient, and just when investigators try to put it aside, it scores new points and returns to the fore.

Over three decades, much has been written on the polyol pathway and the complications of diabetes, and much has been captured in informative reviews [5, 6]. My goal in this writing is to extract from the existing body of knowledge what justifies a continuous interest in the pathway from the
standpoint of human diabetic retinopathy, and to highlight actions needed to give the pathway a role or a dismissal.

2. THE POLYOL PATHWAY IS A PLAUSIBLE BIOCHEMICAL MECHANISM FOR DIABETIC RETINOPATHY

The polyol pathway of glucose metabolism becomes active when intracellular glucose levels are elevated [1, 5]. Aldose reductase (AR), the first and rate-limiting enzyme in the pathway, reduces glucose to sorbitol using NADPH as a cofactor; sorbitol is then metabolized to fructose by sorbitol dehydrogenase that uses NAD⁺ as a cofactor. The effects are several. Sorbitol is an alcohol, polyhydroxylated, and strongly hydrophilic, and therefore does not diffuse readily through cell membranes and accumulates intracellularly with possible osmotic consequences [1]. (Production of intracellular osmotics may be invoked from data in the whole retina because retinal levels of sorbitol increase in diabetic rats only 3–8 fold above control [15, 16], and are far from the concentrations that could induce osmotic stress [1]. However, a cell type that had an especially high ratio of AR to sorbitol dehydrogenase could accumulate sorbitol with intracellular consequences, and yet the amount would be diluted substantially in measurements taken in the whole retina. Investigation that compares and contrasts the kinetics and consequences of polyol pathway activation in the relevant retinal cell types—neurons, Müller glia, pericytes, and endothelial cells—might therefore generate important new insights. At this time, the information from the biochemical measurements and the dose-response studies with ARIs point to oxidative stress as the strongest candidate mechanism for polyol pathway-dependent cellular damage in the diabetic retina.

3. THE POLYOL PATHWAY IS A CONTRIBUTOR TO EXPERIMENTAL DIABETIC RETINOPATHY

Two waves of studies addressed the role of the polyol pathway in experimental diabetic retinopathy. A first wave of studies centered on the galactosemic model. In the early 80’s, Enghardt and Kern described the diabetic-like retinopathy of dogs fed a diet rich in galactose [19], and Robison et al. reported that the basement membrane thickening seen in the retinal capillaries of rats fed a diet rich in galactose was prevented by an AR inhibitor (ARI) [20]. The observation that galactosemia, that is, the isolated elevation of a hexose in blood without other hormonal or metabolic abnormalities [19], could mimic most features of the retinal microangiopathy caused by diabetes, is, to date, the most specific indictment of the role of hyperglycemia in causing retinopathy in diabetes. (The design of the Diabetes Control and Complications Trial [DCCT], where intensive insulin treatment ameliorated the diabetic state comprehensively, cannot isolate precisely the benefits of correcting hyperglycemia, and thus the role of hyperglycemia in the complications.) The galactosemic model was highly relevant to the polyol pathway because the set of enzymes necessary to permit the entry of dietary galactose into the glycolytic pathway is present only in the liver [21]. In congenital disorders where enzymes of galactose metabolism are defective, blood galactose levels increase and many peripheral tissues accumulate two metabolites, galactose-1-phosphate, and galactitol [21]. Galactitol is produced from galactose via the action of AR; and the AR from all species studied—human, dog, and rat—displays a Km for galactose lower than for glucose [22]. An ARI, given at a dose of 65 mg/Kg/day prevented the diabetic-like retinal vascular histopathology developed by rats fed a 50% galactose diet [23]. However, the full complement of retinal microangiopathy developed by dogs fed a 30% galactose diet was only delayed [24] or not prevented at all [25] by the
ARI sorbinil. The dose of sorbinil used in the galactose-fed
dogs (60 mg/Kg/day on average) and devised to inhibit ac-
cumulation of galactitol in erythrocytes was not different
from the dose used in the galactose-fed rats. One group of
investigators noted, however, that sorbinil was metabolized
more rapidly in dogs than in rats, yielding unexpectedly
short plasma half-life [24]. The same group also examined
retinal changes in the galactose-fed dog model treated with
two doses of a sorbinil analog, and found evidence for dose-
dependency of the beneficial effects of ARI treatment [26].

In one of the above studies, experimentally diabetic dogs
were studied alongside galactose-fed dogs [25]. To diabetic
dogs, sorbinil was administered in a lesser dose (20 mg/Kg/
day) than to galactosemic dogs, targeting inhibition of dia-
betes-induced sorbitol accumulation in erythrocytes. The
dose yielded 90% sorbitol inhibition in erythrocytes as well
as retina. However, sorbinil did not prevent the develop-
ment of retinal microangiopathy in the diabetic dogs [25].
Shortly before, the final results of the sorbinil retinopathy trial had
become available. The trial had tested sorbinil at a dose of
250 mg/day (the equivalent of 3.5 mg/Kg/day in a 70 Kg in-
dividual), administered for 3 years to patients with type 1
diabetes with absent or very mild retinopathy. The data indi-
cated that sorbinil did not have a clinically important effect
on the course of human diabetic retinopathy [27]. Interpre-
tative caveats apply to these negative results, as discussed later
in this writing. Nonetheless, at the time the results under-
standably dampened the enthusiasm in pursuing the polyol
pathway as a major player and target in diabetic retinopathy.

However, when new features of diabetic retinopathy be-
came known in the late 90’s, the polyol pathway commanded
a second wave of investigations, showing its resilience. We
developed an interest in the polyol pathway because it was
the rational first choice for a new mechanistic question. We
wished to understand the mechanism for the reactive charac-
teristics of Müller glial cells [28, 29] and apoptosis of neurons
(mostly ganglion cells) [30] occurring early in both human
and experimental diabetic retinopathy; and Müller and gan-
glion cells are the retinal cell types most consistently found
to contain aldose reductase in humans, rats, and dogs [31–
34]. In view of the fact that sorbinil had failed to prevent
the lesions of retinopathy in diabetic dogs when used at a
dose of 20 mg/Kg/day [25], we selected the larger dose used
in the galactosemic models. We observed that, in the retina of
rats with 2.5 months of diabetes, neurons undergoing apop-
tosis indeed contained aldose reductase, and that sorbinil
65 mg/Kg/day prevented neuronal apoptosis, the prominent
increase in glial fibrillary acidic protein (GFAP) in Müller
cells indicating a reactive state, and changes in astrocytes
[15].

The question arose whether in the diabetic rat also the
vascular abnormalities of retinopathy receive a contribution
from the polyol pathway. ARLs had been noted to prevent
hemodynamic changes and vascular permeability changes in
rats with 6 weeks of diabetes [35] and retinal capillary base-
ment membrane thickening in rats with 6 months of dia-
betes [36]. Surprisingly, there were however no published
studies addressing, in diabetic rats, the effect of aldose re-
ductase inhibition on the ultimate manifestations of retinal
microangiopathy in diabetes, apoptosis of pericytes and en-
dothelial cells, and development of acellular capillaries. We
had shown that microvascular cell apoptosis precedes [37]
and predicts [38] the development of acellular capillaries,
which is in turn a key event in diabetic retinopathy [39, 40]
because it heralds retinal ischemia and, in humans, transi-
tion to sight-threatening proliferative retinopathy. We thus
view the development of acellular capillaries as the required
read-out for any modeling, pathogenetic construct, or inter-
vention related to the microangiopathy of diabetic retinopa-
thy. We went on to perform the studies addressing the role of
the polyol pathway, and we targeted vascular abnormalities
that we had documented to occur also in the human diabetic
retina [37, 41]. The retinal vessels of diabetic rats treated with
sorbinil for the 9-month duration of diabetes showed pre-
vention of (i) early complement activation, (ii) decreased lev-
els of complement inhibitors, (iii) microvascular cell apop-
tosis, and (iv) acellular capillaries [13]. Also other investiga-
tors had reported sparing of pericytes by treatment with an
ARI other than sorbinil in rats with 15 months of diabetes
[42]. (In this particular study the pericyte counts were per-
formed in retinal sections, specimens that are suboptimal for
the purpose.) Insofar as the pericytes and endothelial cells of
rat retinal vessels contain AR [13], it is plausible that the ARLs
prevented the microangiopathy by inhibiting polyol pathway
directly in vascular cells.

The diabetic mouse has contributed information that
supports the role of the polyol pathway in diabetic retinopa-
thy, but has generated an important question as yet unan-
swered. We compared and contrasted the mouse to the rat
because of the known differences in polyol pathway activa-
tion between these species. The mouse is known to have, in
the lens, one-tenth of the aldose reductase activity present in
the rat lens [43], and its extreme resistance to cataract un-
der conditions of hyperglycemia [43] and galactosemia [44]
can be overcome only by introduction of a human aldose re-
ductase transgene [44, 45]. We reasoned that the mouse may
have low aldose reductase activity also in the retina. In fact,
C57BL/6J mice, rendered diabetic with streptozotocin and
exhibiting hyperglycemia as severe as diabetic rats, did not
accumulate sorbitol or fructose in the retina [15]. Obrosova
et al. made similar observations, and reported additional and
important biochemical differences between the retinas of di-
betic mice and diabetic rats [46]. The diabetic mice did not
show apoptosis of ganglion cells or reactivity of Müller glial
cells, and this was consistent with the evidence in diabetic
rats that polyol pathway activation is the inducer of the neu-
rogial abnormalities. A different group of investigators con-
cluded the absence of neuronal apoptosis and Müller cell re-
activity in C57BL/6J mice studied up to one year-duration
of streptozotocin-diabetes [47]. Two groups reported instead
loss of retinal neurons in diabetic mice, one group in the
streptozotocin model [48] and the other in the Ins2AKITA
mouse maintained on the C57BL/6J background [49]. These
reports did not present counts of apoptotic cells; the conclu-
sions on neuronal death were based on assays for activated
caspase 3 and/or morphometry of retinal layers. Nor did the
studies investigate retinal polyol pathway activity. However,
the Ins2AKITA mouse was specifically reported not to show
Müller cell reactivity [49], in agreement with the findings in the streptozotocin diabetic mouse [15, 47]. Recent observations in db/db mice, which are a model for type 2 diabetes, indicate that very long duration of diabetes (15 months) leads to increased expression of retinal AR, Müller cell reactivity, neural cell apoptosis, and vascular changes; and that these abnormalities do not appear in db/db mice rendered genetically AR-deficient [50]. Thus, in diabetic mice, retinal neuroglial abnormalities are not found as consistently as in diabetic rats. When neuroglial abnormalities are undetectable, polyol pathway activity is likewise undetectable. When neuroglial abnormalities are present, polyol pathway activity appears to be the inciting cause.

The question generated by the diabetic mouse and as yet unanswered is the relationship of acellular capillaries to the polyol pathway in this model. The streptozotocin-diabetic C57BL/6 mouse model develops a progressively greater number of acellular capillaries with increasing duration of diabetes, and the acceleration over control begins after 6 months of diabetes [47], when neither retinal accumulation of polyols nor neuroglial abnormalities can be demonstrated [15, 47]. Does this indicate that in the diabetic mouse retinal vascular cells activate the polyol pathway and are damaged by the consequences, when neural and glial cells do not, or not as yet? Because vascular cells represent only a minor contribution to total retinal cellularity, their accumulation of polyols would go unnoticed in preparations of whole retina. Unfortunately, the studies in the AR-null db/db mice could not answer the question, because the development of acellular capillaries was not addressed specifically. (In that model, vessels were actually reported to be present in larger number than in nondiabetic mice [50]. An important interpretative caveat is that the vessels were counted as dots or tubes staining for IgG on retinal sections; and the number of such images can be influenced by several confounders, such as the plane and thickness of sections, as well as vessel tortuosity and the state of vessel perfusion.)

To summarize the observations in animal models, there is weighty evidence for the concept that polyol pathway activation is a sufficient mechanism for the retinal abnormalities induced by diabetes in the rat. One missing piece of evidence precludes a similar comprehensive conclusion in the diabetic mouse. The results from the diabetic dog studies and the sorbinil trial do not support the importance of the polyol pathway in the development of diabetic retinopathy in the dog model or in humans. But these latter experiments are the older, and it is becoming apparent that, if designed today, they would be designed differently. We examine the issues in the following sections.

4. DO WE KNOW HOW TO SILENCE THE POLYOL PATHWAY WHEN THE GOAL IS PREVENTION OF TISSUE DAMAGE?

The polyol pathway is, at first glance, a dream target when aiming to develop drugs for prevention of the complications of diabetes. The rate-limiting enzyme of the pathway, AR, acts on the glucose molecule, and therefore at the most upstream possible site in the cascade of glucose toxicity. AR is encoded by one gene [5, 51], has a known structure and kinetic properties [52], and its activity is inhabitable by multiple classes of small molecule compounds [53]. Complete AR deficiency produces only a mild nephrogenic diabetes insipidus [54]. On this basis, AR inhibition appears rational, feasible, and benign; and if we could just add to the tools a reliable indicator of AR inhibition permitting us to target and monitor in tissues the therapeutic effects of ARIs, we could readily implement rigorous preclinical studies and clinical trials.

However, the “reliable indicator of AR inhibition” is turning out to be an elusive target, and the reason is that we do not know for certain how polyol pathway activity causes tissue damage. What we know is that when ARIs have been dosed to prevent sorbitol accumulation, as in the studies with diabetic dogs or the sorbinil trial (where sorbitol was monitored in red blood cells, and not even normalized there), very little tissue benefit has ensued. When ARIs have been used in larger doses targeted to prevent the accumulation of fructose rather than sorbitol, they have been more successful. The concordant dose-dependency for effects on fructose and tissue abnormalities has been demonstrated directly in the nerve [55], and was also seen clearly in the retina. When we tested ARIs on diabetic retinopathy in the rat, we used a 65 mg/kg/day sorbinil dose [13, 15] that was shown in preliminary experiments to inhibit both sorbitol and fructose formation. The greater relevance of fructose than sorbitol as measure of polyol pathway activity is easily understandable when thinking that sorbitol accumulation may be minuscule under conditions in which AR is very active if also sorbitol dehydrogenase is very active. Under such conditions, sorbitol levels may never increase and yet the pathway will have processed a large amount of glucose, and the flux of glucose will have used NADPH and generated NADH and fructose. These may ultimately be the more relevant abnormalities for cells and tissues. Oates et al. are currently showing that in diabetic nerve the ratio of oxidized glutathione (GSSG) to reduced glutathione (GSH) increases, indicating oxidative stress; and that normalization of the ratio requires an even larger dose of AR than the normalization of fructose, at least in acute experiments [56]. The implication of these studies is very important: if we must limit the oxidative consequences of the polyol pathway in order to limit its cellular toxicity, we may need to inhibit AR much more drastically, at least to the degree achieved in recent rat studies [13, 15–17], and such inhibition required doses of ARIs twenty times larger than those used in the sorbinil trial.

A noteworthy issue with ARIs is that they can inhibit also aldehyde reductase, another enzyme in the aldo-keto reductase superfamily that plays a role in the detoxification of reactive aldehydes [22, 57, 58]. All ARIs inhibit AR more than aldehyde reductase, but some ARIs such as sorbinil do not have a high degree of selectivity for AR versus aldehyde reductase [22, 53, 57]. This generates the question of whether some inhibition of aldehyde reductase contributes to the beneficial effects of ARIs, especially at the higher doses; or, conversely, contributes unwanted side effects. We recently had the opportunity to test an ARI from an entirely new structural class, a sulfonylpyridazine characterized as one of
the most potent and selective ARIs yet described. In particular, the IC50 of ARI-809 (compound 19 m in [53]) for aldehyde reductase is 930 nM as compared to 1 nM for AR [53]. Such selectivity permitted us to target critically the role of the polyol pathway in the early stages of the development of experimental diabetic retinopathy. ARI-809 administered to diabetic rats at doses documented to inhibit both sorbitol and fructose accumulation in the retina, improved survival, inhibited cataract development, and protected the retina from all early neuronal, glial, and vascular abnormalities known to also occur in human diabetes [59]. On this basis, it can be stated that aldose reductase is itself the key relay that converts hyperglycemia into glucose toxicity for specific cell types in the retina. Whether ARI-809 or other highly specific ARIs will also help address the problem of toleration and side effects will need to be addressed in humans.

If further experiments confirm that only large ARI doses can block the polyol pathway to the extent required to prevent tissue damage, we are clearly poorly equipped to bring the concept to test in humans. The two chemical classes of ARIs that have been mostly tested in phase III trials, the carboxylic acid inhibitors (e.g., zopolrestat) and the spirohydantoin inhibitors (e.g., sorbinil), have a suboptimal therapeutic index. Both classes have shown side effects: liver and/or renal toxicity in the former, and potentially serious hypersensitivity reactions in the latter [27]. The different type of side effects suggests that they are not consequences of AR inhibition, but rather of other properties of the individual drugs. Nonetheless, the side effects would preclude any escalation of the doses tested to date. There are new ARIs of the spiroimide/hydantoin class that show greater potency than sorbinil, and have achieved in diabetic patients a robust inhibition of the polyol pathway in sural nerves [60], as well as improvement in signs and symptoms of sensorimotor polyneuropathy at well-tolerated doses [61–63]. The results of larger trials with these drugs are expected soon.

5. IS THE POLYOL PATHWAY IMPORTANT IN HUMAN DIABETIC RETINOPATHY? AND WHY SHOULD WE CARE TO KNOW?

The results of the sorbinil retinopathy trial could have been a false negative or a true negative. A false negative could have occurred for at least two reasons. The first is that the dose of sorbinil may have been insufficient to achieve and sustain inhibition of retinal polyol pathway; we found that much larger doses—not usable in humans—were needed to achieve prevention of retinal polyol pathway activation in the diabetic rat [13, 15]. When the intent is to test a pathogenic mechanism for disease, there is a stringent requirement for documentation that the chosen intervention inhibits or attenuates the target mechanism at the sites of interest. The DCCT and United Kingdom Prospective Diabetes Study which set out to test the role of metabolic control in the complications of diabetes implemented laborious strategies to verify before the trial, and document extensively throughout the trial, that two levels of glycemic control could be achieved and maintained, and that they were sufficiently apart in a sufficient number of study participants to permit testing the hypothesis. Uncertainty about whether a drug or intervention is delivered in sufficient dose to achieve effects at target tissue is a recurrent issue in clinical trials. It continues to be one of the most commonly proposed mechanisms to explain discrepancies between encouraging preclinical studies and inconclusive trials. Just recently, it was discussed with regard to the benefits of insulin-like growth factor-1 in motor neuron diseases [64] and exogenous surfactant replacement in the acute respiratory distress syndrome [65]. The second reason for which the sorbinil trial could have yielded false negative results is that it was an intervention trial, where approximately half of the study population had clinical evidence of retinopathy, albeit mild [27]. Interventions do not work as well as prevention in diabetic retinopathy [2]. This is likely to be especially true for interventions such as ARIs that target early events in the cascade that leads to the demise of retinal vascular cells.

It remains possible that the results of the sorbinil trial were a true negative, and it appears wise to investigate how solid is the rationale for advocating new rigorous trials. Information gathered by studying post-mortem eyes is consistent with activity of the polyol pathway in human diabetes. Retinas from diabetic patients with retinopathy show more abundant AR immunoreactivity in ganglion cells, nerve fibers, and Müller cells than retinas from nondiabetic individuals [66]. In our experiments, human retinas from nondiabetic eye donors exposed to high glucose levels in organ culture accumulate sorbitol to the same extent as similarly incubated retinas of nondiabetic rats, as well as retinas dissected from diabetic rats [13]. The comparable biochemical outcome of AR activity in the human and rat retinas underscores that human AR is readily responsive to hyperglycemia. The human enzyme is in fact widely used as a transgene to make the mouse susceptible to diabetic complications, from cataract [45] to atherosclerosis [67]. It is thus apparent that cells in the human retina—including vascular endothelial cells and pericytes [13]—can have an active polyol pathway in the presence of hyperglycemia.

An additional type of new information that justifies revisiting the role of the polyol pathway in human diabetic retinopathy is the finding that several polymorphisms in the promoter region of the AR gene are associated with susceptibility to, or more rapid progression of, diabetic retinopathy (reviewed in [51]). Of particular interest has been the Z–2 allele of the (AC)n dinucleotide repeat sequence located 2.1 kb upstream of the AR transcription start site [68]. The Z–2 allele is in linkage disequilibrium with another polymorphism in the AR promoter that also increases susceptibility to retinopathy [69]; and appears to be associated with higher levels of AR mRNA [70]. Of much interest, the association of the Z–2 allele with increased AR expression was found only in diabetic patients, not among nondiabetic individuals [70], suggesting an interaction with diabetes/hyperglycemia. Although the best-known type of interaction of hyperglycemia with AR is to provide substrate for activity of the enzyme (which has a high Km for glucose), there are reports indicating also an effect of hyperglycemia on AR gene expression [71, 72]. It can be expected that such effect would increase the
magnitude of polyol pathway activation and its tissue consequences.

However, the ultimate question is not whether further investigation of the polyol pathway in diabetic retinopathy is justified, but rather whether it is needed. After all, the polyol pathway is not the only candidate mechanism for diabetic retinopathy on which to base the development of adjunct treatments. In experimentally diabetic animals several interventions targeting pathogenic mechanisms other than the polyol pathway have proven to be capable of inhibiting the development of retinal acellular capillaries—eral interventions targeting pathogenic mechanisms other diabetic retinopathy on which to base the development of polyol pathway is not the only candidate mechanism for investigation of the polyol pathway in diabetic retinopathy sequences.

Experimental Diabetes Research

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The second implication would be that no other drugs but ARIs could be expected to correct this particular mechanism for Müller cell abnormalities. We know that diabetes induces a large number of changes in gene expression in Müller cells indicating both a reactive phenotype and altered functions [83], and the nature of the changes suggests multiple inducing mechanisms. It is thus likely that prevention of the spectrum of Müller cell abnormality does require the high doses of ARIs we tested [15, 59, 78], but it is possible that osmotic consequences of polyol pathway activation may be approachable with lesser doses. Then, ARIs would have three different indications related to diabetic retinopathy—a first and unique one directed at the acute relief of macular edema, a second one directed at the prevention of both macular edema and microangiopathy, and a third one directed at the prevention of macular edema in the context of a drug combination where the other drug targets the microangiopathy. In view of the different duration of treatment required by the different indications and the different specific targets, the three indications could be served by ARIs that differ in potency as well as therapeutic index. New experiments will now address these speculative possibilities.

6. CONCLUSIONS

The latest wave of studies on the polyol pathway has given us a more complete picture of what the pathway can do in the human retina, and how. The polyol pathway can be active in the human retina; it can be active in endothelial cells and not just in pericytes; it can be the mechanism for the changes we see in the Müller cells of human diabetic retinas; through
activity in endothelial and Müller cells the pathway can be a strong contributor to the disturbed fluid homeostasis that occurs in the diabetic retina and leads at times to macular edema; through activity in endothelial cells and pericytes, the pathway can be a strong contributor to the vascular cell apoptosis that eventually results in acellular capillaries and retinal ischemia. The preferred mechanism of cellular damage by the polyol pathway appears to be the induction of oxidative stress, although other mechanisms should not be ignored. Interventions with ARIs are successful when the doses used reduce the flux through the pathway and indices of oxidative stress.

In order to move forward and ascertain if what can happen does in fact happen, several needs must be met. The first is to have available new ARIs, best if more than one chemical type, combining higher levels of efficacy, selectivity, and safety in humans than those exhibited by older drugs. The pharmaceutical industry may need to apply to the problem some new thinking, especially in view of the fact that ARIs could become the "one drug-option" for diabetic retinopathy only if usable at doses that inhibit AR and flux through the pathway more substantially than the older drugs. The second need is clarification of whether distinct cell types in the retina are exposed to specific consequences of, or have specific susceptibilities to, the different mechanisms of cellular damage initiated by the polyol pathway. Satisfying these two needs may yield means with which to satisfy the third, which is the identification of reliable indicators of polyol pathway activity. Indicators are necessary in order to learn whether the polyol pathway is in fact active in the human diabetic retina, and how best to inhibit the pathway with the new ARIs in preparation for longer trials. In general, these needs are not different from those faced by all other candidate mechanisms and drugs seeking a role in human diabetic retinopathy [84]. We all look forward to bringing one or more adjunct treatment to clinical reality, and may ultimately welcome the resilience of the polyol pathway if we were to find that it has unique roles and/or it offers unique solutions to human diabetic retinopathy.

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