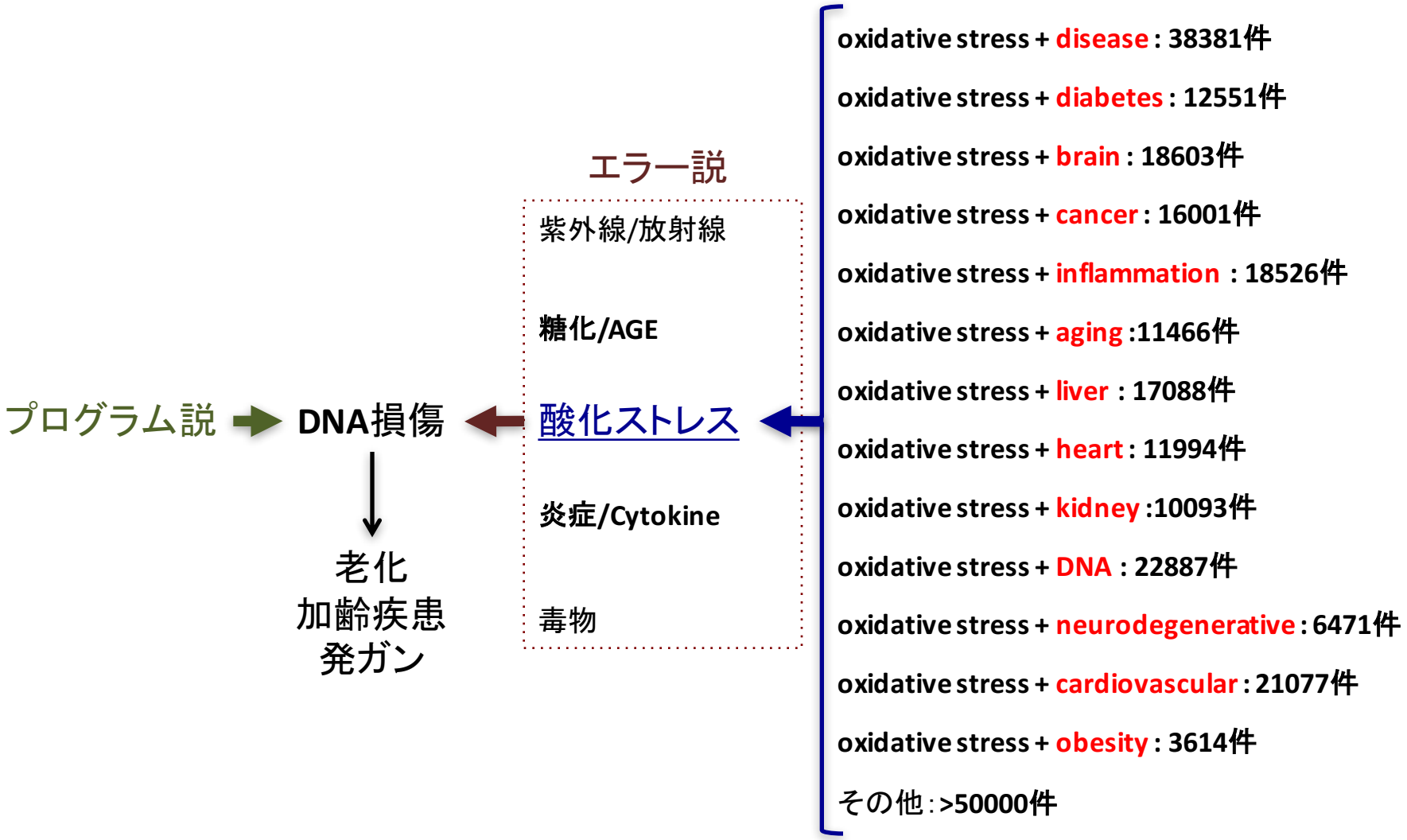
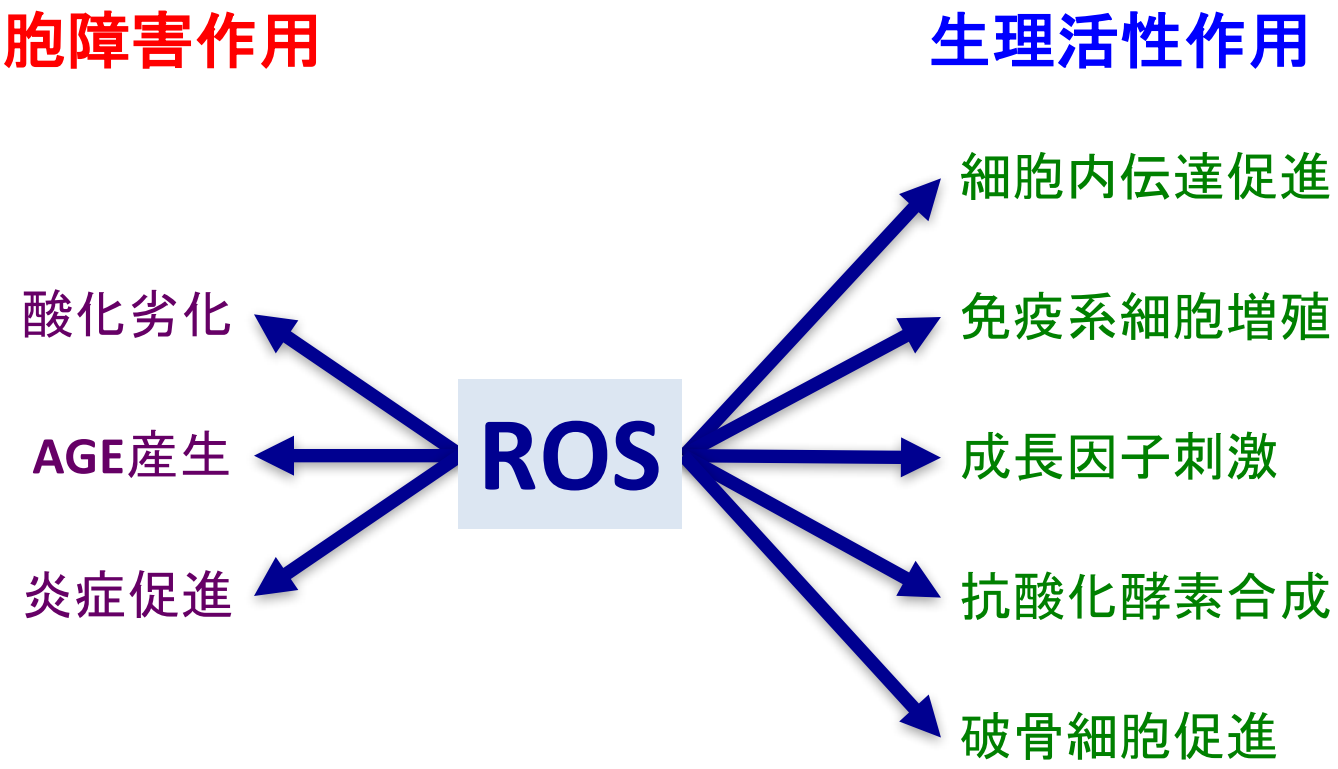
水素の臨床利用と今後の展望

（医）医献会　辻クリニック　理事長
（社）臨床水素治療研究会　代表理事
辻　直樹

酸化ストレスと老化/疾患の研究

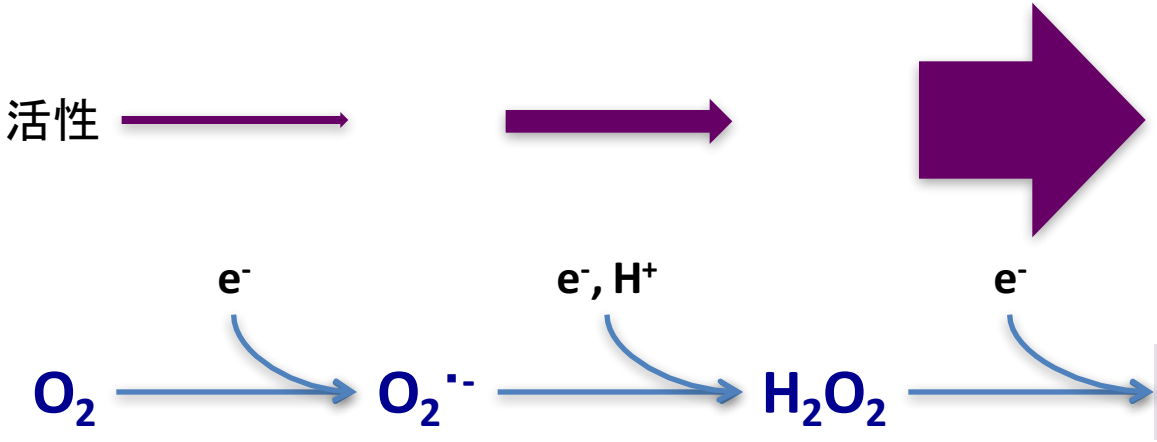


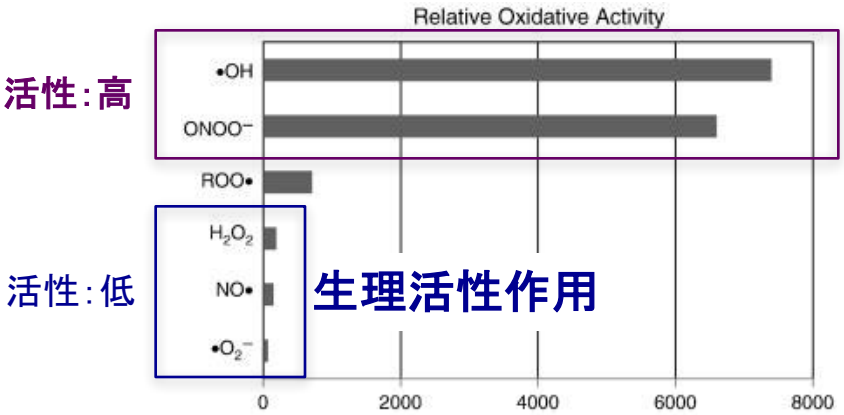
ROSの二つの顔



ROSは善か悪か？

ROSの活性度





活性：高

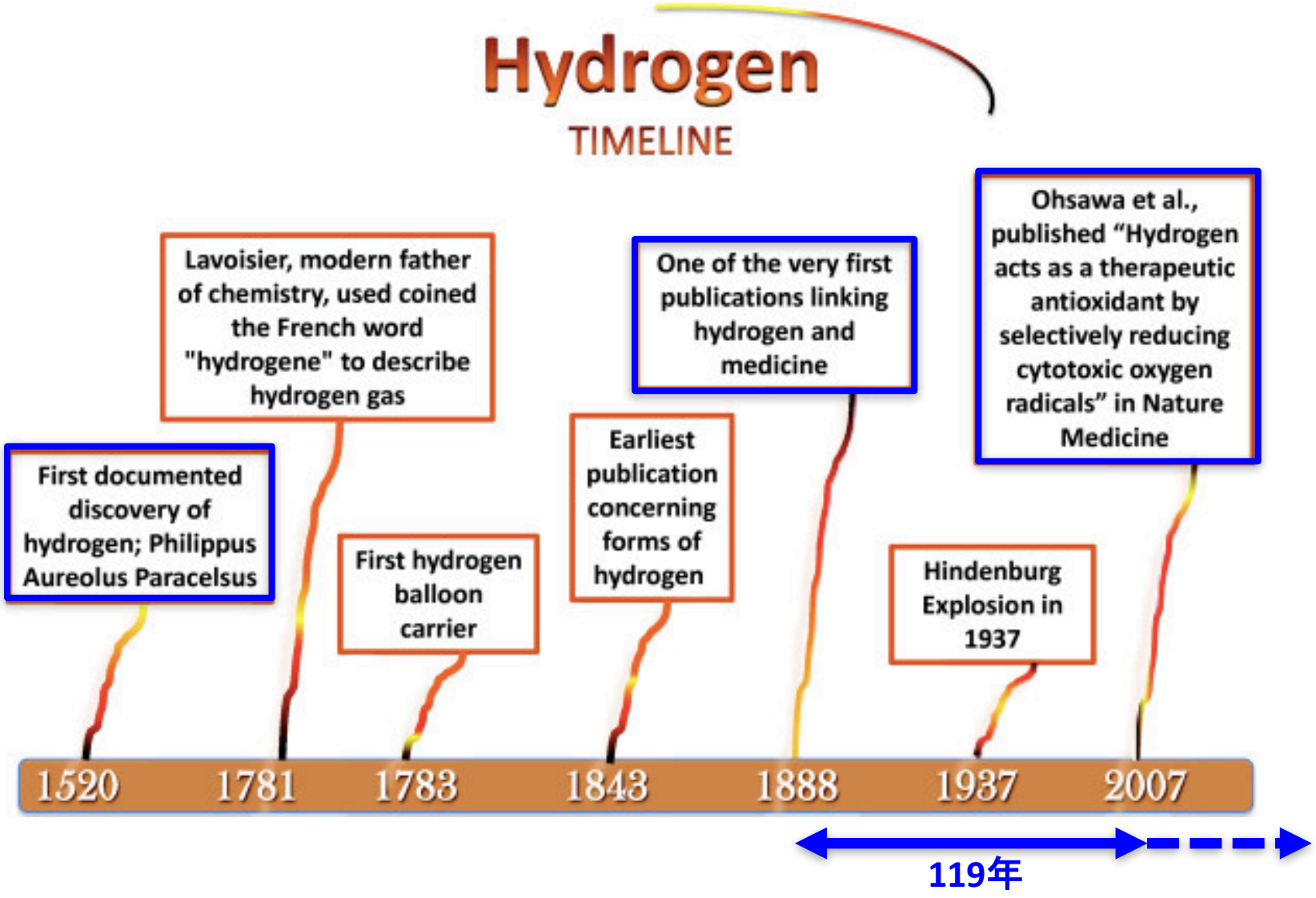
活性：低

生理活性作用

障害 ← 治療ターゲット

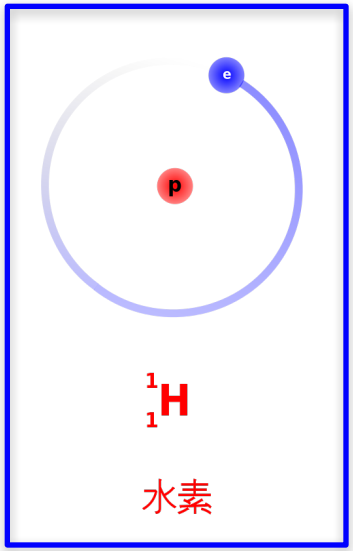
水素と水素医学の歴史

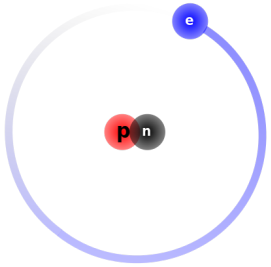
水素と水素の医学利用の歴史

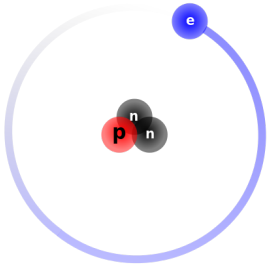


水素の発見と水素

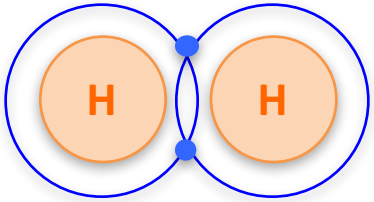
分類：非金属
族/周期/ブロック：1/1/s
原子量：1.00794
電子配置：$1s^1$
電子殻：1
色：無色
相：気体
密度：0.08988g/L（0℃ 100kPa）
酸化数：1, -1
電気陰性度：2.20
ファンデルワールス半径：120pm







マイナス水素イオン
水素原子
プラズマ水素
などもここでは無視する



ここでいう『水素』は『分子状水素』に限定する

1888：水素に関する発の医学論文

EDITORIAL ARTICLES.

SENN ON THE DIAGNOSIS OF GASTRO-INTESTINAL PERFORATION BY THE RECTAL INSUFFLATION OF HYDROGEN GAS.

The fertile mind of Professor Senn is notable for the originality of its conceptions. Our readers have been favored during the last half year with an account of his remarkable work in the treatment of intestinal obstruction, as presented to the Ninth International Medical Congress a year ago. Dr. Senn has not been satisfied to rest content with the laurels won by his previous labors in abdominal surgery, but has continued his vivisection experiments into the diagnosis of intestinal perforation.[1]

The fact that intestinal perforation can be treated by suture with success is now fully established. And it may also be considered as demonstrated that a traumatic perforation of any portion of the gastro-intestinal canal is inevitably fatal unless it be treated by suture.

The fact that a small number of cases are on record in which undoubted perforation of the gut recovered without other than expectant treatment can not be regarded as militating against the truth of this general rule, since they form so small a portion of the total that they may be ignored in the consideration of the subject.

In opposition to this condition may be placed simple perforating wounds of the abdominal parietes without lesion of the viscera, a condition amenable to simple closure of the external wound and comparatively innocuous.

But the great difficulty that presents itself to the surgeon in the ab-

[1]Rectal Insufflation of Hydrogen Gas an Infallible Test in the Diagnosis of Visceral Injury of the Gastro-intestinal Canal in Penetrating Wounds of the Abdomen. By N. Senn, M. D., Ph. D. (Milwaukee, Wis.)—*Journal of the American Medical Association*, June 23 and 30, 1888.

(190)

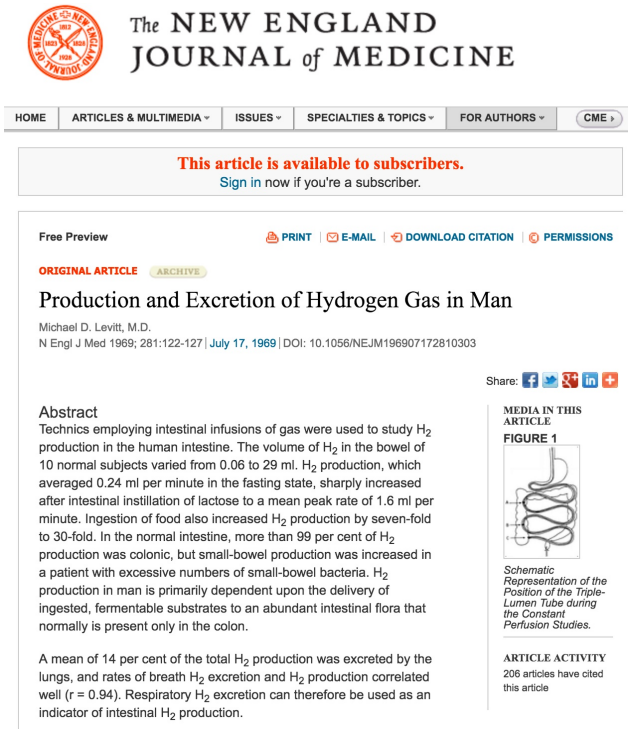
Pilcher JE

胃腸穿孔診断のために水素ガスを利用
（分子状水素をはじめて生体に利用）

水素の効果を示したものではなかった

大量投与においても毒性を認めず
安全に利用できた

1969:正常人における水素ガスの発生



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ORIGINAL ARTICLE ARCHIVE

Production and Excretion of Hydrogen Gas in Man

Michael D. Levitt, M.D.
N Engl J Med 1969; 281:122-127 | July 17, 1969 | DOI: 10.1056/NEJM196907172810303

Share:

Abstract

Technics employing intestinal infusions of gas were used to study H_2 production in the human intestine. The volume of H_2 in the bowel of 10 normal subjects varied from 0.06 to 29 ml. H_2 production, which averaged 0.24 ml per minute in the fasting state, sharply increased after intestinal instillation of lactose to a mean peak rate of 1.6 ml per minute. Ingestion of food also increased H_2 production by seven-fold to 30-fold. In the normal intestine, more than 99 per cent of H_2 production was colonic, but small-bowel production was increased in a patient with excessive numbers of small-bowel bacteria. H_2 production in man is primarily dependent upon the delivery of ingested, fermentable substrates to an abundant intestinal flora that normally is present only in the colon.

A mean of 14 per cent of the total H_2 production was excreted by the lungs, and rates of breath H_2 excretion and H_2 production correlated well ($r = 0.94$). Respiratory H_2 excretion can therefore be used as an indicator of intestinal H_2 production.

MEDIA IN THIS ARTICLE
FIGURE 1

Schematic Representation of the Position of the Triple-Lumen Tube during the Constant Perfusion Studies.

ARTICLE ACTIVITY
206 articles have cited this article

10人の腸内の水素ガス産生を調査

平均:0.06～29ml/分
平均:0.24ml/分
腸に乳糖注入時平均:1.6ml/分
食事によって7～30倍に増加
平均14%が肺から排泄(他は放屁など)

水素分子は血液に溶解している＝安全

正常な腸で水素ガスは99%以上が結腸で産生
小腸に過剰の腸内細菌を持った患者では小腸での産生が増加

よって・・・

水素は無作用？　vs　水素は体内で作用？

最近までこちらが優勢

1975:水素の扁平上皮癌に対する作用

REPORTS

Hyperbaric hydrogen therapy: a possible treatment for cancer

M Dole, FR Wilson, WP Fife

Science 10 Oct 1975:
Vol. 190, Issue 4210, pp. 152-154
DOI: 10.1126/science.1166304

Abstract

Hairless albino mice with squamous cell carcinoma were exposed to a mixture of 2.5 percent oxygen and 97.5 percent hydrogen at a total pressure of 8 atmospheres for periods up to 2 weeks in order to see if a free radical decay catalyzer, such as hydrogen, would cause a regression of the skin tumors. Marked aggression of the tumors was found, leading to the possibility that hyperbaric hydrogen therapy might also prove to be of significance in the treatment of other types of cancer.

M Dole
マウス扁平上皮癌に水素ガスを利用

97.5% 8atmという高濃度/高圧ガス

水素は抗酸化物質であるという認識

水素に抗がん作用の可能性

作用機序については言及せず

2001:肝炎に対する水素の抗炎症作用

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | Advanced

Abstract | Send to:

C R Acad Sci III. 2001 Aug;324(8):719-24.

Anti-inflammatory properties of molecular hydrogen: investigation on parasite-induced liver inflammation.

Gharib B[1], Hanna S, Abdallahi OM, Lepidi H, Gardette B, De Reggi M.

Author information

Abstract

Molecular hydrogen reacts with the hydroxyl radical, a highly cytotoxic species produced in inflamed tissues. It has been suggested therefore to use gaseous hydrogen in a new anti-inflammatory strategy. We tested this idea, with the aid of the equipment and skills of COMEX SA in Marseille, a group who experiments with oxygen-hydrogen breathing mixtures for professional deep-sea diving. The model used was schistosomiasis-associated chronic liver inflammation. Infected animals stayed 2 weeks in an hyperbaric chamber in a normal atmosphere supplemented with 0.7 MPa hydrogen. The treatment had significant protective effects towards liver injury, namely decreased fibrosis, improvement of hemodynamics, increased NOSII activity, increased antioxidant enzyme activity, decreased lipid peroxide levels and decreased circulating TNF-alpha levels. Under the same conditions, helium exerted also some protective effects, indicating that hydroxyl radical scavenging is not the only protective mechanism. These findings indicate that the proposed anti-inflammatory strategy deserves further attention.

PMID: 11510417 [PubMed - indexed for MEDLINE]

水素吸入が住血吸虫感染部（炎症部）に対し抗炎症効果
ヒドロキシラジカルと炎症反応の関係性に加え
ヒドロキシラジカルへの効果を発表

抗酸化酵素を増加、過酸化脂質レベルを低下、循環レベルTNFαを低下
肝組織の繊維化を抑制し、肝損傷に対する有為な保護作用

ヒドロキシラジカルへの選択性については言及せず

nature medicine

Article

Nature Medicine **13**, 688–694 (1 June 2007) | doi:10.1038/nm1577

Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals

Ikuroh Ohsawa , Masahiro Ishikawa , Kumiko Takahashi , Megumi Watanabe , Kiyomi Nishimaki , Kumi Yamagata , Ken-ichiro Katsura , Yasuo Katayama , Sadamitsu Asoh & Shigeo Ohta

Acute oxidative stress induced by ischemia-reperfusion or inflammation causes serious damage to tissues, and persistent oxidative stress is accepted as one of the causes of many common diseases including cancer. We show here that hydrogen (H2) has potential as an antioxidant in preventive and therapeutic applications. We induced acute oxidative stress in cultured cells by three independent methods. H2 selectively reduced the hydroxyl radical, the most cytotoxic of reactive oxygen species (ROS), and effectively protected cells; however, H2 did not react with other ROS, which possess physiological roles. We used an acute rat model in which oxidative stress damage was induced in the brain by focal ischemia and reperfusion. The inhalation of H2 gas markedly suppressed brain injury by buffering the effects of oxidative stress. Thus H2 can be used as an effective antioxidant therapy; owing to its ability to rapidly diffuse across membranes, it can reach and react with cytotoxic ROS and thus protect against oxidative damage.

2007：Prof.太田らによる論文

Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals

☆1975 Dole

Hyperbaric hydrogen therapy
: A possible treatment for cancer

☆2001 Gharib B

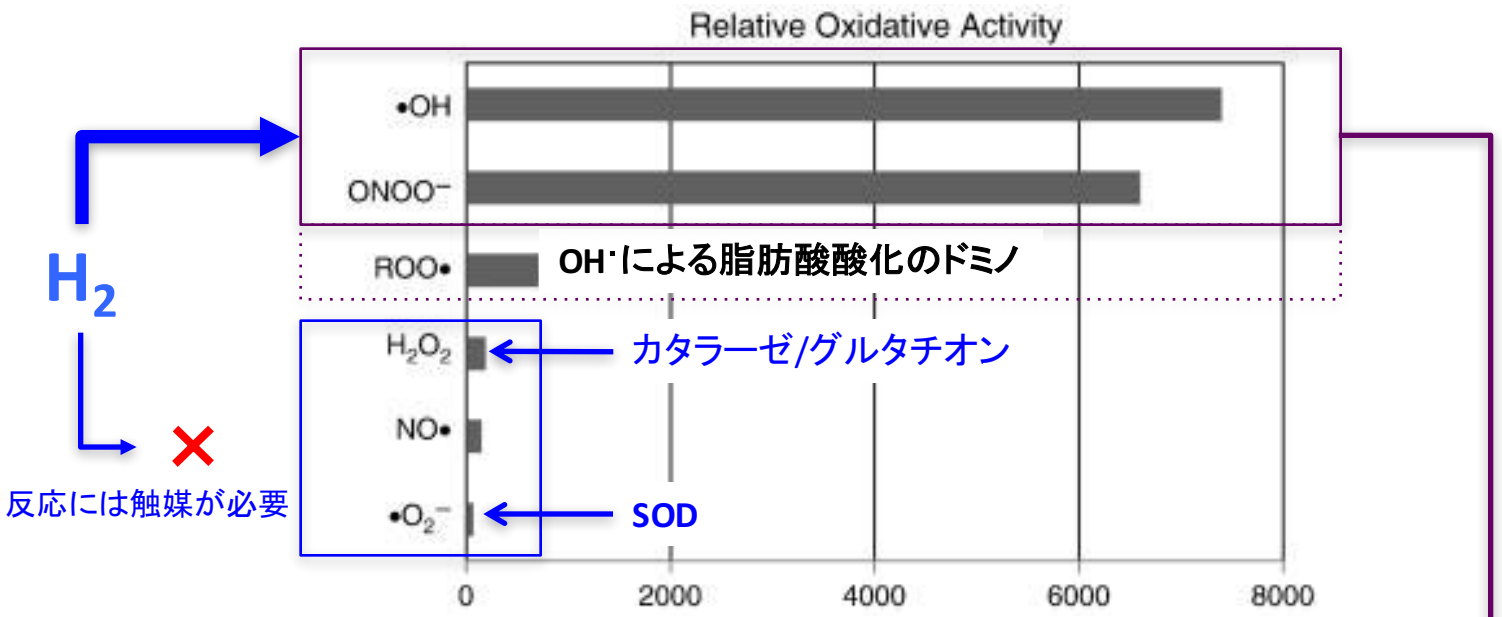
Anti-inflammatory properties of molecular hydrogen
: Investigation on parasite induced liver inflammation

水素の効果を示すもののその理由については不明

水素の作用は選択的な活性酸素の除去

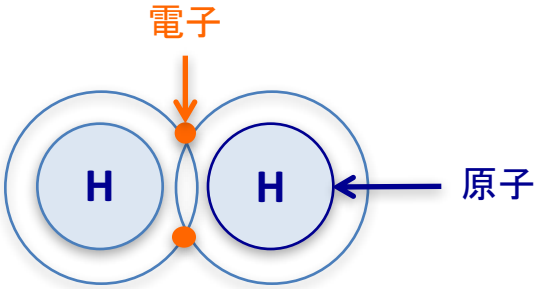
選択的抗酸化作用

活性酸素の善玉/悪玉理論と水素の選択性

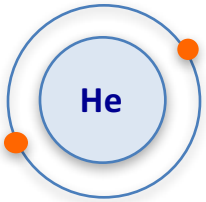


生体内の抗酸化酵素が除去できない活性酸素
生理活性型活性酸素と比べ物にならない酸化活性

水素の特性



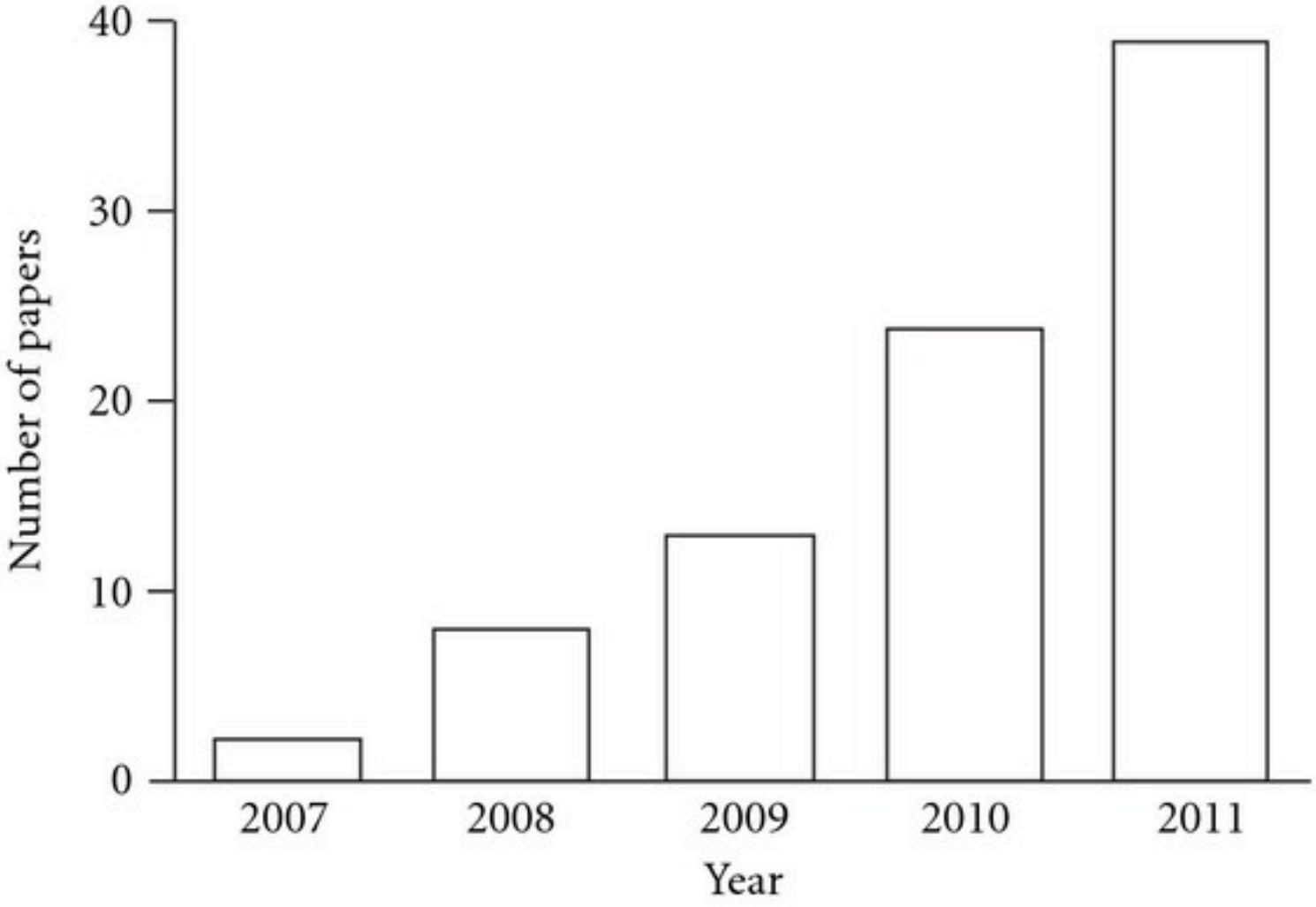
H原子2つで電子殻のS軌道が埋まり安定
ヘリウムに似た状態で安定＝反応性が低い



He: s軌道が埋まり安定

- 安定物質でF（フッ素）以外反応しない
- 触媒なしでは酸素とも反応しない
- 活性の高い活性酸素（$OH^{\cdot}$/$ONOO^{-}$）とのみ反応
- ≒悪玉活性酸素とのみ反応
- 反応物は『H_2O』
- pHには影響しない（イオン化溶解しない）
- 分子状水素は『食品』として許可

2007年以降の水素論文数



2011:酸化ストレス度の違いとシグナル

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Med Gas Res. 2011 Dec 20;1:29. doi: 10.1186/2045-9912-1-29.

Mechanisms of Action Involved in Ozone Therapy: Is healing induced via a mild oxidative stress?

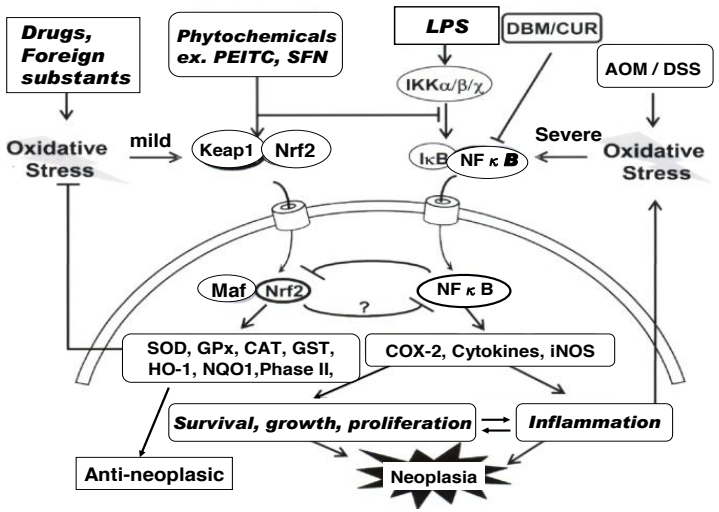
Sagai M[1], Bocci V.

Author information

Abstract

The potential mechanisms of action of ozone therapy are reviewed in this paper. The therapeutic efficacy of ozone therapy may be partly due the controlled and moderate oxidative stress produced by the reactions of ozone with several biological components. The line between effectiveness and toxicity of ozone may be dependent on the strength of the oxidative stress. As with exercise, it is well known that moderate exercise is good for health, whereas excessive exercise is not.Severe oxidative stress activates nuclear transcriptional factor kappa B (NFκB), resulting in an inflammatory response and tissue injury via the production of COX2, PGE2, and cytokines. However, moderate oxidative stress activates another nuclear transcriptional factor, nuclear factor-erythroid 2-related factor 2 (Nrf2). Nrf2 then induces the transcription of antioxidant response elements (ARE). Transcription of ARE results in the production of numerous antioxidant enzymes, such as SOD, GPx, glutathione-s-transferase(GSTr), catalase (CAT), heme-oxygenase-1 (HO-1), NADPH-quinone-oxidoreductase (NQO-1), phase II enzymes of drug metabolism and heat shock proteins (HSP). Both free antioxidants and anti-oxidative enzymes not only protect cells from oxidation and inflammation but they may be able to reverse the chronic oxidative stress. Based on these observations, ozone therapy may also activate Nrf2 via moderate oxidative stress, and suppress NFκB and inflammatory responses. Furthermore, activation of Nrf2 results in protection against neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. Mild immune responses are induced via other nuclear transcriptional factors, such as nuclear factor of activated T-cells (NFAT) and activated protein-1 (AP-1).Additionally, the effectiveness of ozone therapy in vascular diseases may also be explained by the activation of another nuclear transcriptional factor, hypoxia inducible factor-1α (HIF-1a), which is also induced via moderate oxidative stress. Recently these concepts have become widely accepted. The versatility of ozone in treating vascular and degenerative diseases as well as skin lesions, hernial disc and primary root carious lesions in children is emphasized. Further researches able to elucidate whether the mechanisms of action of ozone therapy involve nuclear transcription factors, such as Nrf2, NFAT, AP-1, and HIF-1α are warranted.

PMID: 22185664 [PubMed] PMCID: PMC3298518 Free PMC Article



オゾン療法に関する論文

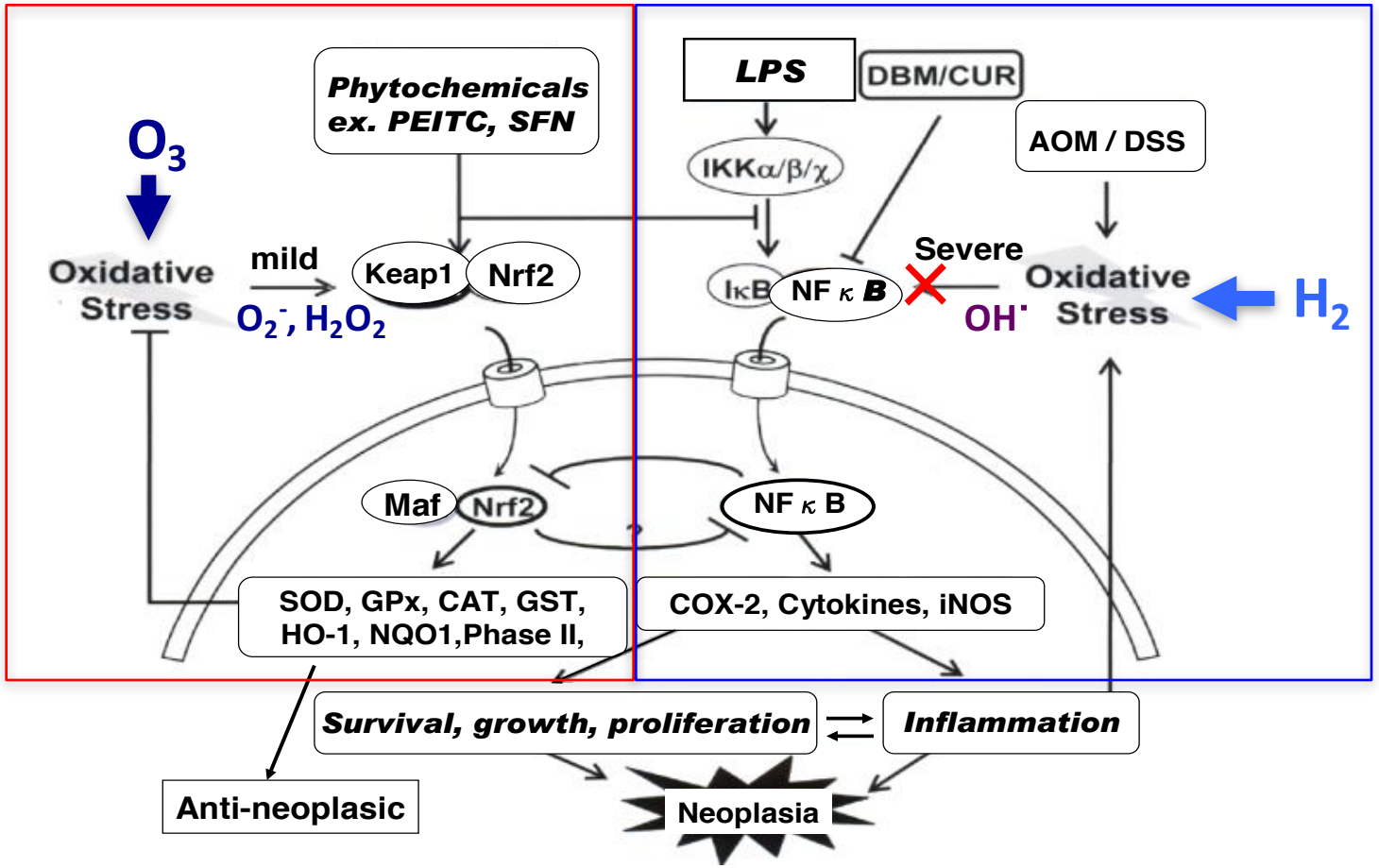
酸化ストレスの強度によって
軽度：Nrf2シグナル
強度：NFκBシグナル
に変化

オゾンによるマイルドな酸化ストレスによってNrf2が活性化
→軽度の酸化ストレスは健康によい

強度の酸化ストレスはNFκBを活性化
→強度の酸化ストレスは除去すべき

付録：酸化（オゾン）療法と抗酸化（水素）療法

共に『気体』を使う治療



2013:水素分子がTNFα誘導性細胞障害を抑制

Mol Cell Biochem. 2013 Jan;373(1-2):1-9. doi: 10.1007/s11010-012-1450-4. Epub 2012 Dec 1.

Treatment with hydrogen molecule alleviates TNFα-induced cell injury in osteoblast.

Cai WW[1], Zhang MH, Yu YS, Cai JH.

Author information

[1]The Centre of Drug Safeguard, Chinese People's Liberation Army General Hospital, Beijing, People's Republic of China.

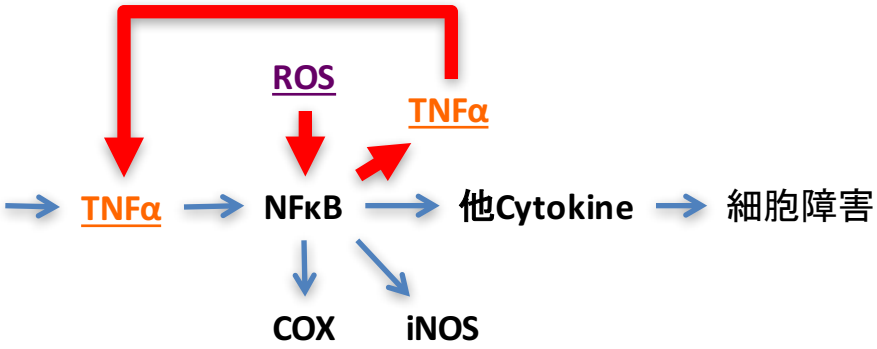
Abstract

Tumor necrosis factor-alpha (TNFα) plays a crucial role in inflammatory diseases such as rheumatoid arthritis and postmenopausal osteoporosis. Recently, it has been demonstrated that hydrogen gas, known as a novel antioxidant, can exert therapeutic anti-inflammatory effect in many diseases. In this study, we investigated the effect of treatment with hydrogen molecule (H(2)) on TNFα-induced cell injury in osteoblast. The osteoblasts isolated from neonatal rat calvariae were cultured. It was found that TNFα suppressed cell viability, induced cell apoptosis, suppressed Runx2 mRNA expression, and inhibited alkaline phosphatase activity, which was reversed by co-incubation with H(2). Incubation with TNFα-enhanced intracellular reactive oxygen species (ROS) formation and malondialdehyde production increased NADPH oxidase activity, impaired mitochondrial function marked by increased mitochondrial ROS formation and decreased mitochondrial membrane potential and ATP synthesis, and suppressed activities of antioxidant enzymes including SOD and catalase, which were restored by co-incubation with H(2). Treatment with H(2) inhibited TNFα-induced activation of NFκB pathway. In addition, treatment with H(2) inhibited TNFα-induced nitric oxide (NO) formation through inhibiting iNOS activity. Treatment with H(2) inhibited TNFα-induced IL-6 and ICAM-1 mRNA expression. In conclusion, treatment with H(2) alleviates TNFα-induced cell injury in osteoblast through abating oxidative stress, preserving mitochondrial function, suppressing inflammation, and enhancing NO bioavailability.

PMID: 23212446 [PubMed - indexed for MEDLINE]

免疫発動/炎症とROS

- **NFκB経路でのTNFα誘導を遮断**
- **iNOS活性の阻害によるNO抑制**
- **IL-6 mRNAの発現を抑制**
- **ICAM-1 mRNAの発現を抑制**
- **ミトコンドリア機能の維持**



2014:心肺停止後に対する水素ガス吸入の効果

Circulation. 2014 Dec 9;130(24):2173-80. doi: 10.1161/CIRCULATIONAHA.114.011848. Epub 2014 Nov 3.

Hydrogen inhalation during normoxic resuscitation improves neurological outcome in a rat model of cardiac arrest independently of targeted temperature management.

Hayashida K[1], Sano M[2], Kamimura N[1], Yokota T[1], Suzuki M[1], Ohta S[1], Fukuda K[1], Hori S[1].

Author information

Abstract

BACKGROUND: We have previously shown that hydrogen (H2) inhalation, begun at the start of hyperoxic cardiopulmonary resuscitation, significantly improves brain and cardiac function in a rat model of cardiac arrest. Here, we examine the effectiveness of this therapeutic approach when H2 inhalation is begun on the return of spontaneous circulation (ROSC) under normoxic conditions, either alone or in combination with targeted temperature management (TTM).

METHODS AND RESULTS: Rats were subjected to 6 minutes of ventricular fibrillation cardiac arrest followed by cardiopulmonary resuscitation. Five minutes after achieving ROSC, post-cardiac arrest rats were randomized into 4 groups: mechanically ventilated with 26% O2 and normothermia (control); mechanically ventilated with 26% O2, 1.3% H2, and normothermia (H2); mechanically ventilated with 26% O2 and TTM (TTM); and mechanically ventilated with 26% O2, 1.3% H2, and TTM (TTM+H2). Animal survival rate at 7 days after ROSC was 38.4% in the control group, 71.4% in the H2 and TTM groups, and 85.7% in the TTM+H2 group. Combined therapy of TTM and H2 inhalation was superior to TTM alone in terms of neurological deficit scores at 24, 48, and 72 hours after ROSC, and motor activity at 7 days after ROSC. Neuronal degeneration and microglial activation in a vulnerable brain region was suppressed by both TTM alone and H2 inhalation alone, with the combined therapy of TTM and H2 inhalation being most effective.

CONCLUSIONS: H2 inhalation was beneficial when begun after ROSC, even when delivered in the absence of hyperoxia. Combined TTM and H2 inhalation was more effective than TTM alone.

- 行動量/認知機能の低下を抑制
- 神経細胞死/炎症反応が著明に低下

1969: 腸内細菌が水素を産生し血中へ移行

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ORIGINAL ARTICLE ARCHIVE

Production and Excretion of Hydrogen Gas in Man

Michael D. Levitt, M.D.
N Engl J Med 1969; 281:122-127 | July 17, 1969 | DOI: 10.1056/NEJM196907172810303

Share:

Abstract

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A mean of 14 per cent of the total H_2 production was excreted by the lungs, and rates of breath H_2 excretion and H_2 production correlated well ($r = 0.94$). Respiratory H_2 excretion can therefore be used as an indicator of intestinal H_2 production.

MEDIA IN THIS ARTICLE
FIGURE 1

Schematic Representation of the Position of the Triple-Lumen Tube during the Constant Perfusion Studies.

ARTICLE ACTIVITY
206 articles have cited this article

2004: アカルボースが心筋リスクを軽減

Eur Heart J. 2004 Jan;25(1):10-6.

Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies.

Hanefeld M[1], Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M.

Author information

Abstract

AIMS: To assess if treatment with the alpha-glucosidase inhibitor acarbose can reduce cardiovascular events in type 2 diabetic patients.

METHODS AND RESULTS: This meta-analysis included seven randomized, double-blind, placebo-controlled acarbose studies with a minimum treatment duration of 52 weeks. Type 2 diabetic patients valid for safety were randomized to either acarbose (n=1248) or placebo (n=932). The primary outcome measure was the time to develop a cardiovascular event. Primary analysis was conducted using Cox regression analysis. The effect of acarbose on metabolic parameters was also investigated. Acarbose therapy showed favourable trends towards risk reduction for all selected cardiovascular event categories. The treatment significantly reduced the risk for "myocardial infarction" (hazards ratio=0.36 [95% CI 0.16-0.80], P=0.0120) and "any cardiovascular event" (0.65 [95% CI 0.48-0.88], P=0.0061). Glycaemic control, triglyceride levels, body weight and systolic blood pressure also improved significantly during acarbose treatment.

CONCLUSION: Intervention with acarbose can prevent myocardial infarction and cardiovascular disease in type 2 diabetic patients while most of them are already on intensive concomitant cardiovascular medication.

Comment in

No evidence for a reduction of myocardial infarctions by acarbose. [Eur Heart J. 2004]

PMID: 14683737 [PubMed - indexed for MEDLINE] **Free full text**

消化管内で発生する水素が OH·を除去し心筋リスクを軽減

2007: 水素がOH·を選択的に除去

nature medicine

nature.com > Journal home > Table of Contents

Article

Nature Medicine **13**, 688–694 (1 June 2007) | doi:10.1038/nm1577

Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals

Ikuroh Ohsawa , Masahiro Ishikawa , Kumiko Takahashi , Megumi Watanabe , Kiyomi Nishimaki , Kumi Yamagata , Ken-ichiro Katsura , Yasuo Katayama , Sadamitsu Asoh & Shigeo Ohta

Acute oxidative stress induced by ischemia-reperfusion or inflammation causes serious damage to tissues, and persistent oxidative stress is accepted as one of the causes of many common diseases including cancer. We show here that hydrogen (H2) has potential as an antioxidant in preventive and therapeutic applications. We induced acute oxidative stress in cultured cells by three independent methods. H2 selectively reduced the hydroxyl radical, the most cytotoxic of reactive oxygen species (ROS), and effectively protected cells; however, H2 did not react with other ROS, which possess physiological roles. We used an acute rat model in which oxidative stress damage was induced in the brain by focal ischemia and reperfusion. The inhalation of H2 gas markedly suppressed brain injury by buffering the effects of oxidative stress. Thus H2 can be used as an effective antioxidant therapy; owing to its ability to rapidly diffuse across membranes, it can reach and react with cytotoxic ROS and thus protect against oxidative damage.

2009: アカルボースがヒドロキシラジカルの生成を抑制

J Cardiovasc Pharmacol. 2009 Jul;54(1):25-30. doi: 10.1097/FJC.0b013e3181a98b53.

Acarbose reduces myocardial infarct size by preventing postprandial hyperglycemia and hydroxyl radical production and opening mitochondrial KATP channels in rabbits.

Minatoguchi S[1], Zhang Z, Bao N, Kobayashi H, Yasuda S, Iwasa M, Sumi S, Kawamura I, Yamada Y, Nishigaki K, Takemura G, Fujiwara T, Fujiwara H.

Author information

Abstract

BACKGROUND: Acarbose, an antidiabetic drug, is an alpha-glucosidase inhibitor that can inhibit glucose absorption in the intestine. A recent large-scale clinical trial, STOP-NIDDM, showed that acarbose reduces the risk of myocardial infarction. We examined whether acarbose reduces myocardial infarct size and investigated its mechanisms.

METHODS AND RESULTS: Rabbits were fed with 1 of 2 diets in this study: normal chow, 30 mg acarbose per 100 g chow for 7 days. Rabbits were assigned randomly to 1 of 4 groups: control (n = 10), acarbose (n = 10), acarbose + 5HD (n = 10, intravenous 5 mg/kg of 5-hydroxydecanoate), and 5HD (n = 10, intravenous 5 mg/kg of 5HD). Rabbits then underwent 30 minutes of coronary occlusion followed by 48-hour reperfusion. Postprandial blood glucose levels were higher in the control group than in the acarbose group. The infarct size as a percentage of the left ventricular area at risk was reduced significantly in the acarbose (19.4% +/- 2.3%) compared with the control groups (42.8% +/- 5.4%). The infarct size-reducing effect of acarbose was abolished by 5HD (43.4% +/- 4.7%). Myocardial interstitial 2,5-dihydroxybenzoic acid levels, an indicator of hydroxyl radicals, increased during reperfusion after 30 minutes of ischemia, but this increase was inhibited in the acarbose group. This was reversed by 5HD.

CONCLUSION: Acarbose reduces myocardial infarct size by opening mitochondrial KATP channels, which may be related to the prevention of postprandial hyperglycemia and hydroxyl radical production.

PMID: 19487955 [PubMed - indexed for MEDLINE]

2015: アカルボースによる水素ガス発生とIL-1β

Eur J Pharmacol. 2015 Sep 5;762:96-101. doi: 10.1016/j.ejphar.2015.04.051. Epub 2015 May 9.

Hydrogen gas production is associated with reduced interleukin-1β mRNA in peripheral blood after a single dose of acarbose in Japanese type 2 diabetic patients.

Tamasawa A[1], Mochizuki K[2], Hariya N[3], Saito M[1], Ishida H[1], Doguchi S[1], Yanagiya S[4], Osonoi T[5].

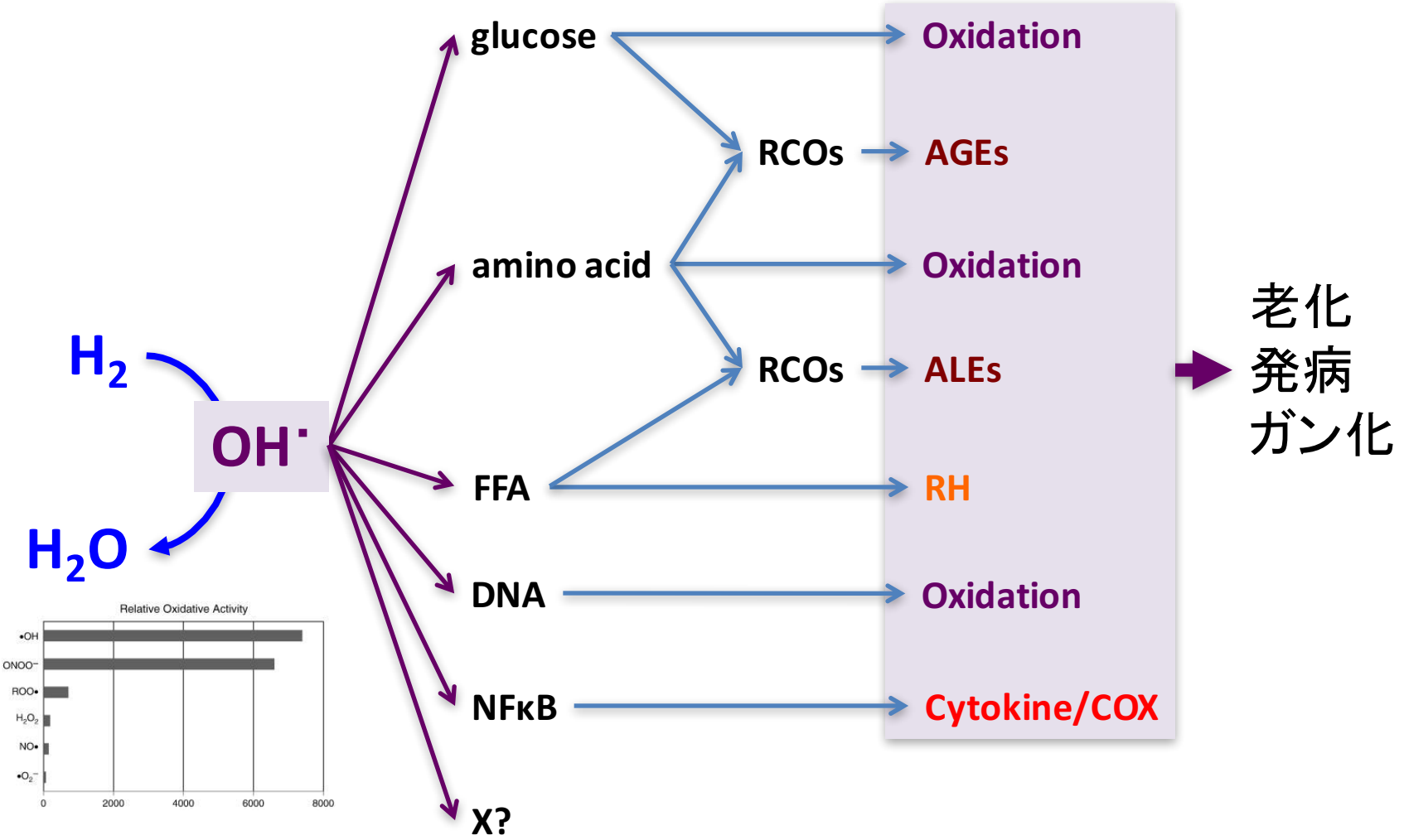
Author information

Abstract

Acarbose, an α-glucosidase inhibitor, leads to the production of hydrogen gas, which reduces oxidative stress. In this study, we examined the effects of a single dose of acarbose immediately before a test meal on postprandial hydrogen gas in breath and peripheral blood interleukin (IL)-1β mRNA expression in Japanese type 2 diabetic patients. Sixteen Japanese patients (14 men, 2 women) participated in this study. The mean±standard deviation age, hemoglobin A1c and body mass index were 52.1±15.4 years, 10.2±2.0%, and 27.7±8.0kg/m(2), respectively. The patients were admitted into our hospital for 2 days and underwent test meals at breakfast without (day 1) or with acarbose (day 2). We performed continuous glucose monitoring and measured hydrogen gas levels in breath, and peripheral blood IL-1β mRNA levels before (0min) and after the test meal (hydrogen gas: 60, 120, 180, and 300min; IL-1β: 180min). The induction of hydrogen gas production and the reduction in peripheral blood IL-1β mRNA after the test meal were not significant between days 1 (without acarbose) and 2 (with acarbose). However, the changes in total hydrogen gas production from day 1 to day 2 were closely and inversely associated with the changes in peripheral blood IL-1β mRNA levels. Our results suggest that an increase in hydrogen gas production is inversely associated with a reduction of the peripheral blood IL-1β mRNA level after a single dose of acarbose in Japanese type 2 diabetic patients.

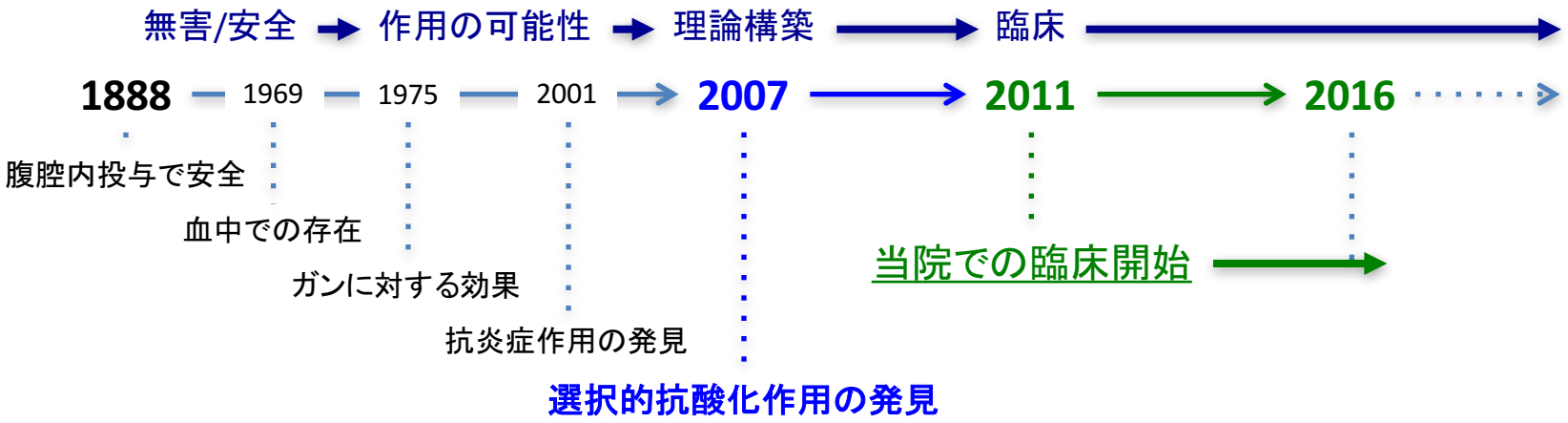
- 2型糖尿病患者16人にアカルボースを投与
- 呼気ガス水素濃度とIL-1β値を「食前」「食後60, 120, 180, 300分」で計測
- 水素ガスの濃度に比例して、IL-1β mRNAの発現低下を認める

水素の作用はOH·除去の作用？



臨床の現場にて

臨床医学の役割



生体に対し毒性はなく
安全に利用でき
各種作用を期待できる

1995年に食品添加物認可

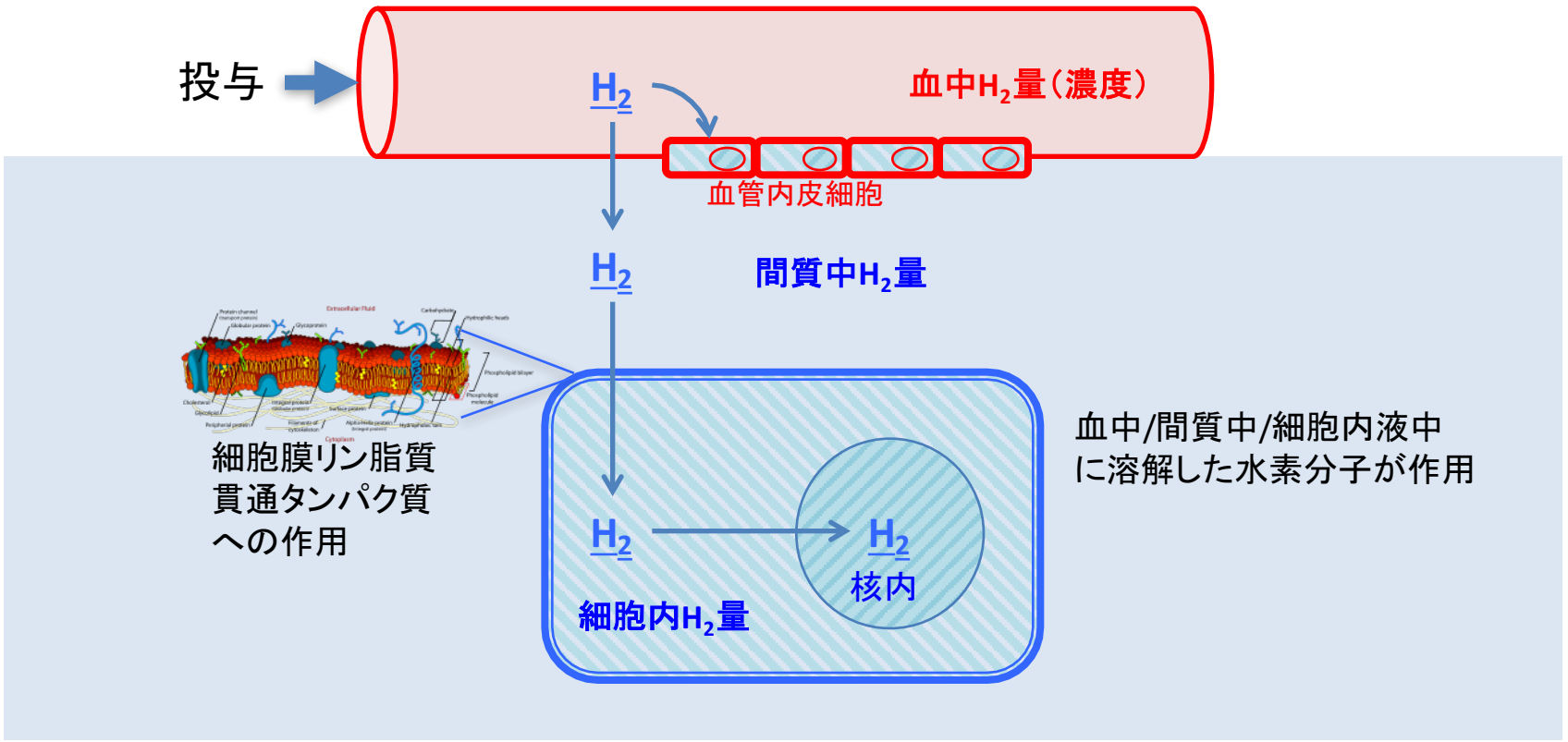
2000年、2004年、2005年、2007年に継続調査

- 延患者数：**1,000人**

<治療内容>

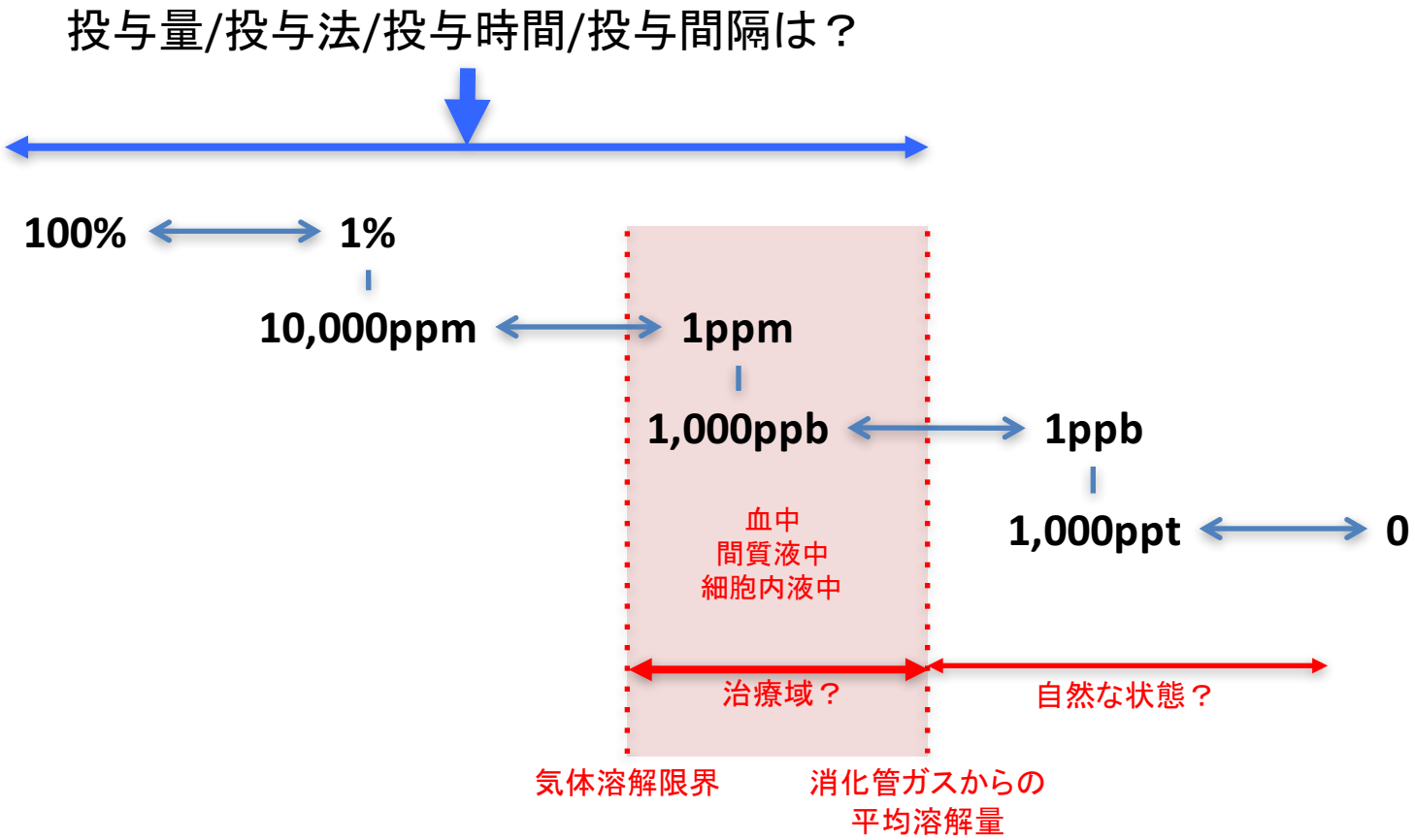
- **水素水点滴**：アンチエジング、予防治療、各種内科系疾患
  疾患では特に糖尿病、高血圧、動脈硬化、神経変性疾患
- **水素注射**：整形外科疾患を中心
  筋肉注射/筋膜間注射/関節内注射
  変形性関節症（膝/股関節）、四十肩/肩こり、腰痛、頸椎症
- **水素発生剤外用（入浴料含）**：皮膚科疾患を中心
- **水素発生剤内服**：**[Mg-H_2]**
- **水素ガス吸入**：試験中/データ収集中

水素が作用するためには



水素分子が液相（血液,間質液,細胞内液）に溶解する必要がある

水素量と治療域



細胞内液
間質液
血液
中の水素濃度限界が作用限界？

過去の論文から考える投与方法の模索

1: 液体に溶解させてから投与

＊水素水（消化管）　＊点滴　＊注射　＊経皮＊

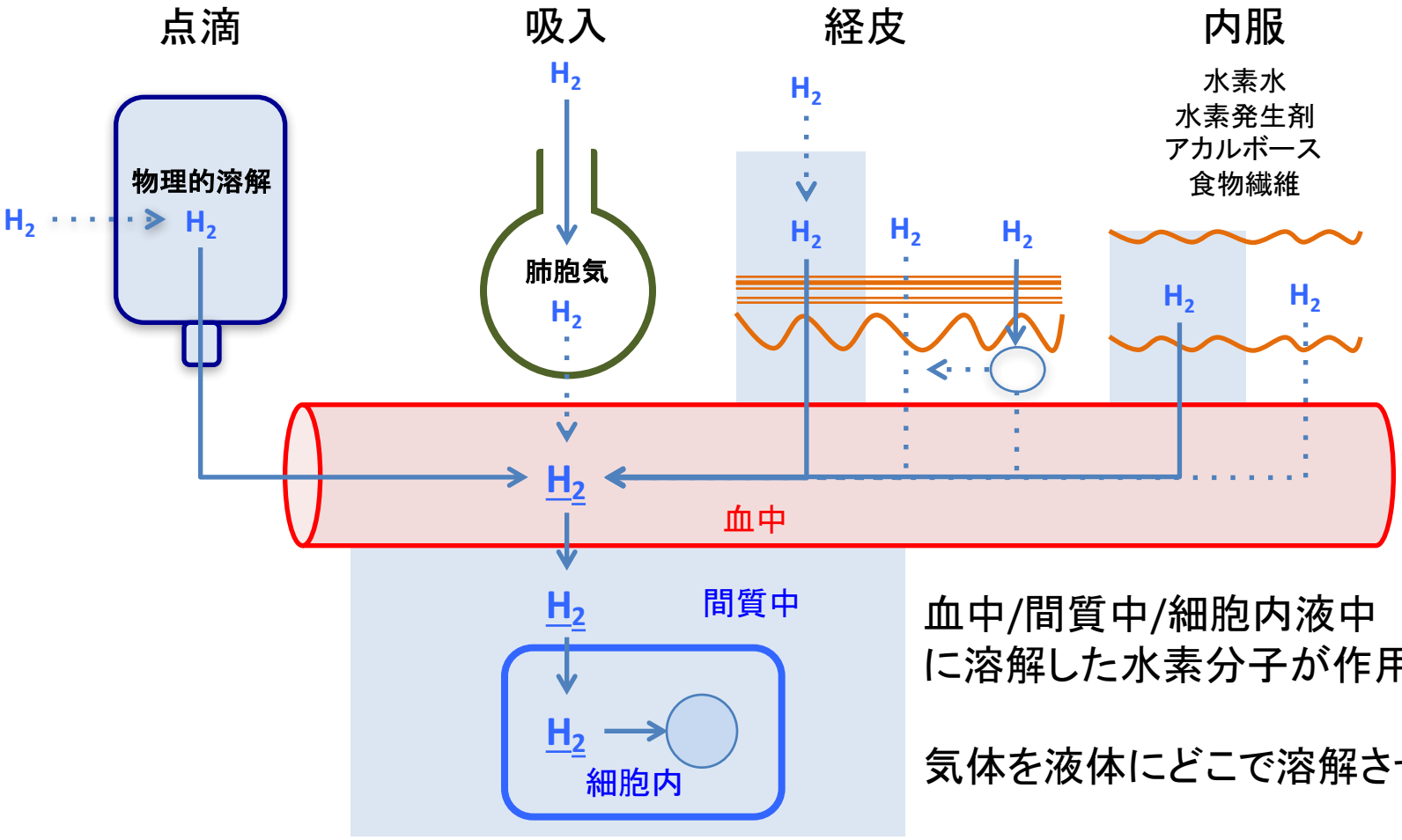
2: 気体を投与し、体内で溶解

＊吸入（肺）　＊経皮＊　＊注入

3: 消化管内で発生させ、体内で溶解

＊水素吸蔵体（内服）　＊腸内細菌による発生促進（アカルボースなど）

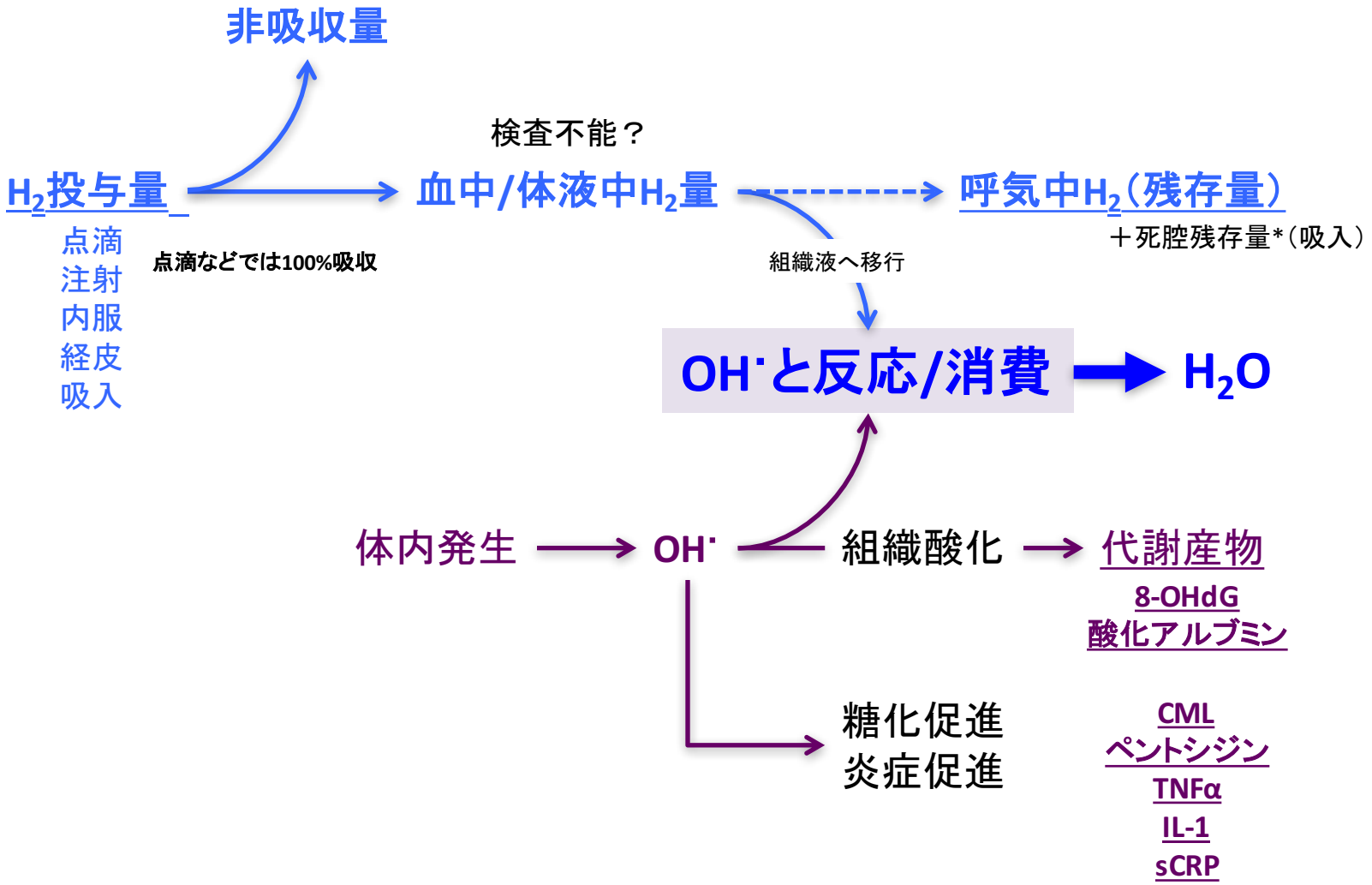
気体の生体の与える影響



血中/間質中/細胞内液中
に溶解した水素分子が作用

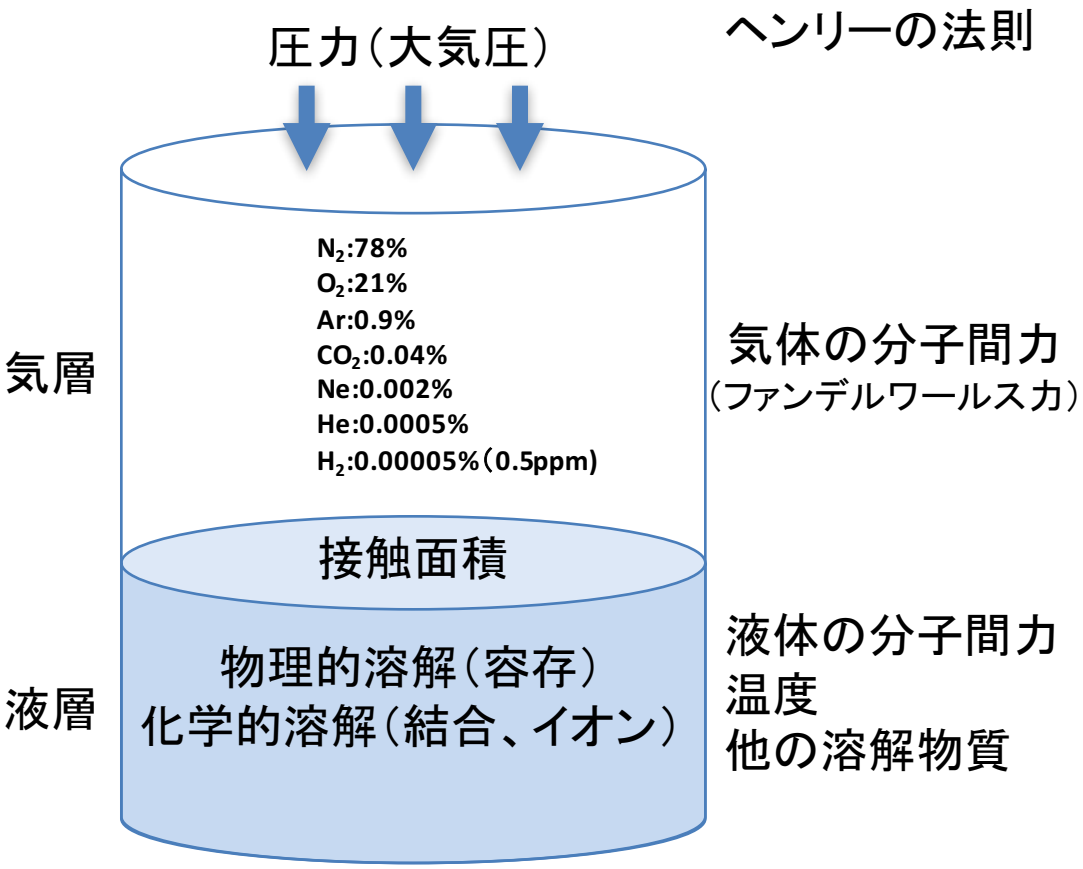
気体を液体にどこで溶解させるか

検査の模索


非吸収量
検査不能？
H_2投与量
血中/体液中H_2量
呼気中H_2（残存量）
＋死腔残存量*（吸入）
点滴
注射
内服
経皮
吸入
点滴などでは100%吸収
組織液へ移行
$OH^{\cdot}$と反応/消費
H_2O
体内発生
$OH^{\cdot}$
組織酸化
代謝産物
8-OHdG
酸化アルブミン
糖化促進
炎症促進
CML
ペントシジン
TNFα
IL-1
sCRP

点滴

大気中での気体溶解


圧力（大気圧）
ヘンリーの法則
N_2:78%
O_2:21%
Ar:0.9%
CO_2:0.04%
Ne:0.002%
He:0.0005%
H_2:0.00005%（0.5ppm）
気層
気体の分子間力
（ファンデルワールス力）
接触面積
物理的溶解（容存）
化学的溶解（結合、イオン）
液層
液体の分子間力
温度
他の溶解物質

点滴/注射溶液
水素化生理食塩水

<生食中への水素溶解>
物理的溶解のみ

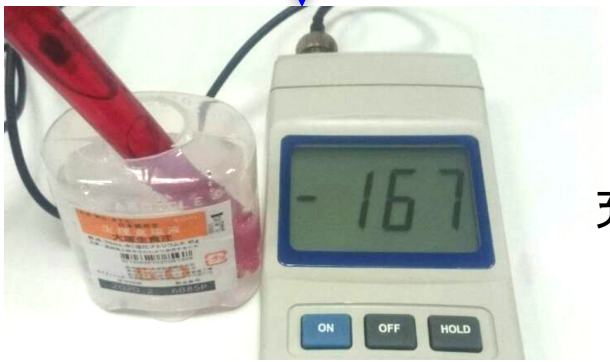
ボンベ内ガス濃度	: >99.999%
充填ガス濃度	: 99.9999%
湿度	: 0%
充填圧	: 0~100kPa

ガス充填によるORPの変化

充填前

他の成分追加なし

ORPを約300低下



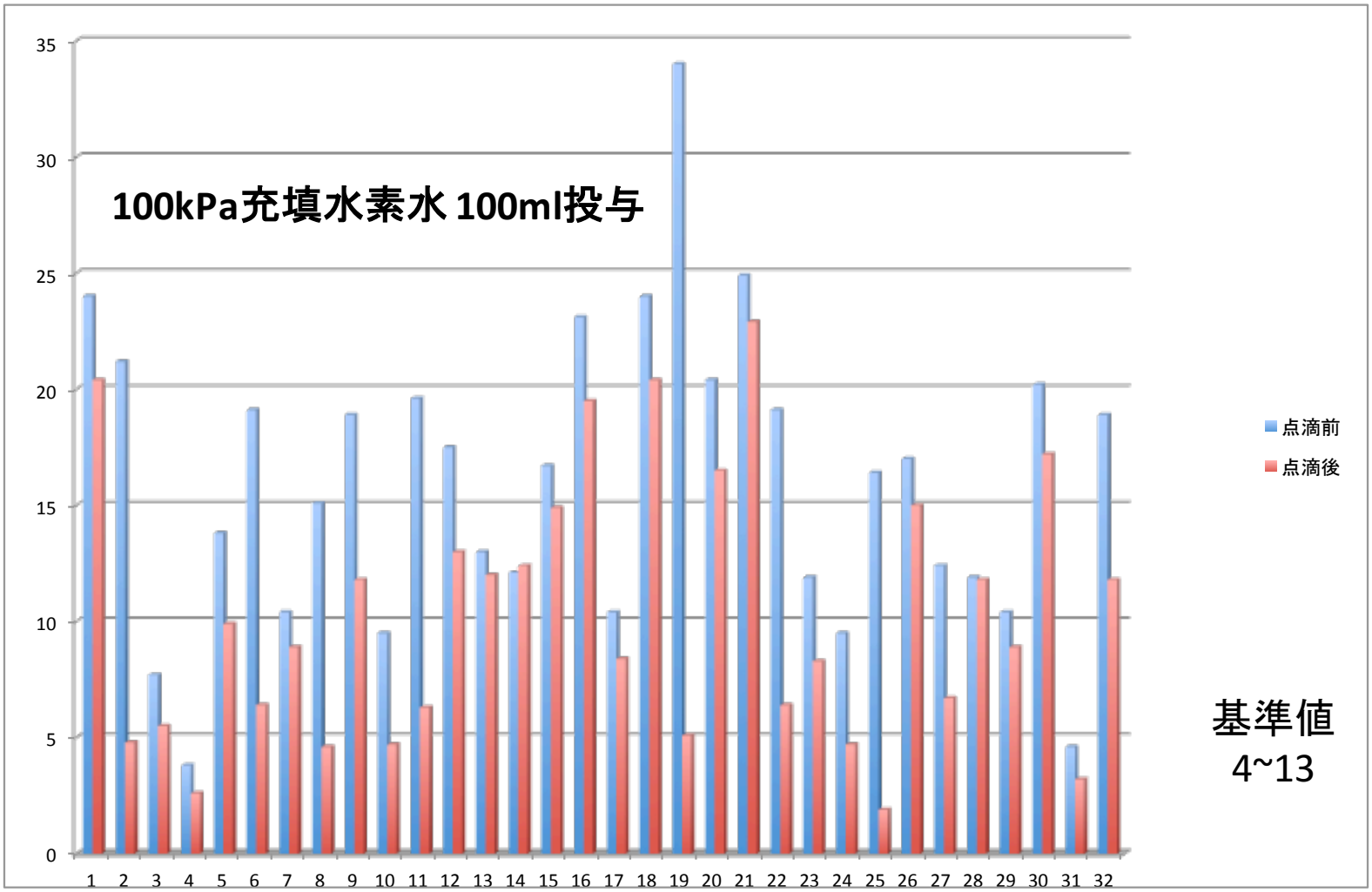
充填後 → 約20分変化なし

水素点滴

水素ガスを注入

容存処置後点滴

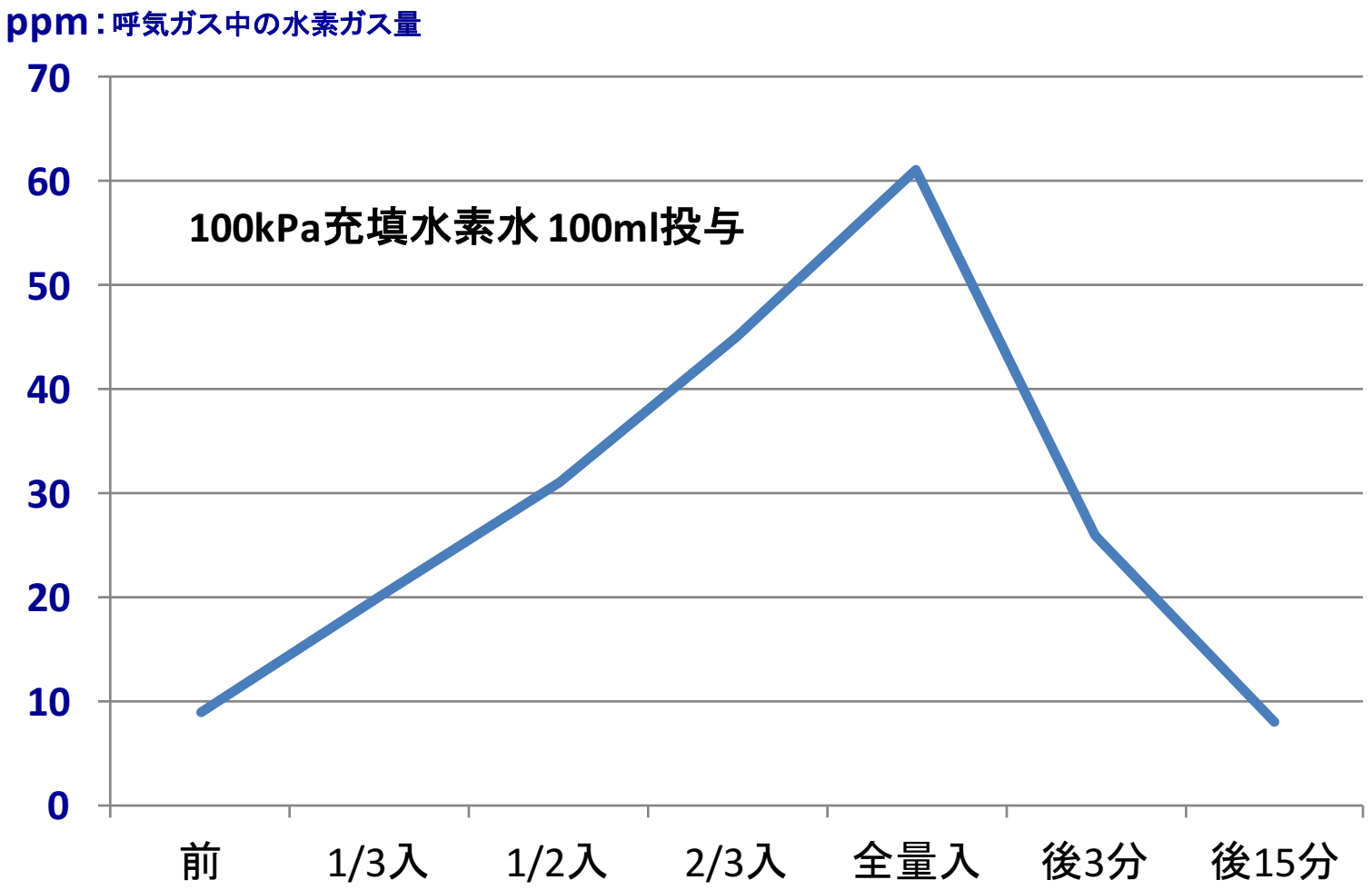
水素水点滴前後の8-OHdGの変化



水素は核内の酸化還元に作用している

水素点滴時の呼気中水素ガスの変化

100ml生食バッグに100%水素ガスを100kPaで注入したものを15分で投与



注射

関節内注射の検討

- 肩関節周囲炎
- 変形性膝関節症
- 慢性関節リウマチ
- 股関節臼蓋形成不全
- 足関節捻挫後遺症
- 顎関節症

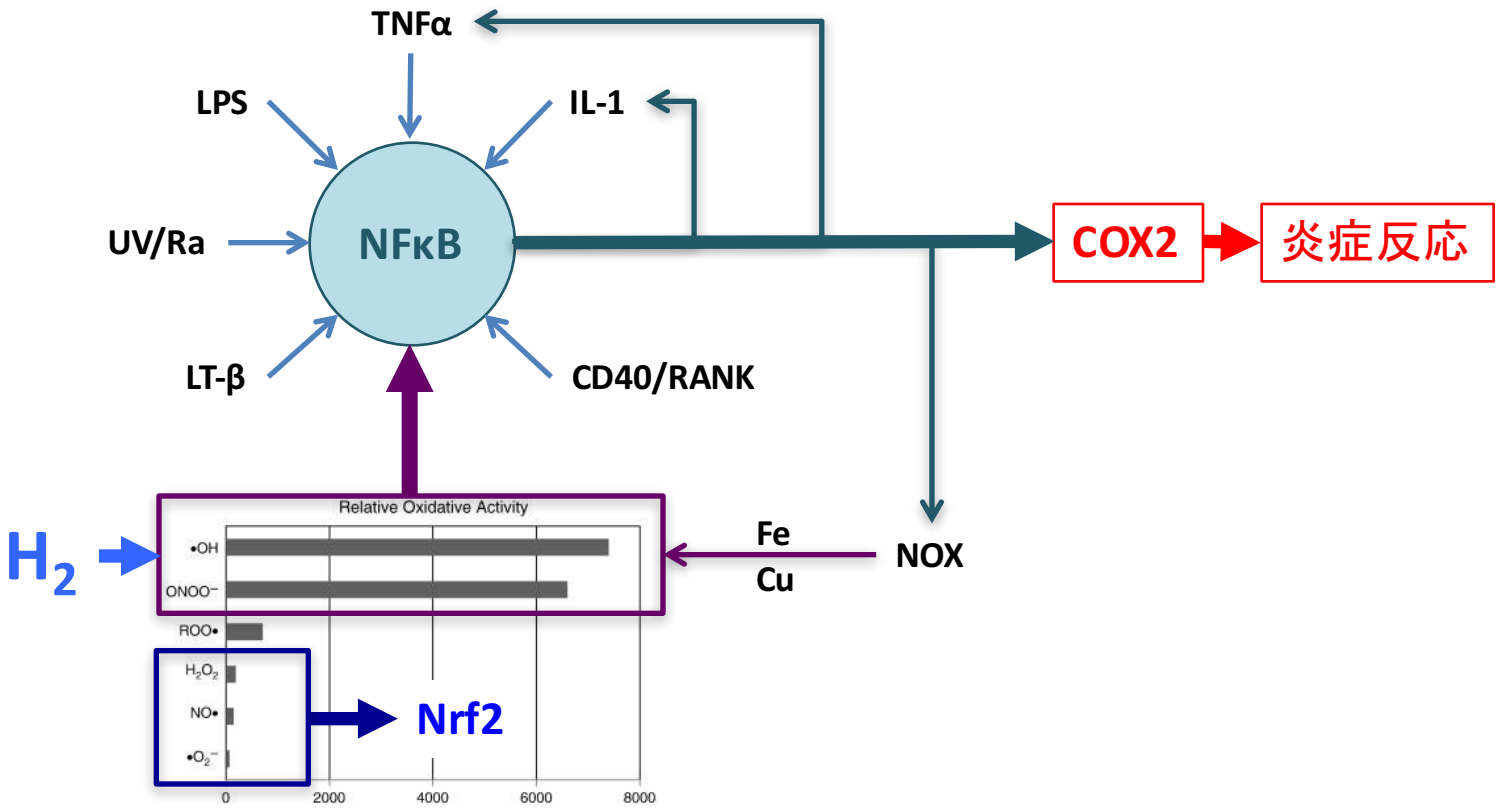
に対する関節内注射

加齢変化
アスリート
膠原病
外傷後　　など

疼痛の軽減
稼働時/歩行時痛の軽減
関節腫脹の軽減
可動域の拡大

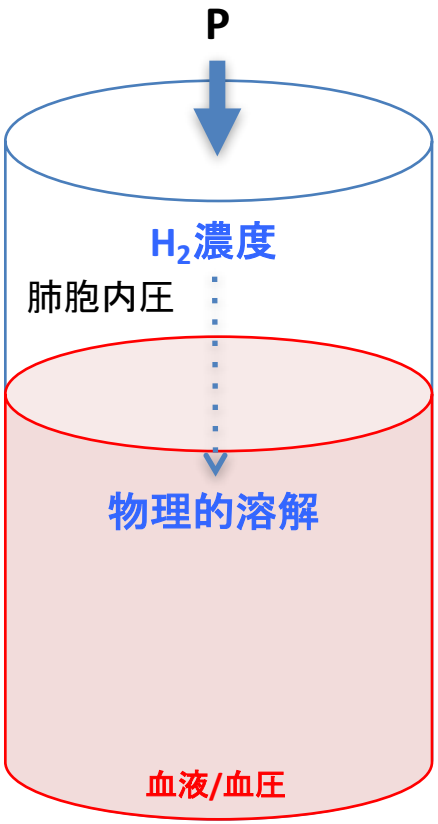
を認める

炎症と活性酸素


TNFα
LPS
IL-1
UV/Ra
NFκB
COX2
炎症反応
LT-β
CD40/RANK
H2
Relative Oxidative Activity
•OH
ONOO⁻
ROO•
H2O2
NO•
•O2⁻
0
2000
4000
6000
8000
Fe
Cu
NOX
Nrf2

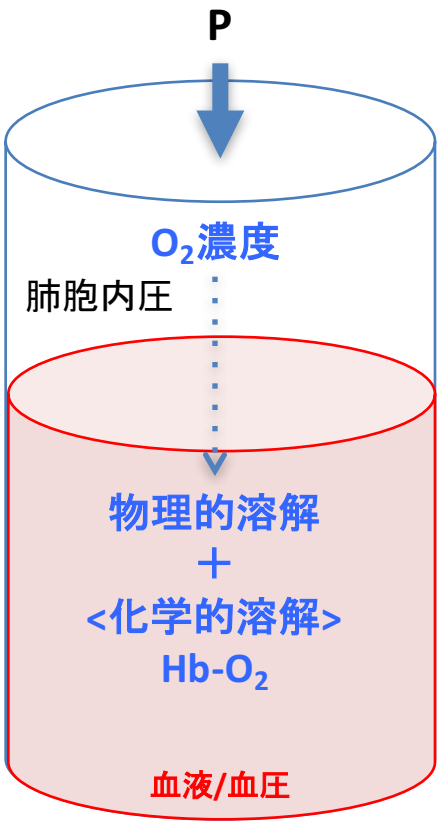
吸入

生体における気体の溶解

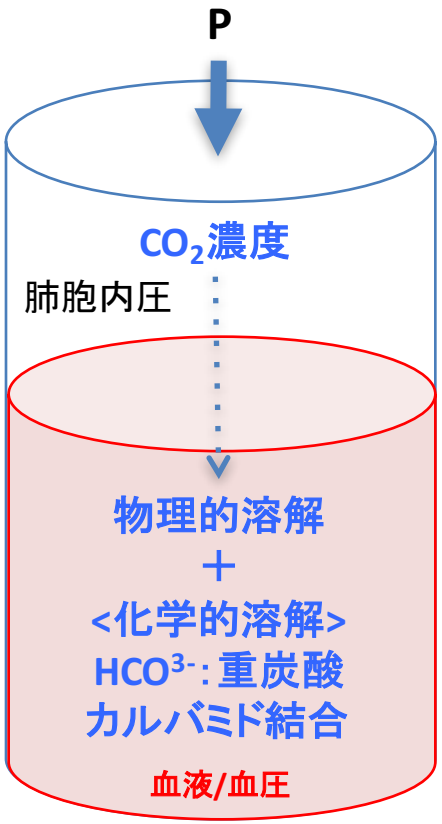


血中H_2濃度
肺胞内H_2濃度×内圧
に依存？

血中濃度限界は？
X ppm

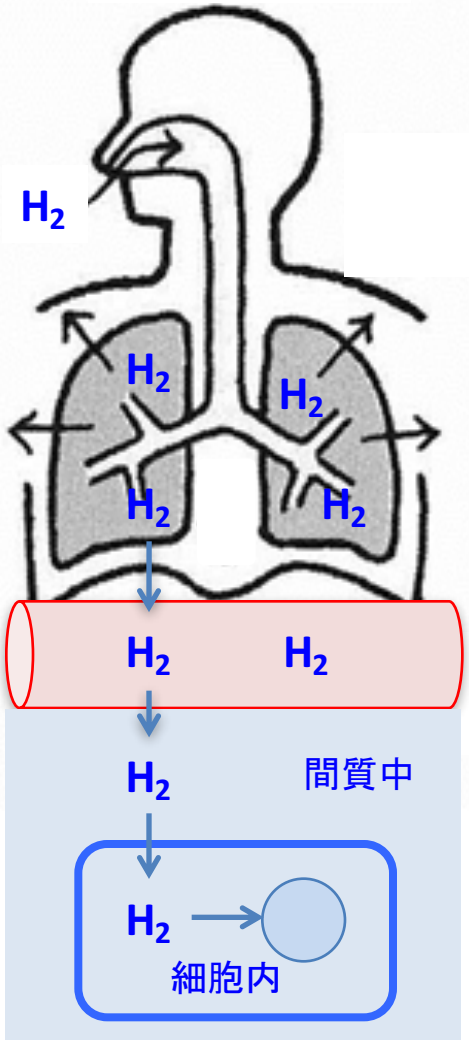


動脈血100mℓ中に20mℓ
物理的溶解は0.3ml
化学的溶解は大部分がヘモグロビンと結合して赤血球内に結合し、酸化ヘモグロビン（HbO2）として存在



動脈血100mℓ中に40～50mℓ
物理的溶解は5%
化学的溶解 80～90%は血漿中に重炭酸塩として存在
5～10%は血漿タンパク質やデオキシヘモグロビンとカルバミノ結合

吸入水素ガスの肺胞→血管移行



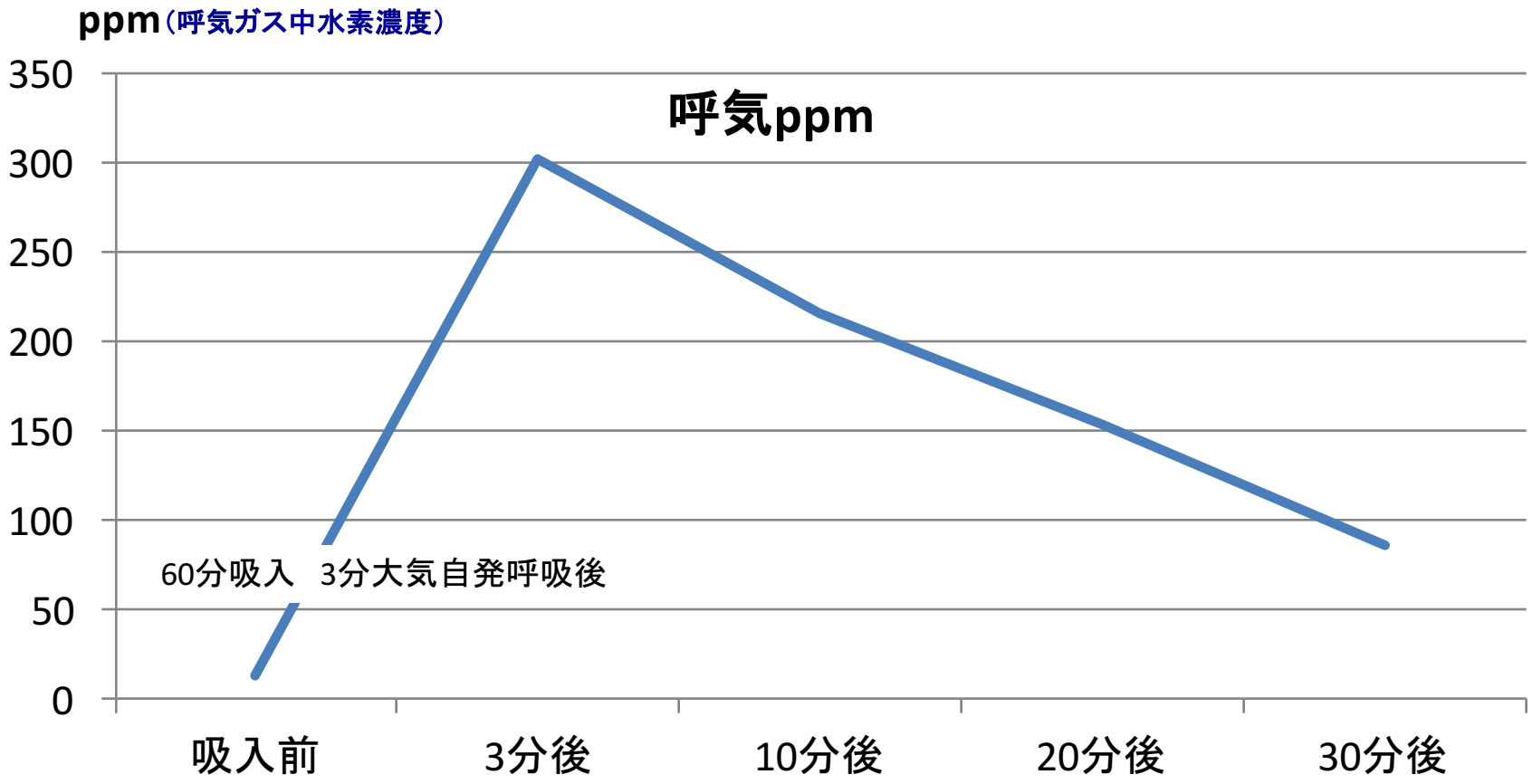
吸入H_2濃度　:1～60%（O_2:21%は必要）
温度（体温）　:37℃
吸入圧　:1～α（CPAP/陽圧呼吸など）
接触面積　:肺胞面積 約70m^2

血中/間質液中/細胞内液中H_2濃度
飽和限界は？
限界に達するまでの時間は？

体内液量
体重の60%
細胞内液:40%
組織液」15%
血漿・リンパ液:4.5%
体腔液:0.5%

研究段階の水素吸入について

吸入ガス成分　<水素:60%　酸素:30%　水蒸気:10%>



現段階で血中からの遊離か死腔の残存水素なのかは不明

内服

種類

水素水

- 分子状水素を含ませた水
- 『水素』として摂取
- 投与できる水素分子量が少ない
- **1.5ppm**上限として**11.5cc/ℓ**の水素摂取
- 不安定で抜けやすい

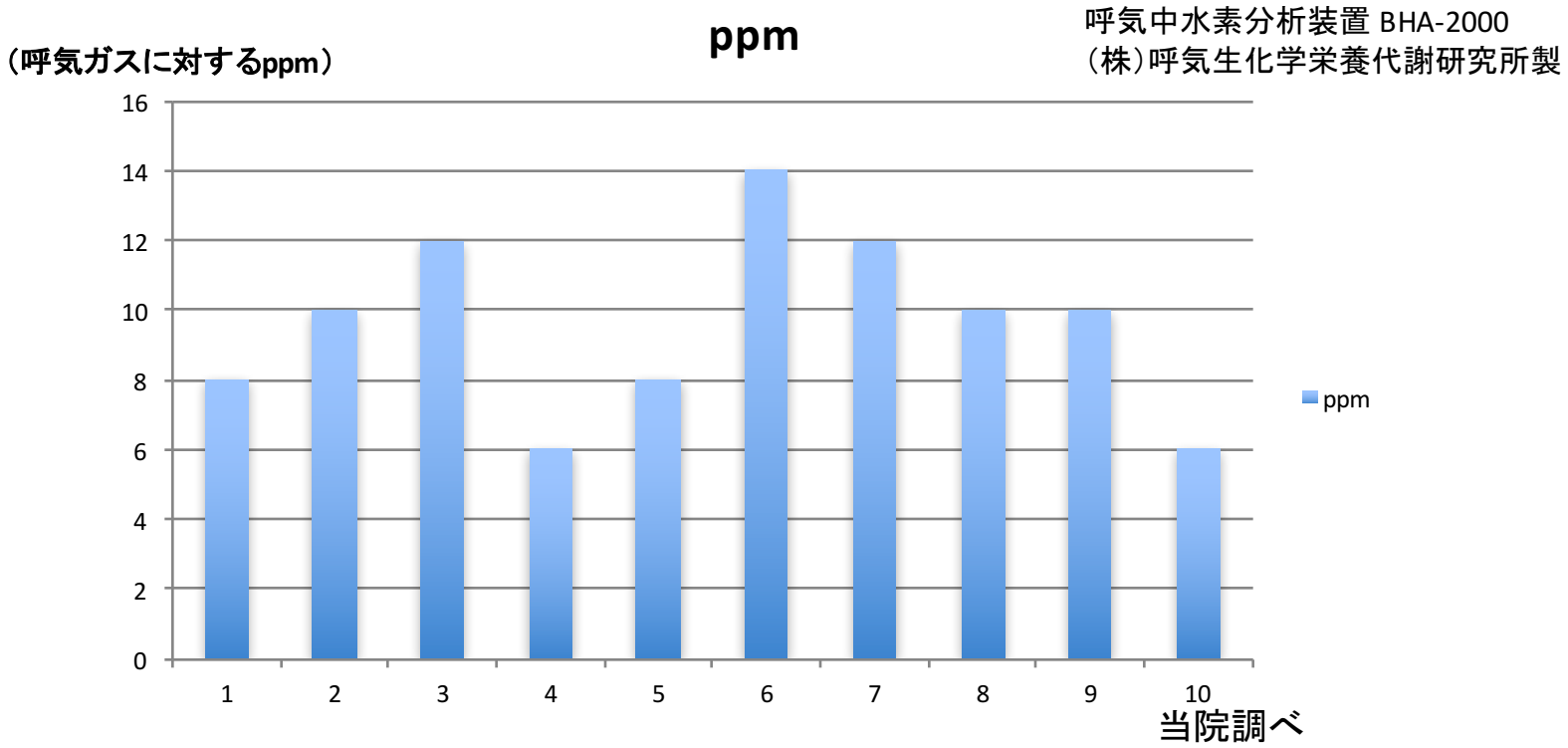
水素吸蔵体

- 体内で分子状水素を発生させる物質
- **MgH_2**、フラナガン、珊瑚カルシウムなどが存在
- **<g**あたりの発生量**>**が明確なのは**MgH_2**
- **発生理論（化学式）が明確はのはMgH_2**
- **<時間あたりの発生量>は不明（変動）**
- **食品未認可のためMgH_2は『研究用試薬』として処方**

糖質吸収遅延剤

- 腸内細菌による水素ガス発生を促す
- アカルボースによる論文が存在
- 腸内細菌量/種類によって発生量が違う

安静時の呼気中水素濃度



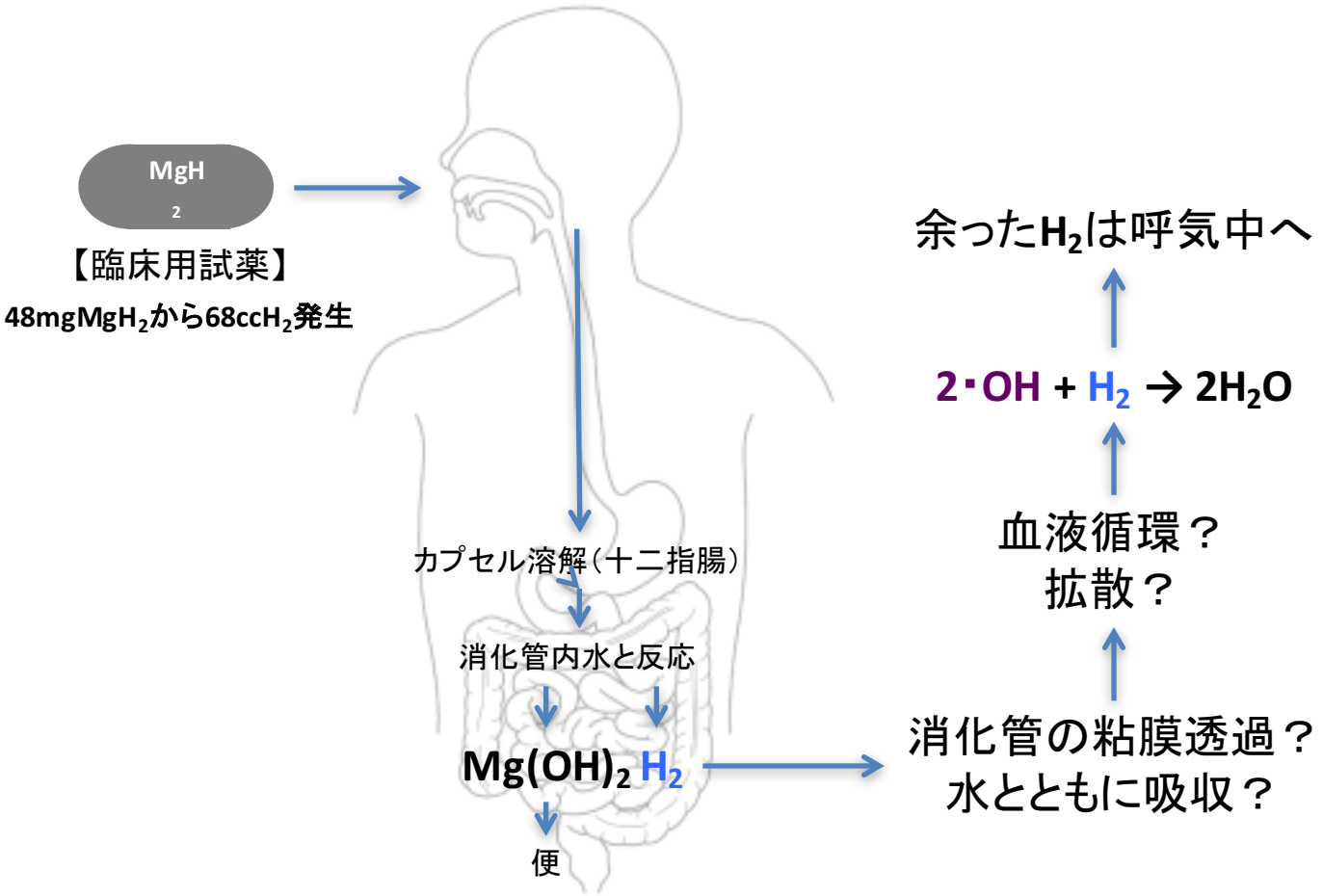
大気中水素ガスは『**0.5ppm**』と考えられているため、この呼気中水素ガスは、消化管内（腸内細菌）および体内（細胞）で産生されたものと考えられる

摂取内容/摂取時間などで発生量は大きく変動

アカルボースによる水素ガス発生は現在データ収集中

Mg吸蔵体カプセルによる投与

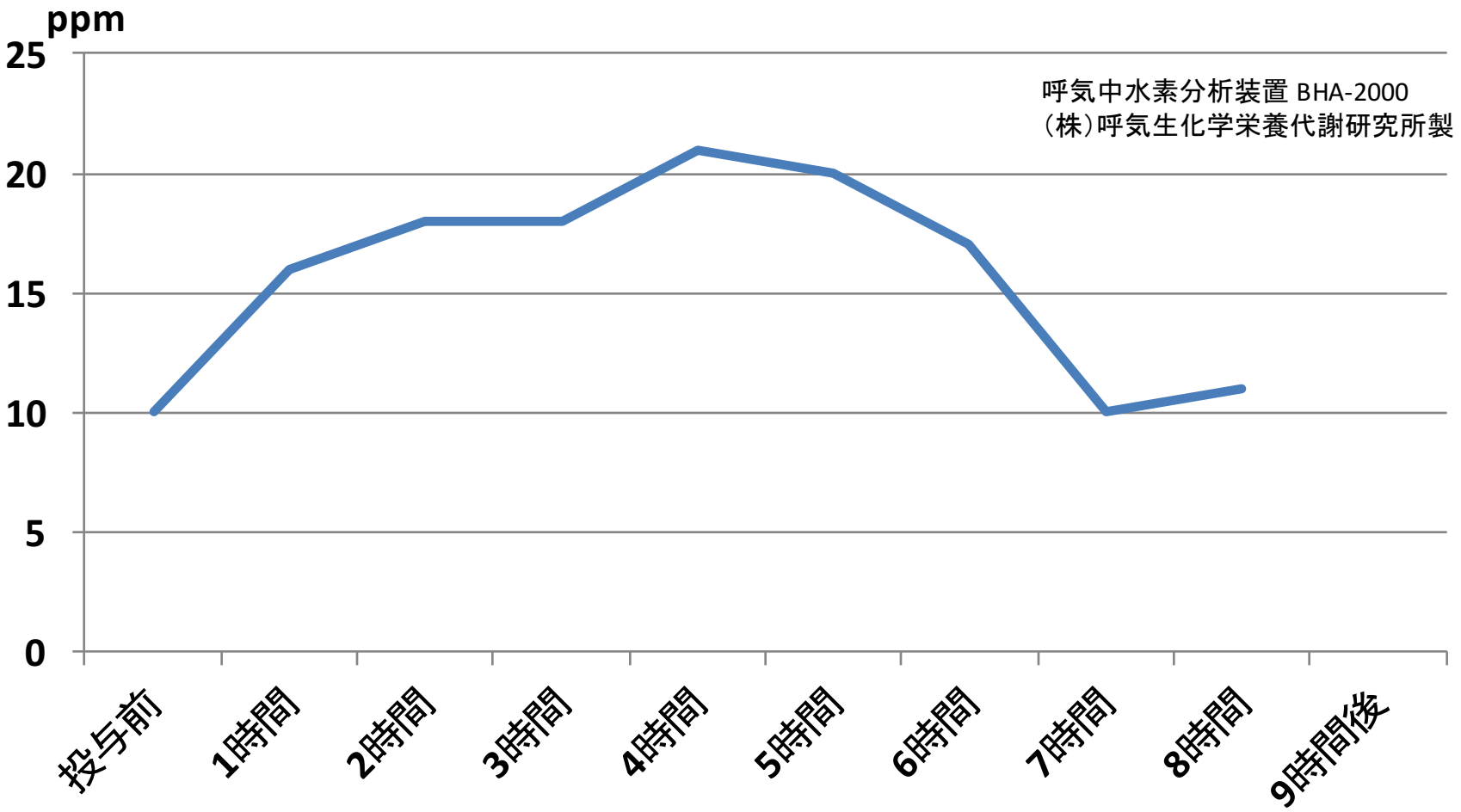
$$MgH_2 + 2H_2O \rightarrow Mg(OH)_2 + 2H_2$$



腸内細菌が水素ガスを発生する状態を再現

内服による呼気中H_2ガスの変化

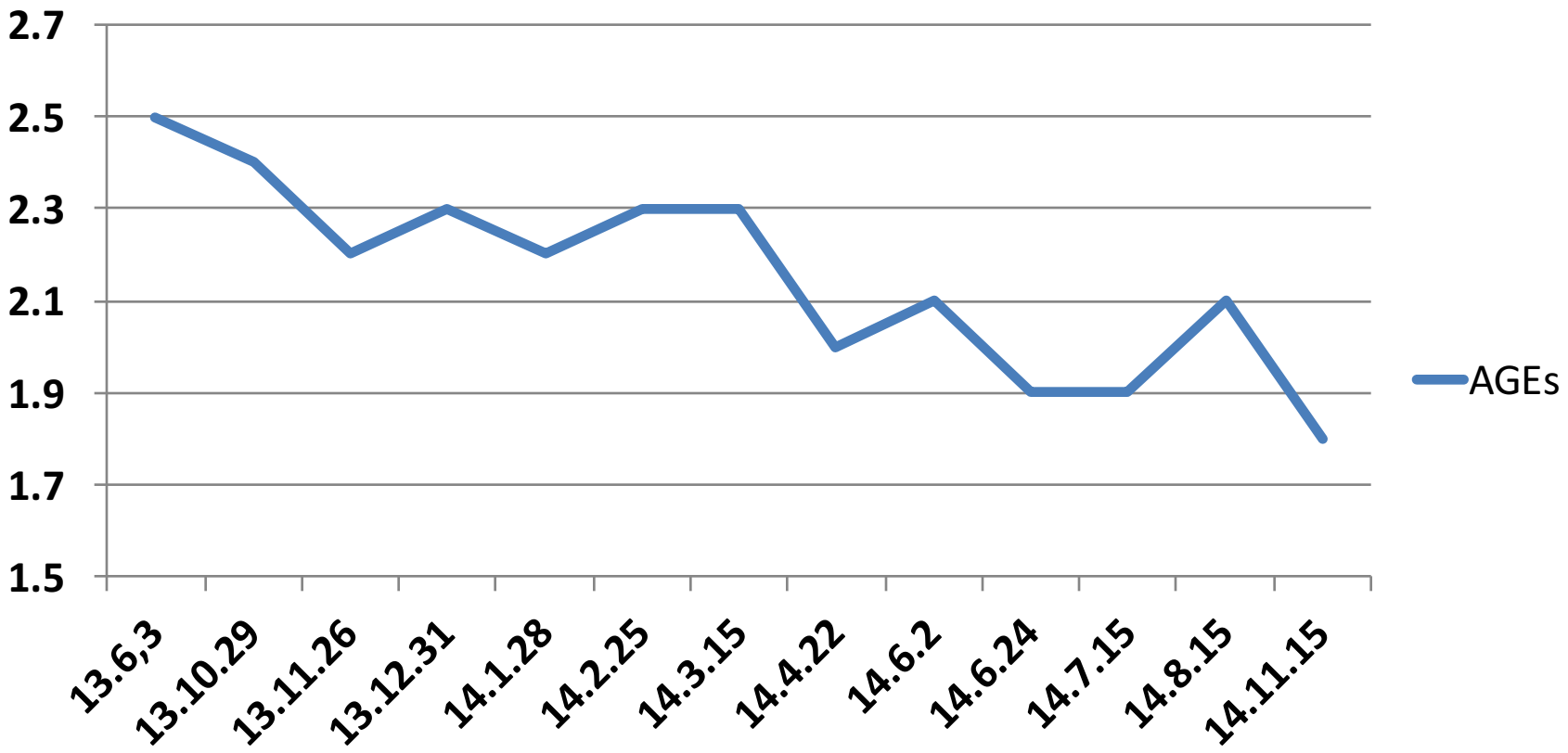
1カプセル（40mgMg-H_2≒68ccH_2）投与による検査



2012年当院調べデータ

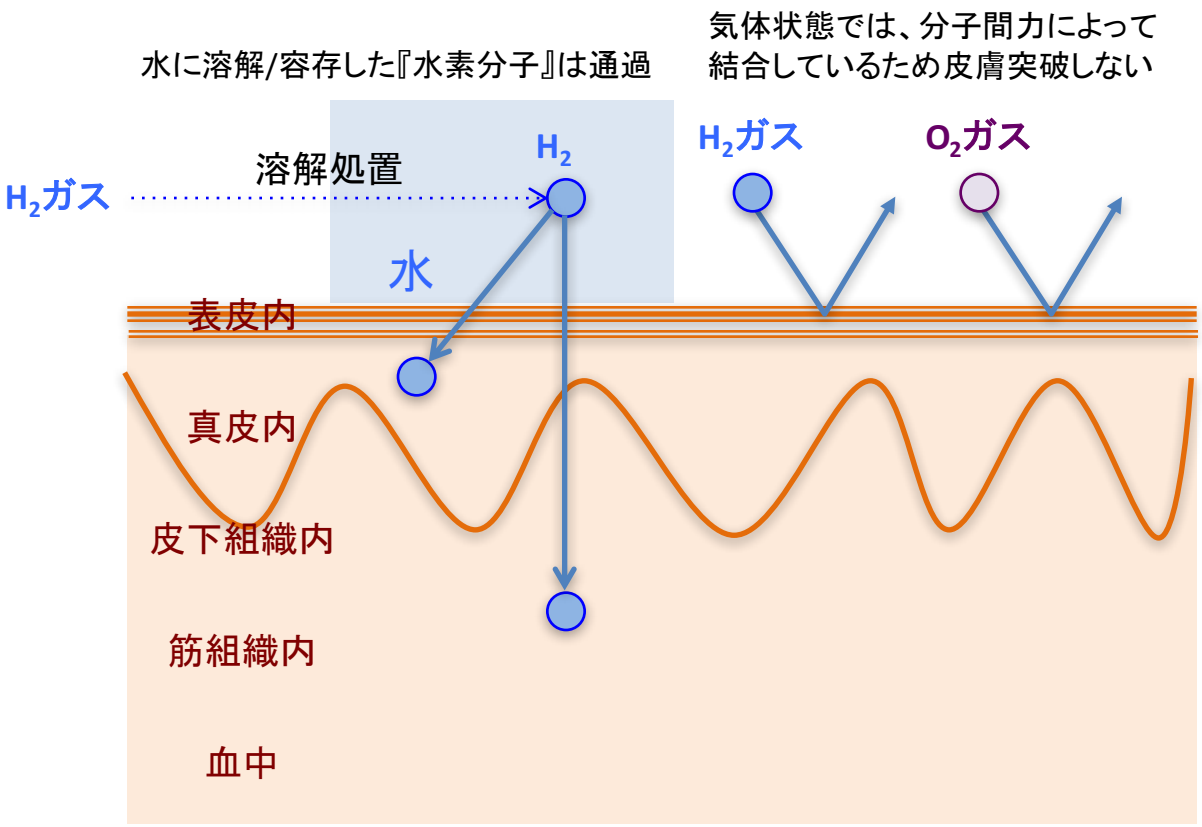
長期内服による皮下AGEsの変化

[Mg-H_2 : 40mg≒68ccH_2]カプセルを1日1カプセル摂取



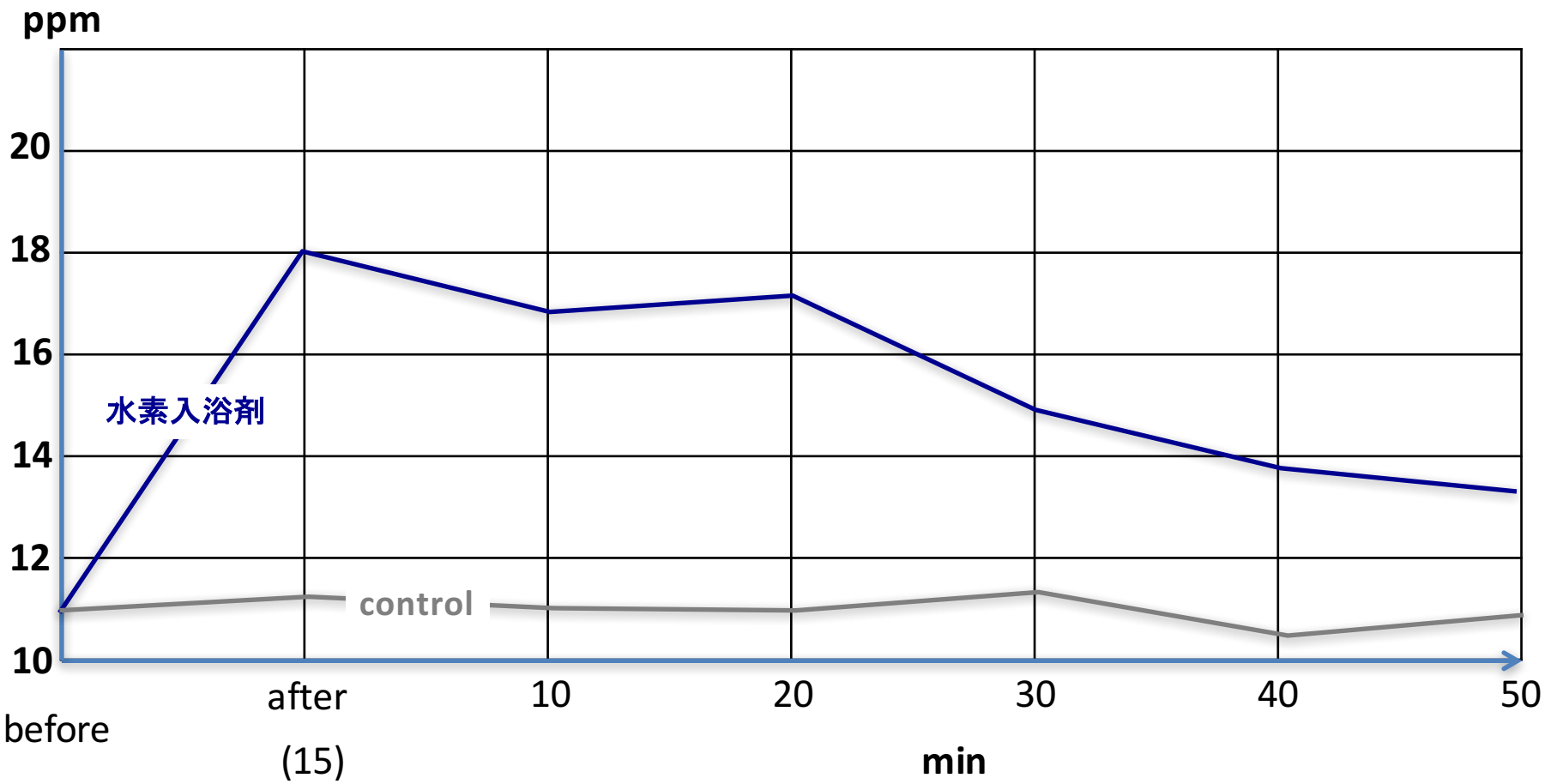
その他

経皮吸収
外用/入浴剤


水に溶解/容存した『水素分子』は通過
気体状態では、分子間力によって
結合しているため皮膚突破しない
H_2ガス
溶解処置
H_2
H_2ガス
O_2ガス
水
表皮内
真皮内
皮下組織内
筋組織内
血中

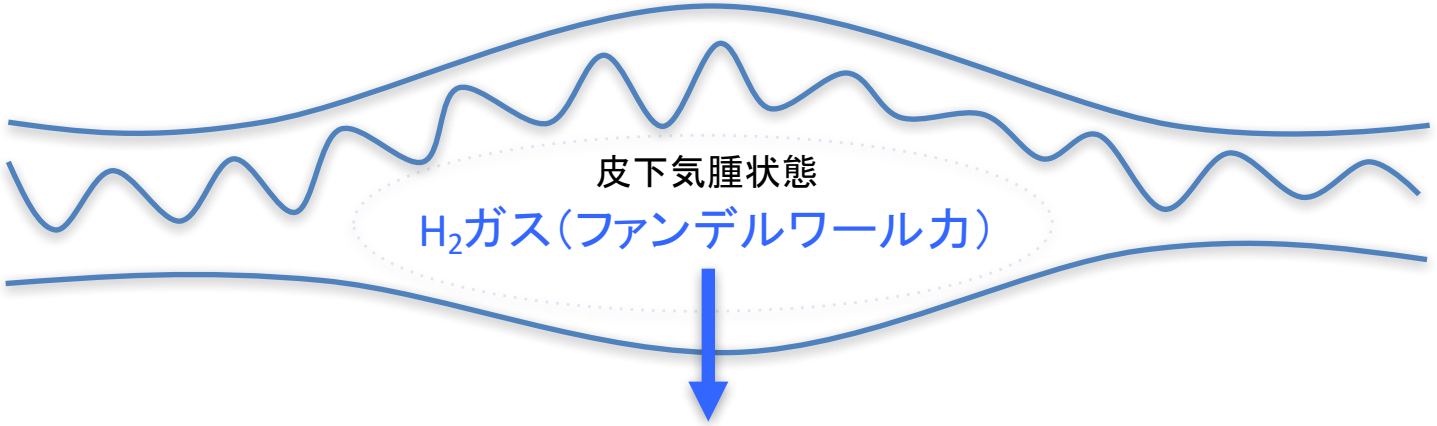
入浴による体内水素ガス動態

入浴による呼気ガス中水素濃度変化



皮内/皮下への水素ガス注射

分子間力が存在するため、すぐに吸収されるわけではない



体液/間質液への拡散（分子状水素） → 作用

↓

血中/リンパ液中へ移行？ → 作用

投与による呼気ガスは現在計測中

今後の課題

1:投与方法と投与量

- 腸内細菌水素ガス量から考えると、さらに高用量？
- →慎重に増量を検討中

2:Drug Delivery（拡散機序など）

- 素早い拡散スピードのコントロール法は？
- 脂肪層への拡散は？

3:患部（目的部位）の濃度

- 抗炎症に必要な用量は？
- 抗AGEに必要な用量は？

thank you !