表4　PDT前，PDT3か月後の視力，CNV径，中心窩厚の変化

	PDT前		PDT3か月後		p値
	平均	標準偏差	平均	標準偏差	
全88症例					
logMAR	0.82	0.31	0.77	0.33	0.108
CNV径(μm)	2756	1421	1469	1645	<0.001
中心窩厚(μm)	252.4	160	197	94	0.018
1回PDT群					
logMAR	0.75	0.31	0.67	0.32	0.065
CNV径(μm)	2796	1413	0	0	<0.001
中心窩厚(μm)	275	217	150.5	69	0.007

全88症例，1回PDT群ともに視力では有意な改善はみられなかったが，CNV径と中心窩厚は有意に改善した．
CNV：choroidal neovascularization

表5　PDT前，PDT3か月後の網膜剝離の有無の変化

	消失	不変	出現
全88症例	30(34)	55(62.5)	3(3.5)
1回PDT群34眼	19(56)	15(44)	0

全88症例では34%の症例で網膜剝離が消失した．　(眼(%))

すいのではないかと考えた．「心の健康」スコアの有意な改善は線維組織があること以外にも，VFQ-25の「心の健康」スコアについての4つの設問に関連していると考えた．「心の健康」スコアに関する「物の見え方に不安を感じますか？」「物が見えにくいために欲求不満を感じますか？」「物が見えにくいためにしたいことが思うようにできないですか？」「物が見えにくいために自分が気まずい思いをしたり，他の人を困らせたりするのではないかと心配ですか？」という4つの設問は，物の見え方あるいは物の見えにくさに対する患者の感じ方(主観)を問うものであり，患者自身が見え方が改善したと感じれば，実際に今まで出来なかったことができるようになるなどの変化がなくても改善する可能性がある．またPDTは，これまで手術や薬物療法などで有効な治療法が確立されていなかった加齢黄斑変性の中心窩下CNVに対して，正常組織に与える障害が少なく，CNVをより選択的に閉塞・退縮させるための新しい治療法として有用性が大きいと期待されて始まった治療法であり，新聞やテレビ，インターネットなどを通じて広く一般に情報が公開されている．事前情報が患者に十分に与えられていたことが治療に対する期待感を生み，その治療を受けた満足感が「心の健康」に好影響を及ぼした可能性もあると考えた．また，前述の通り，今回の研究では比較対照群がないため，眼科的変化とQOLの関連を統計学的に検討することはできないが，眼科的な所見の変化からQOLの変化を推察した．眼科的変化では，視力には有意な改善がみられなかったものの，CNV径，中心窩厚が有意に減少し，34%で網膜剝離が消失したので，網膜感度が上がったと考えられた．すなわち，患者は固視点付近の物の見え方が改善したと感じ，また治療を受けた満足感から「心の健康」スコアが改善した可能性があると考えた．これは「心の健康」スコアは，視力の改善がなくても改善する場合があることを示している．

1回PDT群では，線維組織がある場合以外にも，対側眼所見が滲出型AMDの場合に「心の健康」スコアが有意に改善した．対側眼が滲出型AMDでは他の状態に比べて対側眼の視力が最も不良であった．このことは，患者が患眼の治療による見え方の変化を自覚しやすいことを示していると考えた．

Armbrechtら[5]は，中心窩下のpredominantly classic CNVを有するAMD患者に対するPDT1年後のQOLについて，遠見視力，近見視力，コントラスト感度，CNV径の4つ全てが悪化していたにもかかわらず，QOLに関するいくつかの質問項目で有意な改善がみられたと報告した．その理由は明らかではないが，PDT治療により重篤な視力低下を起こしていないためと考察している．今回の検討でも，1回PDTで視力の有意な改善はみられなかった．

また，病型がPCVの場合，所見に線維組織がある場合にPDTが1回で奏効しやすいことが認められたが，VFQ-25のベースラインのどの下位尺度も1回PDTの奏効との関連が認められなかった．PDTは通常複数回治療を必要とする治療法であるので，著者らも今後さらに長期間に渡って経過を調査し，複数回治療におけるQOLとの関連を検討していく予定である．

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39. 加齢黄斑症の読書困難に対する
ロービジョンケア前後のQOL評価

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研究要旨　両眼性加齢黄斑症（ARM）では読書困難のためにクオリティオブライフ（QOL）が損なわれる。本検討では、読書困難を有する両眼性ARMを、ロービジョンケア群（6か月間介入）と対照群（6か月間無介入）に無作為に割り付け、6か月後のQOLを群間で比較した。主要評価項目である「近見視力による行動」ではロービジョンケア群、対照群でQOLスコアに有意差はみられなかったがロービジョンケア群で改善していた。副次的評価項目では「心の健康」がロービジョンケア群で有意に改善した。

A．研究目的

ARMは50歳以上にみられる黄斑異常であり、早期ARMと晩期ARMに分類され、早期ARMは晩期ARMの前段階と位置づけられている。いずれの病型も、中心窩を含んで病巣がみられる場合には、程度の差はあれ、見ようとするところが見えづらくなり、読書が困難になる。その読書困難に対し、拡大鏡の選定などロービジョンケアが行われるが、その有用性を比較検討した報告は少ない[1)]。今回は、被検者をロービジョンケア群（ケア群）と対照群に無作為に分け、両群のQOLを比較検討した。

B．研究方法

適格症例は両眼性に黄斑部に加齢に伴う萎縮を有し、読書困難がみられる50歳以上80歳未満の患者で、普段読書に用いる方の眼に活動性のある脈絡膜新生血管がみられない症例である。適格症例100例を、登録後すぐにロービジョンケアを行うケア群50例、登録後6か月間はロービジョンケアを行わない対照群50例に無作為に割り付け、QOL調査を登録時、6か月後に行った。QOL質問票はthe National Eye Institution Visual Function Questionnaire(VFQ-25)日本語版[2)]を用い、主要評価項目は「近見視力による行動」、副次評価項目は「社会生活機能」、「役割制限」、「自立」、「心の健康」、「遠見視力による行動」とした。眼科的検査として視力測定、MNREAD-Jによる読書検査、固視検査、カラー眼底写真撮影を登録時、3か月後（カラー眼底のみ）、6か月後に行った。ロービジョンエイドは、患者が読みたいと希望する読書材料を読むために必要な倍率を読書

評価からえられた臨界文字サイズを指標に決定し、その倍率が得られるエイドを至近距離眼鏡、拡大鏡、拡大読書器の中から選定した。

今回は6か月後のケア群、対照群のQOLを比較した。

（倫理面への配慮）

研究参加に際し、十分な説明を行い、研究参加の同意の得られた症例のみ対象とした。

C．研究結果

各群50例ずつ登録されたうち、解析が可能であったのはケア群42例、対照群38例で、両群とも男性約7割、平均年齢72歳、加齢黄斑変性滲出型瘢痕期が約6割で、背景に差はみられなかった。6か月後の主要評価項目である「近見視力による行動」の平均スコアは、介入群で44±20点、対照群35±21点であり、介入群でQOLスコアが高い傾向が認められたものの5%水準では有意ではなかった（p=0.084)。副次評価項目の「心の健康」はケア群が48±25点、対照群が33±24点で、ケア群で有意にQOLスコアが高かった(p=0.014)。「社会生活機能」はケア群が55±30点、対照群が55±27点（p＝0.948)、「役割制限」はケア群が49±30点、対照群が41±31点（p＝0.282)、「自立」はケア群が50±26点、対照群が43±30点（p＝0.293)、「遠見視力による行動」はケア群が42±20点、対照群が38±20点（p＝0.284）であり、有意差はみられなかった。

D．考察

加齢黄斑変性の読書困難に対してロービジョンエイドの選定がおこなわれるが、その有用性について検討したランダム化比較試験の報告は少ない[1)]。そこで今回、読書困難を有する患者に対するロービジョンケアの有用性をQOLの観点から検証するため、多施設無作為非盲検ランダム化比較試験を行った。

主要評価項目である「近見視による行動」にケア群、対照群でQOLスコアに有意差はみられなかったものの、ケア群で改善していた。副次評価項目の中では、「心の健康」で有意にケア群のQOLスコアが改善していた。加齢黄斑変性は正常者と比較して抑鬱傾向が強く、特に視機能不良例、日常生活困難度の高い症例でその傾向が顕著であると報告されている[3) 4)]。すなわち日常生活困難度を軽減することが抑鬱の改善につながるといえる。今回行ったロービジョンケアで、少なからず日常生活困難度が軽減した結果、「心の健康」が改善したと考えた。

E．結論

ARMの読書困難に対するロービジョンケアはQOLの観点から有用であった。

F．健康危険情報　なし

G．研究発表

1．論文発表　なし

2．学会発表　なし

H．知的財産権の出願・登録状況

1．特許取得　なし

2．実用新案登録　なし

3．その他　なし

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40. 加齢黄斑変性の新しい診断基準

加齢黄斑変性診断基準作成ワーキンググループ
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研究要旨　わが国において広く一般眼科医にも通用する標準的な加齢黄斑変性の分類と診断基準を作成した。前駆病変として軟性ドルーゼンと網膜色素上皮異常、加齢黄斑変性として滲出型加齢黄斑変性と萎縮型加齢黄斑変性に分類し、滲出型加齢黄斑変性の特殊病型としてポリープ状脈絡膜血管症と網膜血管腫状増殖を採用した。さらに滲出型加齢黄斑変性の確信例の規定を含めた診断基準を明文化した。

A．研究目的

加齢黄斑変性はわが国の高齢者の社会的失明原因の第4位として増加傾向にあり、正確な診断の重要性が増すとともに、様々な新しい治療が検討されている。本研究の目的は、わが国において一般眼科医にも通用し、広く用いられる標準的な加齢黄斑変性の診断基準を作成し確立することである。

B．研究方法

加齢黄斑変性の専門家4名からなる加齢黄斑変性診断基準作成ワーキンググループで2回の会合を持ち、昨年の班会議で報告した加齢黄斑変性の分類[1)]をもとに、分類の改訂を行い、確診例の規定を含めた診断基準を作成した。また診断基準の各項目に合致する標準的な眼底写真と画像所見を再確認した。

C．研究結果

考案した加齢黄斑変性の分類を表1に、診断基準を表2に示す。

1．前駆病変
　1）軟性ドルーゼン
　2）網膜色素上皮異常
2．加齢黄斑変性
　1）滲出型加齢黄斑変性*
　2）萎縮型加齢黄斑変性

＊滲出型加齢黄斑変性の特殊型
①ポリープ状脈絡膜血管症
②網膜血管腫状増殖

表1．加齢黄斑変性の分類

D．考察

加齢黄斑変性に対して、近年種々の新しい治療が出現し、正確な治療適応決定と治療評価のために診断の重要性が増している。加齢黄斑変性の診断基準については平成4年に本研究班において診断の手引き[2)]のなかで暫定基準案として記載されたが、それからすでに10年以上が経過した。その後、加齢黄斑変性に関連する新しい疾患概念が生じ[3)]、さらに患者数の増加もあって多くの基礎、臨床研究がなされるようになったが、疾患の捉え方と　(次ページに続く)

表２．加齢黄斑変性の診断基準

年齢50歳以上の症例において、中心窩を中心とする直径3000μm以内の領域に以下の病変がみられる。

１．前駆病変

軟性ドルーゼン*1、網膜色素上皮異常*2が前駆病変として重要である。

２．滲出型加齢黄斑変性

主要所見：以下の主要所見の少なくとも一つを満たすものを確診例とする。

① 脈絡膜新生血管*3
② 漿液性網膜色素上皮剥離*4
③ 出血性網膜色素上皮剥離*5
④ 線維性瘢痕

随伴所見：以下の所見を伴うことが多い。

①滲出性変化：網膜下灰白色斑（網膜下フィブリン）硬性白斑、網膜浮腫、漿液性網膜剥離
②網膜または網膜下出血

３．萎縮型加齢黄斑変性

脈絡膜血管が透見できる網膜色素上皮の境界鮮明な地図状萎縮*6を伴う。

４．除外規定

近視、炎症性疾患、変性疾患、外傷などによる病変を除外する。

（付記）

＊1 軟性ドルーゼンは直径 63μm 以上のものが１個以上見られれば有意とする。
＊2 網膜色素上皮異常とは網膜色素上皮の色素脱失、色素沈着、色素むら、小型の漿液性網膜色素上皮剥離（直径１乳頭未満）をさす。
＊3 脈絡膜新生血管は、検眼鏡所見、蛍光眼底造影によって診断する。検眼鏡所見として、網膜下に灰白色または橙赤色隆起病巣を認める。蛍光眼底造影はフルオレセイン蛍光眼底造影またはインドシアニングリーン蛍光眼底造影所見に基づく。
＊4 漿液性網膜色素上皮剥離は、直径１乳頭径以上のもので、脈絡膜新生血管を伴わないものも含める。
＊5 出血性網膜色素上皮剥離は大きさを問わない。
＊6 網膜色素上皮の地図状萎縮は大きさを問わない。　（以上、診断基準）

表２．加齢黄斑変性の診断基準

（考察続き）診断は研究者によってなお隔たりがみられ、統一された基準での診断が望まれる。今回、本研究班において４名の加齢黄斑変性の専門家が検討を行い、加齢黄斑変性の新しい分類と診断基準を作成した。

加齢黄斑変性の分類としては、国際加齢黄斑症疫学調査グループによって 1995 年に報告された加齢黄斑症および加齢黄斑変性に関する国際分類とグレードシステムが国際的に最もよく用いられている[4]。この分類はわが国でもかなり浸透しており、今回我々が作成した分類は基本的にこの分類の概念を踏襲したものである。ただし、この国際分類で用いられている「加齢黄斑症」という用語は紛らわしいので使用せず、「加齢黄斑変性」と統一した。また、近年、滲出型加齢黄斑変性の疾患範疇に入る新しい疾患概念として多数報告されるようになったポリープ状脈絡膜血管症、網膜血管腫状増殖を滲出型加齢黄斑変性の特殊病型として正式に採用した。さらに、加齢黄斑変性の診断基準として、分類を行った前駆病変、滲出型加齢黄斑変性、萎縮型加齢黄斑変性

について規定し、鑑別診断として、近視、炎症性変化、変性疾患、外傷など他疾患に続発する脈絡膜新生血管を除外する規定を設けた。特に、滲出型加齢黄斑変性では多彩な眼底所見を生じるため、疾患に特異性の高い主要所見として、①脈絡膜新生血管、②漿液性網膜色素上皮剥離、③出血性網膜色素上皮剥離、④線維性瘢痕の4所見を選択し、この主要所見の少なくとも一つを満たすものを滲出型加齢黄斑変性の確診例と規定した。脈絡膜新生血管に続発する滲出性変化、網膜/網膜下出血については、網膜静脈閉塞症や網膜動脈瘤などの他疾患でも生ずることがあるため随伴所見として記載した。

この診断基準のもうひとつの要点として漿液性網膜色素上皮剥離の取り扱いが挙げられる。本診断基準では、大きさによって直径1乳頭径未満の小型のものを前駆病変とし、1乳頭径以上の大型のものは、脈絡膜新生血管を伴わなくても、網膜色素上皮下に強い滲出を生じた病態として滲出型加齢黄斑変性として取り扱っていることに注意が必要である。

E．結論

加齢黄斑変性について、新しい分類と診断基準を作成した。今後、詳細な記述を加えて論文化する予定である。

F．健康危険情報　　なし

G．研究発表

1．論文発表　　なし
2．学会発表　　なし

H．知的財産権の出願・登録状況

1．特許取得　　なし
2．実用新案登録　　なし
3．その他　　なし

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41. 正常眼圧緑内障の視野障害に対する アンジオテンシン変換酵素阻害薬の効果

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研究要旨 正常眼圧緑内障の視野障害に対する ACE 阻害薬の効果について retrospective に検討した。対象は 3 年以上経過観察の可能であった正常眼圧緑内障患者 36 例 36 眼。その内訳は、高血圧の既往のない（コントロール群）13 例 13 眼、高血圧に罹患しており ACE 阻害薬を内服している（ACE（＋）群）12 例 12 眼、高血圧に罹患しており ACE 阻害薬以外の薬を内服している（ACE（－）群）13 例 13 眼の 3 つに分類した。視野はハンフリー自動視野計を用いた。経過観察期間中の平均眼圧はコントロール群 14.0 mmHg、ACE（＋）群 13.1 mmHg、ACE（－）群 13.5 mmHg で 3 群間に有意差は認めなかった。MD slope はコントロール群-0.37 dB、ACE（＋）群+0.48 dB、ACE（－）群-0.49 dB で、ACE（＋）群で有意に高い値となった。ACE 阻害薬を内服することにより、緑内障性視野障害の進行が抑制される可能性が示唆された。

A．研究目的

アンジオテンシン変換酵素（ACE）阻害薬はブラジキニンを介した一酸化窒素産生の増加により血管拡張反応が改善することが報告されているが、我々は正常眼圧緑内障患者では内因性のブラジキニンが少ないことを既に報告した[1]。そこで正常眼圧緑内障の視野障害に対する ACE 阻害薬の効果について検討する。

B．研究方法

対象は 3 年以上経過観察を行い、ハンフリー自動視野計による Mean Deviation (MD) 値が-11 dB 以上、矯正視力が 0.5 以上であった正常眼圧緑内障患者 36 例 36 眼。その内訳は、高血圧症の既往のない（コントロール群）13 例 13 眼、高血圧症に罹患しており ACE 阻害薬を内服している (ACE(＋) 群）12 例 12 眼、高血圧症に罹患しており ACE 阻害薬以外の薬を内服している (ACE（－）群）13 例 13 眼の 3 つに分類した。

HfaFiles 5 を用いて MD slope を算出し、統計学的処理は ANOVA (Tukey-Kramer) を用い、危険率 5%未満を有意水準とした。

C．研究結果

年齢はコントロール群 63.5 歳、ACE（＋）群 69.8 歳、ACE（－）群 68.5 歳であり、経過観察期間中の平均眼圧はコントロール群 14.0 mmHg、ACE (＋) 群 13.2 mmHg、ACE（－）群 13.8 mmHg で 3 群間に有意差は認めなかった。MD slope はコントロール群-0.38 dB、ACE (＋) 群+0.48 dB、ACE（－）群-0.50 dB であった。

D．考察

以前我々は正常眼圧緑内障患者では内因性のブラジキニンが少ないことを報告した[1]が、ACE 阻害薬を長期間使用することにより、血漿中のブラジキニンのレベルが上昇することが報告されている[2]。またグルタミン酸毒性に対してブラジキニンは神経細胞死を抑制することが報告されており[3]、ACE 阻害薬を内服することにより血漿中のブラジキニンが上昇し、正常眼圧緑内障の視野障害に対し保護的に働いたのではないかと考えられる。

E．結論

今回の研究は retrospective であり、また少数例ではあるが、ACE 阻害薬を内服することにより、緑内障性視野障害の進行が抑制される可能性が示唆された。

F．健康危険情報　　なし

G．研究発表

1．論文発表

Hirooka K, Baba T, Fujimura T, Shiraga F: Prevention of visual field defect progression with angiotensin-comverting enzyme inhibitor in eyes with normal-tension glaucoma. Am J Ophthalmol 142: 523-525, 2006.

2．学会発表

正常眼圧緑内障の視野障害に対するアンジオテンシン変換酵素阻害薬の効果
第 16 回日本緑内障学会

H．知的財産権の出願・登録状況

1．特許取得　　なし

2．実用新案登録　　なし

3．その他　　なし

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Prevention of Visual Field Defect Progression With Angiotensin-Converting Enzyme Inhibitor in Eyes With Normal-tension Glaucoma

Kazuyuki Hirooka, MD, Tetsuya Baba, MD, Takashi Fujimura, MD, and Fumio Shiraga, MD

PURPOSE: To report the effect of angiotensin-converting enzyme (ACE) inhibitor on visual field changes in normal-tension glaucoma (NTG).

DESIGN: Retrospective observational case series.

METHODS: We retrospectively reviewed a total of 38 patients with NTG. Control subjects had no previous history of hypertension. NTG hypertension patients were divided into two groups, those receiving ACE inhibitor and those receiving other antihypertensive drug treatments. HfaFiles 5, an analytical program for the Humphrey Field Analyzer, was used to calculate the slope for the mean deviation (MD) change per year.

RESULTS: In the ACE inhibitor-treated group, the mean MD change per year was 0.48 ± 0.19 dB, in control subjects was −0.38 ± 0.23 dB, and in the other antihypertensive drug-treated group was −0.50 ± 0.39 dB.

CONCLUSIONS: Although the present study is retrospective and the sample size is small, ACE inhibitor might have a favorable effect on the visual field in patients with NTG in this small study. (Am J Ophthalmol 2006; 142:523–525. © 2006 by Elsevier Inc. All rights reserved.)

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ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS have been shown to lower intraocular pressure (IOP) in patients with ocular hypertension or primary open-angle glaucoma.[1] Additionally, ACE inhibitors may have a protective role against some diseases such as diabetic retinopathy[2] and the development of Alzheimer's disease.[3] Thus, we evaluated the effect of ACE inhibitors on visual field defects that occur in normal-tension glaucoma (NTG).

We retrospectively reviewed data for 63 patients who had been previously diagnosed with NTG at Kagawa University Hospital. A diagnosis of NTG was made if patients had any of the following conditions: glaucomatous optic disk abnormalities and corresponding glaucomatous visual field defects, normal open angle, and IOP (measured using Goldmann applanation tonometry) of 21 mm Hg or lower without medication. Of these 63 patients, 38 patients met the following selection criteria: follow-up periods that were longer than three years; visual acuity equal to or better than 20/40; and reliable perimetric examination with the Humphrey Field Analyzer (Humphrey Instruments, Inc, San Leandro, California, USA) (<20% fixation loss and <33% false-positive or false-negative answers). Patients with a history of sudden visual loss, hemodynamic crisis, any intraocular surgery, or development of clinically significant cataract during follow-up were excluded. All patients had no previous history of surgery or laser. We divided the NTG patients into three groups: (1) no previous history of hypertension (control); (2) hypertensive patients treated with ACE inhibitor; and (3) hypertensive patients treated with another antihypertensive drug. We saw these patients at least four times a year. At each visit, the IOP was measured using a Goldmann applanation tonometer. The visual fields were examined at least once a year using the central 30 to 2 program of the Humphrey Field Analyzer. The change over time was evaluated using HfaFiles 5, an analytical program of the Humphrey Field Analyzer, which performs a liner regression analysis of the mean deviation (MD) of the visual fields obtained during the follow-up period for use in calculating a slope for the MD change per year.

All statistical data were presented as means ± SEM and analyzed using analysis of variance (ANOVA) with a Tukey-Kramer correction. A level of $P < .05$ was considered to indicate statistical significance.

Mean MD changes per year were 0.48 ± 0.19 dB in the ACE inhibitor-treated group (n = 12), −0.38 ± 0.23 dB in the control subjects (n = 13), and −0.50 ± 0.37 dB in other antihypertensive drug-treated group (n = 13) ($P = .04$) (Table 1). In the ACE inhibitor-treated group, MD changes per year were positive in 10 subjects. Linear regression analysis revealed no correlation between IOP and MD change per year (Table 2).

We previously reported that NTG patients were more sensitive to exogenous bradykinin than normal subjects.[4]

TABLE 1. Background Data for Patients with Normal-tension Glaucoma, by ACE Inhibitor-treated Group, Another Antihypertensive Drug-treated Group, and No History of Hypertension (Control)

	Control	ACE Inhibitor-treated Group	Another Antihypertensive Drug-treated Group	*P* Value
Age (yrs)	63.5 ± 2.2	69.8 ± 2.9	68.5 ± 3.1	.24
Gender (M/F)	6/7	5/7	6/7	.97
Duration of follow-up (mos)	49.8 ± 3.0	42.4 ± 2.2	46.8 ± 2.8	.17
History of diabetes mellitus (no. positive/negative)	2/11	4/8	2/11	.45
History of cardiac diseases	0/13	4/8	4/9	.07
Number of visual field tests performed	6.2 ± 0.4	5.6 ± 0.2	5.5 ± 0.2	.18
Antiglaucoma medications (no. receiving/not receiving)	10/3	7/5	10/3	.50
Refraction (D)	−3.9 ± 1.5	−1.2 ± 0.5	0.7 ± 1.0	.09
Visual acuity	1.1 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	.75
Initial systemic blood pressure (mm Hg)				
Systolic	129.7 ± 6.1	143.0 ± 10.9	149.0 ± 7.2	.26
Diastolic	78.7 ± 4.3	82.4 ± 4.6	80.9 ± 5.0	.89
IOP (mm Hg)				
Maximum	17.0 ± 0.5	15.8 ± 0.7	17.3 ± 0.5	.24
Minimum	11.5 ± 0.4	11.0 ± 0.6	10.9 ± 0.4	.62
Mean	14.0 ± 0.3	13.2 ± 0.6	13.8 ± 0.3	.42
Initial MD (dB)	−5.9 ± 0.5	−5.0 ± 0.9	−5.0 ± 0.9	.69
MD change/year (dB)	−0.38 ± 0.23	0.48 ± 0.19	−0.50 ± 0.37	.04*
CPSD (dB)	8.7 ± 1.2	6.0 ± 1.1	6.0 ± 1.0	.17

ACE = angiotensin-converting enzyme; M = male; F = female; D = diopter; IOP = intraocular pressure; dB = decible; MD = mean deviation; CPSD = corrected-pattern standard deviation.
*Statistically significant at $P < .05$ level.

TABLE 2. Linear Regression Analysis of Intraocular Pressure and Mean Deviation Change per Year

	Linear Regression	R^2	*P* Value
Control	y = 4.381 − 0.34x	0.227	.10
ACE-treated group	y = 1.479 − 0.075x	0.048	.52
Another antihypertensive drug-treated group	y = −2.817 + 0.162x	0.021	.65

y = MD change per year; x = IOP; IOP = intraocular pressure; MD = mean deviation; ACE = angiotensin-converting enzyme.

These data suggest that endogenous bradykinin levels may be lower in NTG patients than in normal subjects. Long-term treatments with ACE inhibitors have been shown to increase plasma bradykinin levels.[5] Yasuyoshi and associates[6] recently reported that bradykinin had a protective effect on neurotoxicity induced by glutamate through the bradykinin-B_2 receptors in cultured retinal neurons. The lower angiotensin II levels during ACE inhibitor treatments may have beneficial effects on the outcome by lowering vascular superoxide anion production.[7] Therefore, ACE inhibitor might have a favorable effect on the visual fields in NTG patients. In our study, there was no relationship between IOP and MD change per year. This result suggests that visual field loss may not correlate with IOPs in some patients with NTG.

In conclusion, although the present study is retrospective and the sample size is small, the long-term use of ACE inhibitors might have a favorable effect on the visual fields in a subset of patients with NTG. A randomized controlled study is needed to prove the effect for ACE inhibitors in the prevention of visual field defect progression in patients with NTG.

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Neuroprotective Effects of D-Allose against Retinal Ischemia–Reperfusion Injury

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Purpose. To investigate the effect of D-allose, a rare sugar, against ischemia reperfusion injury in the rat retina.

Methods. Retinal ischemia was induced by increasing intraocular pressure to 130 mm Hg and maintaining that level for 45 minutes. Morphometric studies were performed to study the effect of D-allose on the histologic changes induced by ischemia in the rat retina. Glutamate release from the rat retina and intravitreal Po_2 profiles were monitored during and after ischemia with a microdialysis biosensor and oxygen-sensitive microelectrodes. The release of hydrogen peroxide stained with diaminobenzidine hydrochloride was monitored by an in vitro retinal ischemia model.

Results. Seven days after the ischemia, significant reductions in both the number of ganglion cells and the thickness of the inner plexiform layer were observed. Pretreatment with D-allose significantly inhibited the ischemic injury of the inner retina. A large release of glutamate occurred during the ischemia. After the recirculation, glutamate levels were increased again and reached a maximum in approximately 20 minutes. The increases in extracellular glutamate during and after ischemia tend to be suppressed by administration of D-allose. D-Allose attenuated the increase in intravitreal Po_2 during reperfusion. After the ischemia, production of hydrogen peroxide was detected within approximately 30 minutes. D-Allose suppressed the production of hydrogen peroxide.

Conclusions. These results suggest that D-allose may protect neurons by decreasing extracellular glutamate and attenuating oxidative stress in ischemic insult. (*Invest Ophthalmol Vis Sci.* 2006;47:1653–1657) DOI:10.1167/iovs.05-1018

A rare aldo-hexose sugar, D-allose, is derived from D-psicose by microorganisms and their enzymes.[1] Rare sugars have received increasing attention in recent years for a variety of usages such as low-calorie carbohydrate sweeteners and bulking agents.[2] Arnold and Silady[3] have reported that D-allose substantially inhibits segmented neutrophil production and lowers platelet count without other detrimental clinical effects. Hossain et al.[4] has recently studied the immunosuppressive effect of D-allose and compared it with that of FK506 on the basis of neutrophil count and animal survival in liver transplantation experiments using rats. Their study showed that the rate of allograft survival was significantly increased with less tissue damage when low-dose FK506 was administered in combination with D-allose compared with the administration of each drug separately.[4] They also performed a series of experiments using hepatic ischemia-reperfusion in a rat model to evaluate the protective effect of D-allose and found that the ameliorative effect was achieved mainly by reducing the number of total neutrophils during or after reperfusion.[5]

Ischemic injury to the retina is a major cause of visual loss and morbidity. Some studies have demonstrated that oxygen-derived free radicals generated during ischemia and on reperfusion may trigger ischemic cell damage in various organs, such as the brain, heart, kidney, liver, bowel, and retina.[6–8] In the central nervous system, free radicals lead to the hypersecretion of excitatory amino acids, such as glutamate and aspartate,[9] which bind to receptor sites and augment cellular destruction by increasing membrane permeability to calcium and sodium ions and water.[10] Injured neurons release massive amounts of glutamate, which induce neuronal cell death by continuous overexcitation of postsynaptic receptors.[10,11] In this way, the initial trauma is amplified and causes the damage to spread to neighboring cells. During or after ischemia, reactive oxygen species can be produced in large quantity and act as cytotoxic metabolites.[12] The species of primary concern include superoxide anion ($O_2\ddot{y}^{-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^{\cdot}$). It appears that reactive oxygen species can provoke cell death, either by reacting with cell components, leading to necrosis, or by activating specific targets and triggering apoptosis.

The purpose of the present study was to investigate the mechanism of the protective effects of D-allose on neuronal death in retinal ischemia.

Material and Methods

Animals

Female Sprague-Dawley rats, weighing 200 to 250 g, were obtained from Charles River Japan (Yokohama, Japan). Transient retinal ischemia was induced for 45 minutes in the right eye of each rat. Rats were anesthetized by intraperitoneal injection of pentobarbital (40–50 mg/kg). Animal care and experiments were approved by the standard guidelines for animal experimentation of the Kagawa University Faculty of Medicine and adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. D-Allose was administered at a dose of 50, 100, 200, and 400 mg/kg. The animals were divided into two groups according to treatment: a D-allose group and a control group (saline instead of D-allose). In the D-allose group, intraperitoneal injection of D-allose was administered 30 minutes before ischemia was induced. In the control group, an intraperitoneal injection of 0.9% normal saline was administered as a vehicle 30 minutes before ischemia was induced.

Ischemia

After anesthesia, the anterior chamber of the right eye was cannulated with a 27-gauge infusion needle connected to a reservoir containing

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normal saline. The intraocular pressure (IOP) was raised to 130 mm Hg for 45 minutes by elevating the saline reservoir. Retinal ischemia was confirmed by the whitening of the iris and fundus. Sham-treated control left eyes underwent a similar procedure, but without the elevation of the saline bag, so that normal ocular tension was maintained. The 45-minute duration of ischemia was chosen on the basis of previous studies.[13,14] Because body temperature may influence ischemia-induced retinal ganglion cell death,[15] rectal and tympanic temperatures were maintained at approximately 37°C, using a feedback-controlled heating pad (CMA, Stockholm, Sweden) during the operation. After restoration of blood flow, temperature was still maintained at 37°C.

Histologic Examination

For histologic examination, rats were anesthetized by intraperitoneal injection of pentobarbital (40–50 mg/kg) 1 week after ischemia and perfused intracardially with phosphate-buffered saline (PBS), followed by perfusion with 4% paraformaldehyde in PBS. The retinas were removed and embedded in paraffin, and thin sections (5 μm thickness) were cut with a microtome. Each retina was mounted on a silane-coated glass slide and then stained with hematoxylin and eosin (HE).

Morphometric analysis was performed to quantify ischemic injury. These sections were selected randomly in each eye. A light microscopic examination was performed by a person with no prior knowledge of the groups. A microscopic image of each section within 0.5 to 1 mm of the optic disc was scanned. In each computer image, the number of cells in the ganglion cell layer (GCL) was counted. The thickness of the inner plexiform layer (IPL), inner nuclear layer (INL), and outer nuclear layer (ONL) at the entire frame were measured. The number of cells in the GCL was normalized as linear cell density (cells per millimeter). Finally, in each eye, the thicknesses of the IPL, INL, and ONL were obtained as the mean values of the four measurements, and the linear cell density in the GCL was defined as the mean value of the four measurements. For each animal, these parameters in the right eye were normalized to those in the intact left eye and shown as a percentage.

Measurements of Glutamate in the Vitreous Body

The measurements were performed as described elsewhere.[16] Briefly, a dialysis electrode (Microdialysis Biosensor; Applied Neuroscience, London, UK) was used.[17] The electrode was composed of a platinum wire located inside a hollow semipermeable dialysis membrane (500 Da) with an outside diameter of 230 μm. Two additional electrodes, a reference electrode (Ag/AgCl) and a counter electrode (Ag), comprised the electrochemical cell, and these were collectively installed in a glass capillary, away from the main sensing area. For the measurement of glutamate, the probe was filled with 10 mM phosphate-buffered saline (PBS; pH 7.4), with or without glutamate oxidase (100 U/mL; Yamasa Co. Ltd., Chiba, Japan), and perfused at a flow rate of 0.2 μL/min by means of a microinfusion pump (IP-2 microinfusion pump; Bio Research Center Co. Ltd., Nagoya, Japan). Each substance diffuses across the dialysis membrane into the electrode, and the respective oxidase produces hydrogen peroxide which is detected by the electrode. The current detected by the electrode is sent to an amplifier and is recorded on a polygraph in real time. In each experiment before and after in vivo measurements, glutamate and H_2O_2 were determined with and without glutamate oxidase solution in the test tube respectively and a regression line was obtained from known concentration. The current detected by the electrode was sent to the amplifier (EPS-800; Eicom, Kyoto, Japan). The change of 1 nA was equivalent to 8 μM of glutamate. D-Allose (200 mg/kg) or saline was administered 30 minutes before ischemia, and glutamate was monitored in the D-allose and control groups (n = 4 per group) before, during, and after ischemia. Body temperature was maintained at approximately 37°C during measurement. In each experiment, a regression line was obtained from the known glutamate concentration.

Measurements of Po_2 in the Vitreous Body

Intravitreal oxygen was monitored with a Po_2 probe (Intermedical Co. Ltd., Nagoya, Japan) of 0.1-mm diameter. After the fiber-optic probe was dipped into the oxygen-saturated PBS solution, the value of the amplifier was adjusted to 155 mm Hg. The probe was inserted into the vitreous in the same manner as for glutamate measurement (n = 4 per group).

In Vitro Histologic Detection of Released H_2O_2

Rats were killed after 200 mg/kg D-allose or saline was administered. For in vitro detection of released hydrogen peroxide, the retina was quickly removed and immersed in ice-cold artificial cerebrospinal fluid (ACSF) with 10 mM glucose bubbled in a gaseous mixture of 95% O_2 and 5% CO_2. The composition of ACSF was as follows: 124 mM NaCl, 4.4 mM KCl, 2.5 mM $CaCl_2$, 1.3 mM $MgSO_4$, 1 mM NaH_2PO_4, and 26 mM $NaHCO_2$. The retina was incubated in an interface-recording chamber maintained at 37°C for at least 30 minutes before the experiment and constantly infused with gas-saturated ACSF with 10 mM glucose at 1.2 mL/min. The retina was then put in an observation chamber and continuously bathed in a circulating fluid of ACSF with 10 mM glucose bubbled in a gaseous mixture of 95% O_2 and 5% CO_2. In vitro detection was performed by applied immunohistochemical staining with horseradish peroxidase (HRP) (anti-mouse IgG, peroxidase-linked species-specific F(ab')2 fragment from sheep; GE Healthcare, Piscataway, NJ) and diaminobenzidine (DAB) solution (1 mg/mL; Vector Laboratories Inc., Burlingame, CA). A colorized solution was made by adding equal amounts of HRP and DAB solution. Ten microliters of this solution was added to the retina, followed by observation under a stereoscopic microscope for the development of brown color as an indicator of the release of H_2O_2. The DAB solution, on binding to H_2O_2, undergoes a polymerization reaction to yield a brown color.[16] For ischemia induction, the circulating solution was changed to ACSF bubbled with 100% N_2 gas. After circulating for 45 minutes, the solution was changed back to the original solution. A stereoscopic microscope (MZ FL II; Leica Microsystems, Tokyo, Japan) was used with acharge-coupled device digital camera (DP70; Olympus, Inc., Tokyo, Japan) and analytical software (DP70-WPCP; Olympus, Inc.).

Appearance of D-Allose in Vitreous

D-[1-^{14}C]allose was obtained from GE Healthcare Biosciences (Buckinghamshire, UK). Four female Sprague-Dawley rats were used. D-[1-^{14}C]allose (100 mg/1.11 MBq/2.0 mL PBS/kg body weight) was intraperitoneally injected 30 minutes before enucleation of the eye. Rats were deeply anesthetized with pentobarbital. To minimize contamination of the intraocular tissue and blood, enucleation, and dissection of the eye were performed by the following procedure. A cut was made along the edge of the orbit. After enucleation with surrounding tissue, the eye was immersed immediately in PBS for 5 minutes. Vitreous was exfoliated from the vitreous side of the posterior cup. Radioactivity was measured by a liquid scintillation counter (Tri-Carb Liquid Scintillation Analyzer 2500TR; PerkinElmer, Meriden, CT).

Statistical Analysis

All statistical values are presented as the mean ± SEM. Data were analyzed using an independent Student's t-test where appropriate. $P < 0.05$ was considered statistically significant.

Results

Histologic Change in the Retina after Ischemia with and without D-Allose

Figure 1A shows a normal retina. Light microscopic photographs were taken 7 days after ischemia and treatment with saline (Fig. 1B) or D-allose (Figs. 1C–F). In animals pretreated with the saline control, significant reductions in the number of

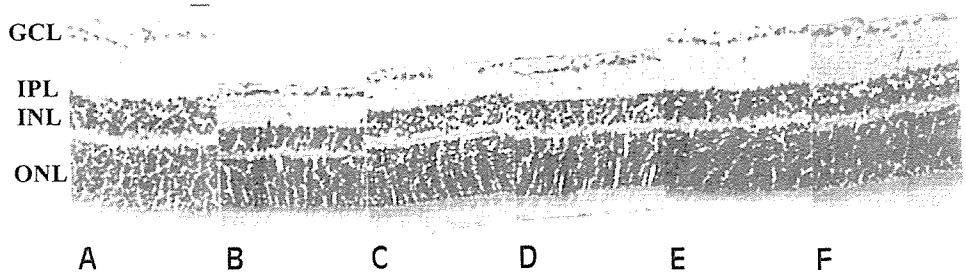

FIGURE 1. Light micrographs of a cross-section through normal rat retina (A) and 7 days after ischemia and treatment without D-allose (B) or with 50 (C), 100 (D), 200 (E), or 400 (F) mg/kg D-allose. Bar, 10 μm.

cells in the GCL and the thickness of the IPL were observed. The number of cells in the GCL was reduced to 52.5% ± 1.4% of the control ($P < 0.01$) and the thicknesses of the IPL was reduced to 71.5% ± 8.4% ($P = 0.02$), of the INL to 93.0% ± 9.6% ($P = 0.5$), and of the ONL to 95.0% ± 4.5% ($P = 0.3$; $n = 4$) of the control (Fig. 2). In animals pretreated with 200 mg/kg D-allose, the number of cells in the GCL was 95.0% ± 2.0% of the control ($P = 0.05$) and the thickness of the IPL was 95.8% ± 2.3% ($P = 0.7$), of the INL was 100.4% ± 3.0% ($P = 0.9$), and of the ONL was 102.4% ± 5.0% ($P = 0.7$; $n = 4$) of the control (Fig. 2). The co-injection of glucose (200 mg/kg) with D-allose had no protective effect against retinal ischemia reperfusion injury (data not shown).

Effect of D-Allose on Extracellular Glutamate by Ischemia

The time course of glutamate efflux in the vitreous body during the 45-minute ischemia and reperfusion in the control and D-allose groups is shown in Figure 3. A remarkable increase in glutamate was observed during ischemia. After recirculation, glutamate levels were increased again and reached a maximum in approximately 20 minutes. D-Allose suppressed increased extracellular glutamate by ischemia. The increase in glutamate efflux in the vitreous body during reperfusion tended to be suppressed by the administration of D-allose.

Effect of D-Allose on Po_2 in the Vitreous Body after Ischemia

The time course of Po_2 in the vitreous body during the 45-minute ischemia and reperfusion in the control and D-allose groups is shown in Figure 4. After recirculation, Po_2 levels were increased and, in approximately 10 minutes, reached the same levels as before ischemia. During reperfusion, D-allose enhanced Po_2 levels and reached a maximum in approximately 15 minutes.

Effect of D-Allose on Released H_2O_2

Figure 5A shows a normal flat-mounted retina. Light-microscopic photographs were taken of treatment without D-allose (Fig. 5B) and with D-allose (Fig. 5C). Without D-allose treatment, brown color was first observed 30 minutes after ischemia and was stronger 75 minutes later (Fig. 5B). However, in the presence of D-allose, a brown color was first observed 60 minutes after ischemia (15 minutes after recirculation). Decreased brown staining was observed compared with the ischemic retina (Fig. 5C).

The specificity for H_2O_2 was determined by DAB solution without hydrogen peroxide. No specific color development was observed (data not shown). This observation does not exclude the possibility of other reactive oxygen species such as superoxide, nitric oxide, peroxinitrite. However, at least the color development must be dependent on the release of H_2O_2.

Appearance of D-Allose in Vitreous

When 555 Bq/μL D-[1-^{14}C]allose was intraperitoneally injected, it appeared in the vitreous and blood at 46.4 ± 5.2 Bq/μL and 42.8 ± 3.0 Bq/μL, respectively, at 30 minutes ($n = 4$; Table 1). The concentration of D-allose in vitreous was shown to be almost same as that in blood.

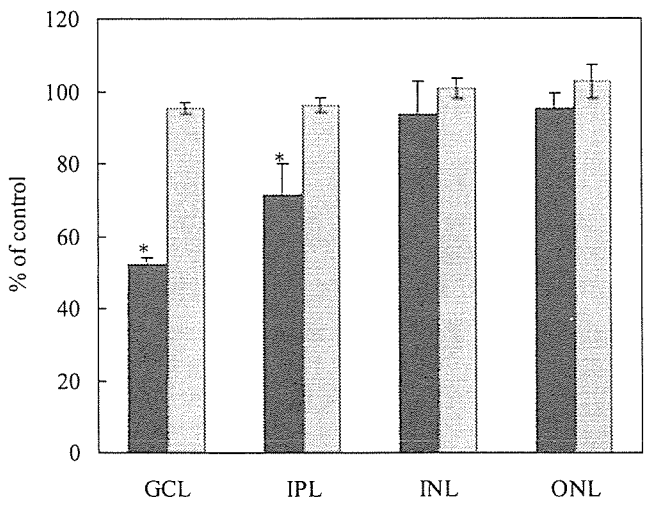

FIGURE 2. Percentage of change relative to control values in the number of GCL cells and the thicknesses of the IPL, INL, and ONL 7 days after ischemia without D-allose (■) or with 200 mg/kg D-allose (▨). Results are expressed as the mean ± SEM (*$P < 0.05$).

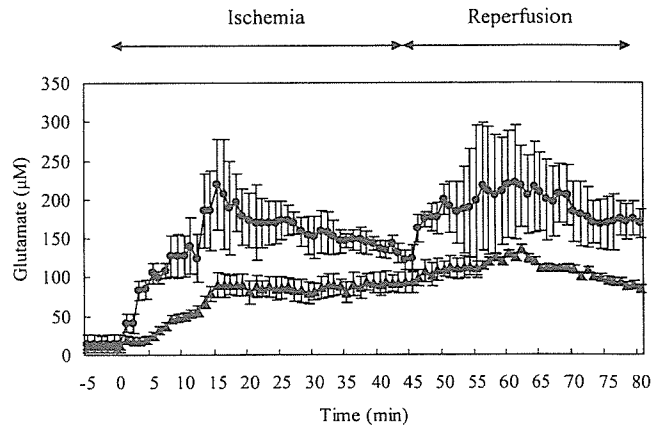

FIGURE 3. Effect of D-allose on the release of glutamate from rat retina. (●) Control; (▲) D-allose. Ischemia was induced by elevating the intraocular pressure for 45 minutes. D-Allose (200 mg/kg, intraperitoneally) was administered 30 minutes before ischemia in the D-allose group, and glutamate was measured by an electroenzymatic method of microdialysis. Glutamate was significantly increased by ischemia. Glutamate during both ischemia and reperfusion was suppressed by D-allose. Data represent the mean ± SEM.

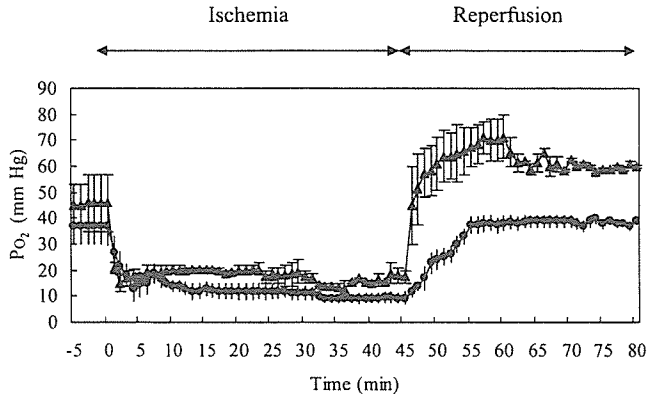

FIGURE 4. Effect of D-allose on Po_2 levels. (●) Control; (▲) D-allose. Ischemia was produced by elevating intraocular pressure for 45 minutes D-allose (200 mg/kg, intraperitoneally) was administered 30 minutes before ischemia in the D-allose group and Po_2 was measured by a Po_2 probe. The Po_2 levels were significantly increased after ischemia. The Po_2 levels during reperfusion were enhanced by D-allose. Data represent the mean ± SEM.

DISCUSSION

In the present study, the release of glutamate from the rat retina was observed during the ischemic period, and a larger increase occurred during reperfusion. Similar observations were reported in rabbit[18] and feline[19] retinas. A delayed increase in the efflux of glutamate was observed during the recirculation period in the CA1 field of the hippocampus where most presynaptic fibers were eliminated, and the extracellular glutamate level returned very gradually to the baseline range in the setting.[20] Mitani et al.[21] suggested that presynaptic terminals in the CA1 field play a major role in the uptake of glutamate after ischemia. The prolonged release of glutamate after ischemia in the retina may reflect such a defective glutamate uptake system in the retinal neurons, because retinal neurons did not show a significant affinity for glutamate uptake.[21] Glutamate receptors have been subdivided into ionotropic and metabotropic receptors.[22] Although the details of the pathway are not clear, there is compelling evidence to suggest that neurons that contain ionotropic glutamate receptors are particularly susceptible to ischemia-reperfusion. The neurons in the retina that express such receptors are the ganglion cells and a subset of amacrine cells.[23] In ischemia-reperfusion, neurotransmitters are related, and they overactivate their appropriate receptors. Such overstimulation, particularly of ionotropic glutamate receptors, generally leads to cell death.[24–27] In this study, D-allose prevented retinal damage by reducing extracellular glutamate levels.

TABLE 1. Distribution of D-Allose in Vitreous and Blood

Vitreous	46.4 ± 5.2	(8.4 ± 1.0)
Blood	42.8 ± 3.0	(7.7 ± 0.5)

D-[1-^{14}C]Allose (555 Bq/μL) was intraperitoneally injected, and radioactivity in vitreous and blood were measured at 30 minutes after injection. Data are mean Bq/μL ± SEM (% of distribution) of four preparations.

To clarify the role of D-allose as an antioxidant, a research group at Kagawa University Faculty of Medicine and the Nation Agriculture Research Center for Western Region, Kagawa, has examined the scavenging activities of D-allose and other sugars using electron spin resonance. They found scavenging activities in rare sugars, although the activities were much weaker than those of other common scavengers such as superoxide dismutase and carotinoids.[28] Significant inhibition of reactive oxygen species production was detected only when D-allose was added, although the inhibition was found to be dose dependent.[28] The ameliorative effect of D-allose has been observed after liver transplantation[4] and ischemia-reperfusion injury of the liver.[5]

A considerable amount of reactive oxygen species is produced in ischemia, especially during reperfusion, due to the increase in oxygen supply and metabolism, and this exacerbates neuronal cell damage (reperfusion injury).[29] In a recent study, using a technique based on electron spin resonance trapping analysis of the signals obtained in microdialysates of the retina, Muller et al.[30] directly showed that $OH^{\cdot}$ radicals were generated during the ischemic episode itself and remained elevated at reperfusion. This $OH^{\cdot}$ production was in-

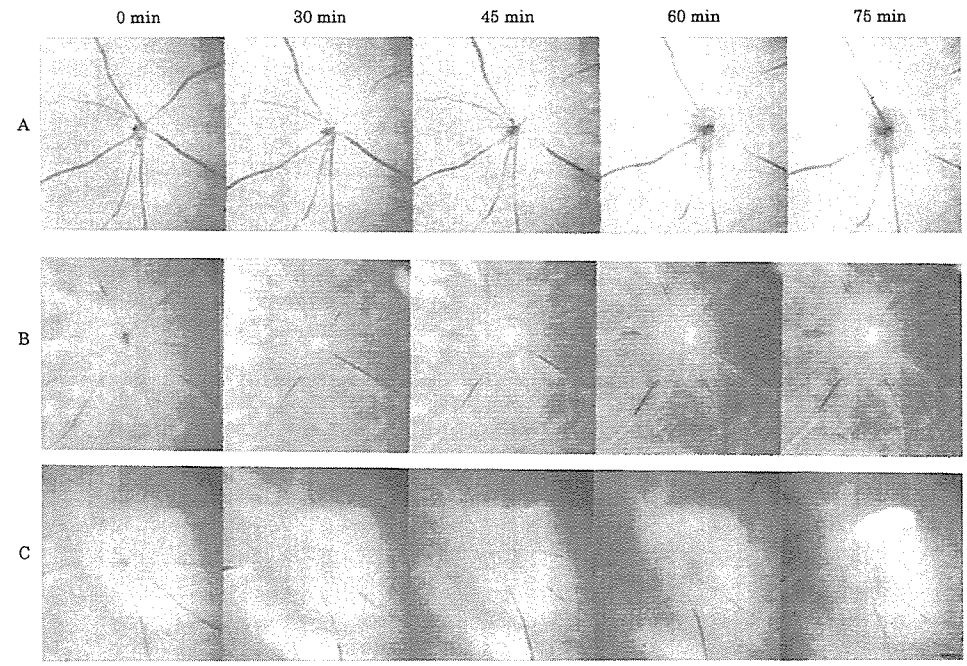

FIGURE 5. Effect of D-allose on the release of H_2O_2. The brown color indicates the release of H_2O_2. Ischemia induction was for 45 minutes. Color photographs were taken before ischemia induction and at 30, 45, 60, and 75 minutes after starting ischemia induction. (**A**) There was no brown staining in a control flat-mounted retina. Rats were killed 30 minutes after the instillation of saline (**B**) or D-allose (**C**). With D-allose treatment, the retina became brown 60 minutes after ischemia and was lighter stained than the retina without D-allose treatment at every time point. Bar, 500 μm.

hibited by superoxide dismutase/catalase and deferoxamine, suggesting that H_2O_2 is an intermediate in radical formation. Molecular oxygen (O_2) can be reduced by various enzymatic reactions, mainly by oxidases and an oxygenase cascade.[31] Superoxide is dismutated to H_2O_2. Ullrey and Kalckar[32] previously reported that D-allose may inhibit hexose transport. D-Allose could reduce the production of H_2O_2 by modulating the glycolytic response. In the present study, D-allose affected increased Po_2 levels in the vitreous body by reperfusion. D-Allose may enhance Po_2 levels in the vitreous body after ischemia due to a decrease in the production of H_2O_2, consequently preventing reperfusion injury.

In conclusion, preischemic administration of D-allose suppressed glutamate release during and after ischemia. Furthermore, D-allose reduced the production of H_2O_2 during recirculation. The present study suggests that D-allose may protect neurons by decreasing extracellular glutamate and attenuating oxidative stress in ischemic insult.

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42. OPA1 遺伝子異常を有する常染色体優性視神経萎縮の網膜電図所見

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研究要旨　目的：常染色体優性視神経萎縮（以下 ADOA）は、両眼の視神経萎縮および機能異常を呈する疾患であり、原因遺伝子の１つとして OPA1 が同定されている。今回我々は、OPA1 遺伝子異常を有する DOA の網膜電図（ERG）所見を検討したので報告する。
対象と方法：OPA1 遺伝子に変異が認められた DOA 8 例 8 眼（年齢、24-55 歳; 平均、41.0 歳）および正常眼 25 例 25 眼を対象とした。国際臨床視覚電気生理学会（ISCEV）のガイドラインに従い、杆体応答、最大応答、律動様小波（OPs)、錐体応答、30-Hz フリッカー応答、および Photopic negative response (PhNR)を記録し、各応答の振幅を正常群の値と比較した。さらに OCT3 による網膜視神経線維層（RNFL）の計測および静的視野検査を行ない、ERG の結果との相関を調べた。
結果：DOA では、正常群と比較して PhNR および OPs の振幅が有意に減弱していた。($p<0.001$)。他の成分は正常群と比較してやや減弱する傾向を認めたが、有意差はなかった。PhNR および OPs の振幅と、視力、静的視野、および RNFL の厚みとの間に有意な相関はみられなかった。
結論：PhNR および OPs の起源は網膜内層であると考えられており、今回の結果により OPA1 遺伝子異常を有する DOA の網膜は、網膜神経節細胞およびアマクリン細胞を主体とした網膜内層の機能異常を有していることが示唆された。

A．研究目的

常染色体優性視神経萎縮（ADOA)は主要な遺伝性視神経症のひとつであり、原因遺伝子として OPA1 遺伝子が同定されている[1)2)]。過去の報告では病理組織学的に視神経萎縮に先立って神経節細胞の変性が確認されており、電気生理学的に Holder らは神経節細胞からの応答と考えられる patternERG に異常を認めることを報告している[3)]。ただし、視神経疾患であるので一般的には全視野網膜電図（ERG）は正常と考えられている。今回我々は OPA1 遺伝子に変異を認める ADOA の ERG 所見について検討したので報告する。

B．研究方法

OPA1 遺伝子に変異が認められた ADOA8 例 8 眼（年令、24-55 歳；平均、41.0 歳）を対象とした。国際臨床視覚電気生理学会（ISCEV）のガイドラインに従い、杆体応答、最大応答、律動様小波（OPs)、錐体応答、30-Hz フリッカー応答、および Photopic

negative response (PhNR)を記録し、各応答の振幅を正常群25例25眼の値と比較した。さらにOCT3による網膜視神経線維層（RNFL）の計測および静的視野検査を行ない、ERGの結果との相関を調べた。

C．研究結果

最大応答、錐体応答のADOA各8例および正常眼の代表波形を示す（図1および2）。ADOAでは、正常群と比較してPhNRおよびOPsの振幅は有意に減弱していた（$p<0.001$）。

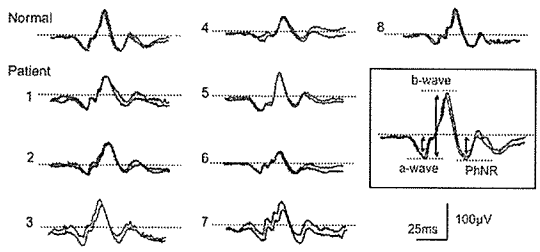

図1

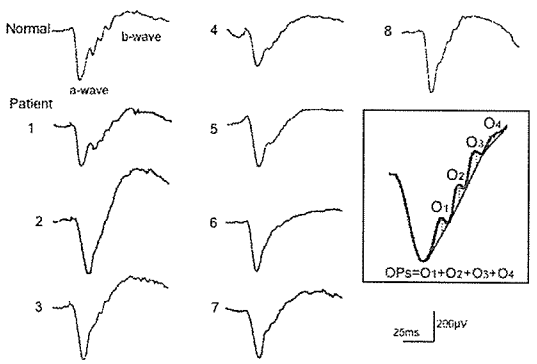

図2

全ての応答のa波およびb波は正常群と比較してやや減弱する傾向を認めたが、有意差はなかった。波形全体の振幅の減弱がPhNRおよびOPsの振幅に与える影響を調べるため、b波と各応答との比を正常群と比較したが、同様にADOAでは有意に低下していた（$p<0.05$）。PhNRおよびOPsの振幅と、静的視野検査による平均偏差（MD）およびRNFLの厚みとの間に有意な相関はみられなかったが、OPsと年令に有意な相関が認められた（$p=0.02$）。一方PhNRと年令に相関はなかった。

D．考察

ADOAの主要な病変部位は神経節細胞であるため、全視野網膜電図は一般に正常と考えられてきた。今回、我々はOPA1遺伝子異常を有するADOAにおいてPhNRが減弱することが分かった。PhNRはb波に続く陰性成分であり、過去の動物モデルや臨床実験により主に神経節細胞を起源とすることが分かっている[4]。ADOAでPhNRの振幅が有意に減弱していることより、PhNRが神経節細胞の活動性を反映していることが過去の報告と一致して確認された。興味深い結果として、我々はADOAにおいてOPsが年令とともに徐々に減弱していくこと見出した。OPsは一般的に内網状層付近、特にアマクリン細胞の機能を反映していると考えられている[5]。この結果よりOPA1遺伝子は神経節細胞のみならずアマクリン細胞を含んだ内網状層付近にも影響を与えていることが示唆された。これを裏付けるように、過去の免疫組織学的検討でもOPA1蛋白が網膜の神経節細胞以外の層にも発現していることが報告されている[6]。また、年令とOPsとの相関よりOPA1遺伝子異常による内網状層付近の機能異常が進行性である可能性も示唆された。一方、PhNRは年令に関わらず振幅が減弱していることから、神経節細胞は発症早期より変性が生じている可能性がある。ただし、今回の検討では最も若い症例が22才であること、同一症例での長期経過を検討してい