Redox Biochemistry

How Energy is Captured in order for Life to Exist

Dance of the Universe

From the cosmic to the nano-it is all about energy exchange

Super novae: Produce energy and create galaxies
Within a few seconds after a star (white dwarf) collapses--nuclear fusion releases $1–2\times10^{44}$J of energy

Luminosity 5 billion times brighter than the sun

10000000000000000000000000000000000000 Joules

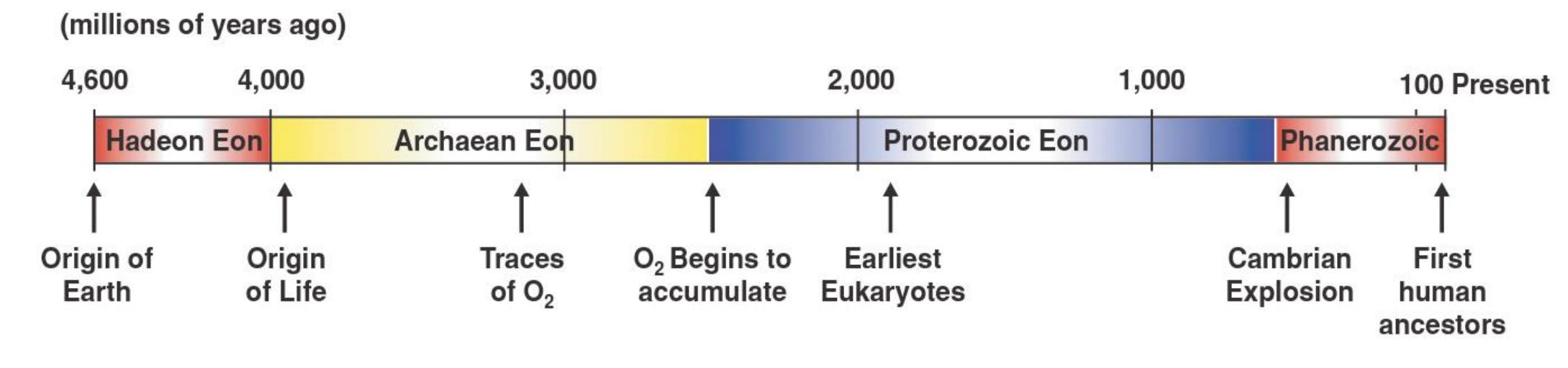
Brightness of 10 Billion Suns!
The total energy output **=** 10^{44}**joules**, as **much** as the total output of the sun during its 10 billion year lifetime

Black Holes

- Every large galaxy contains a supermassive black hole at its center.
- The supermassive black hole at the center of the Milky Way galaxy is called Sagittarius A.
- A few million Earths could fit through the hole
- It’s mass is equal to about 4 million suns
- Gravitational force is greater than the speed of light hence “black”

Literally “Eats” Everything

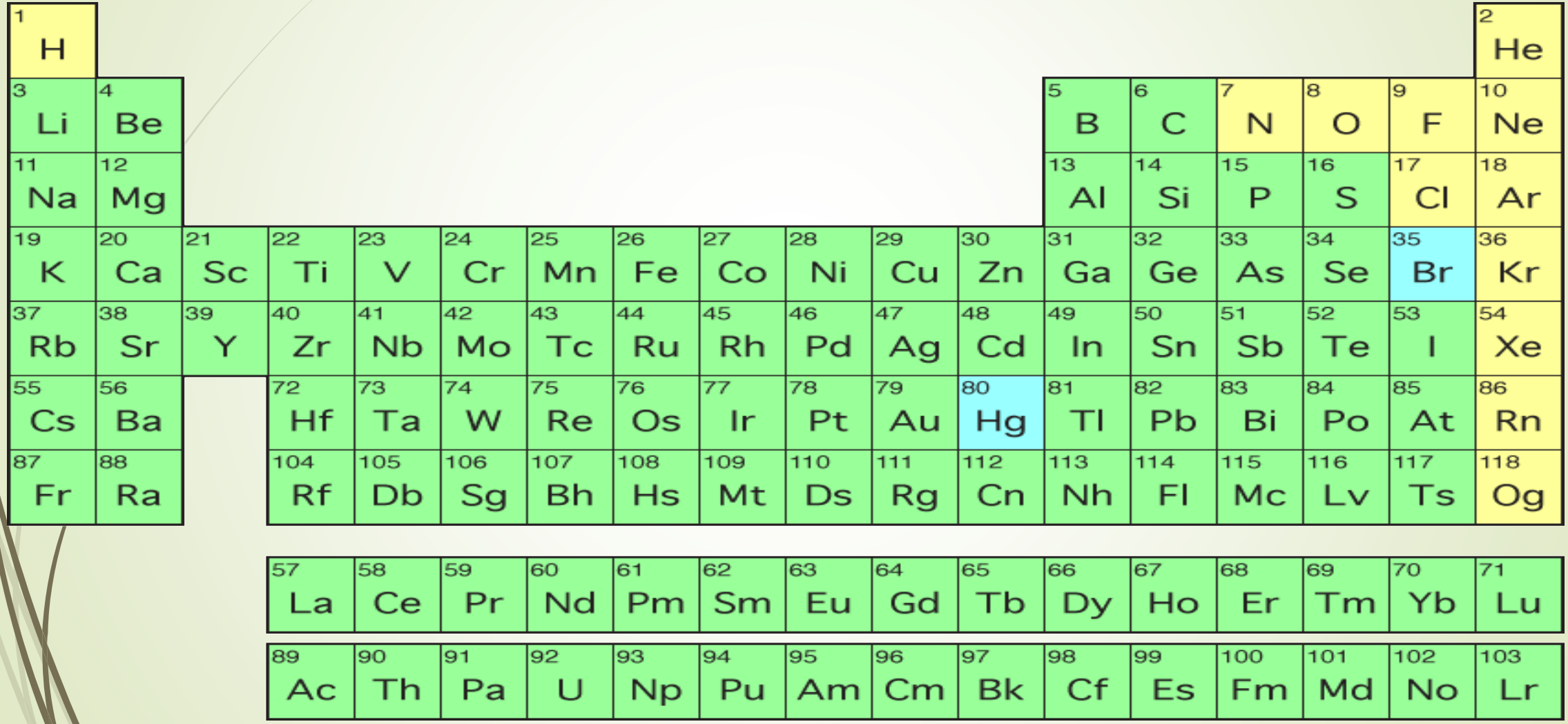
Life Arose 3.8 Billion Years Ago



What is Life?

Life can be said to exist when energy is captured, transformed for use to power metabolism (vital processes to maintain separate existence) and reproduction.

Tools


1 H
2 He
3 Li
4 Be
5 B
6 C
7 N
8 O
9 F
10 Ne
11 Na
12 Mg
13 Al
14 Si
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16 S
17 Cl
18 Ar
19 K
20 Ca
21 Sc
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33 As
34 Se
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36 Kr
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39 Y
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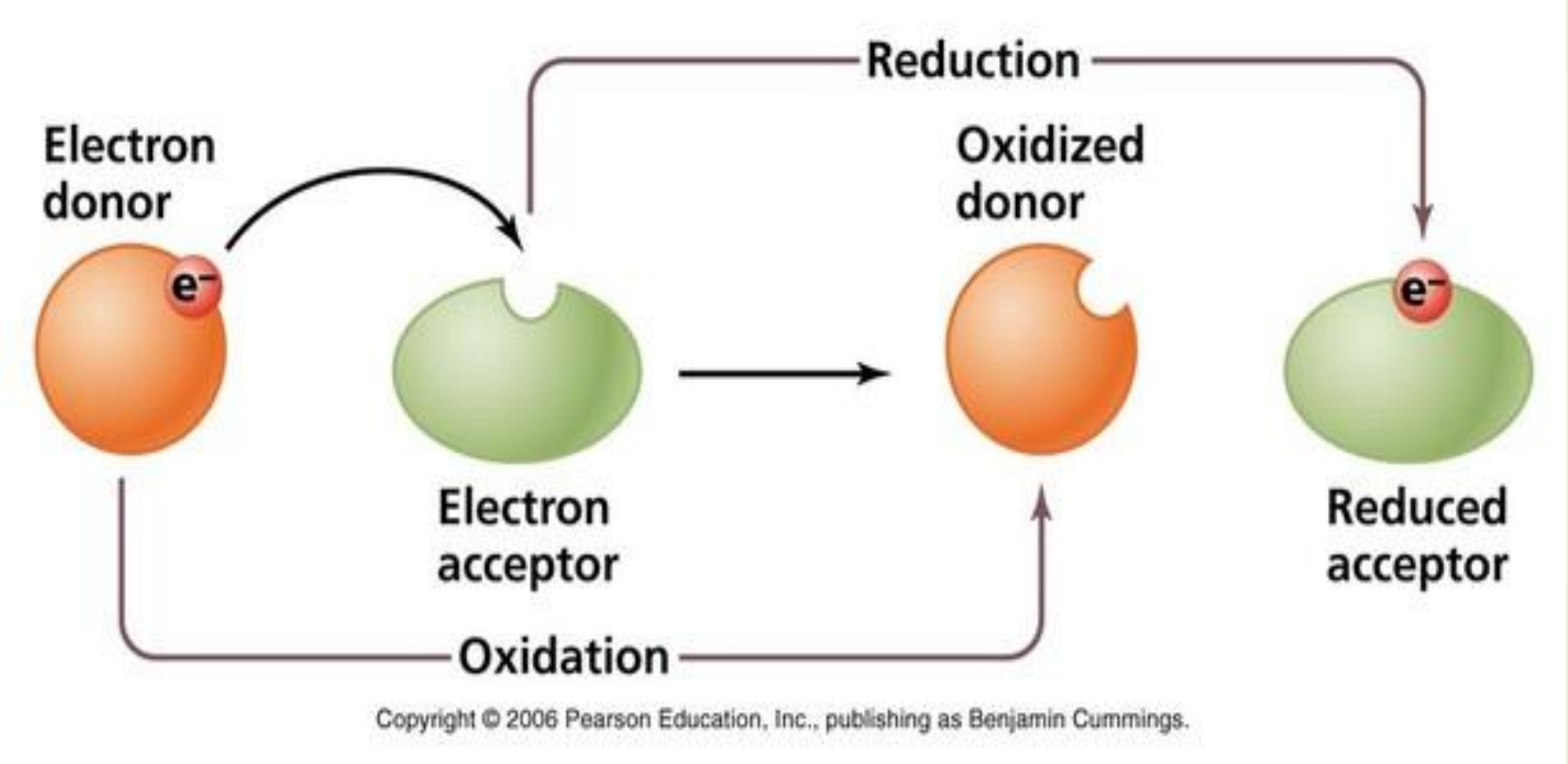
REDOX Biochemistry



Early Life Forms

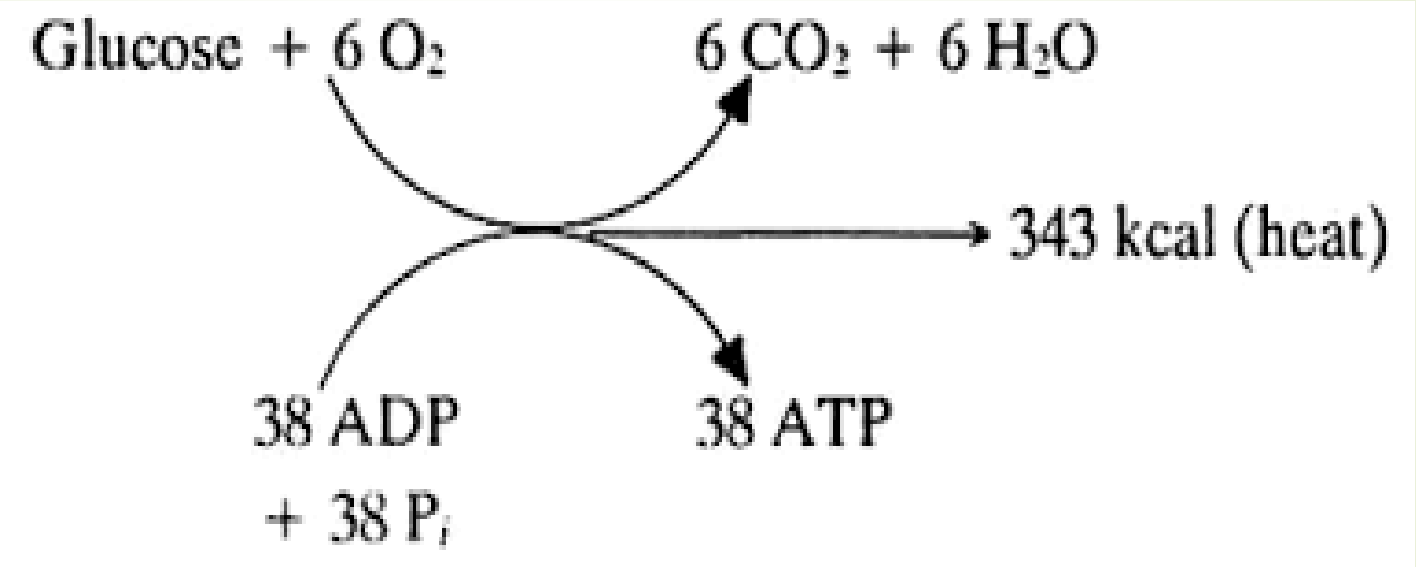
- Fermenting Heterotrophs using abiotic, organic compounds
- Chemotrophs hydrogen, hydrogen sulfide and methane
- Carbon Dioxide and sulfates served as electron acceptors
- Use of nitrogen was limited because of cost of reduction to NH4+
- Purple and green sulfur bacteria and heliobacteria = 1st photosynthetic organisms
- Between 3.2 and 2.4 million years ago cyanobacteria able to photosynthesize
- Ability to split water yielded oxygen – $2H_2O \rightarrow O_2 + 4H^+ + 4e^-$
- 1 electron reduced intermediates ROS $O_2 \rightarrow O_2^{\cdot -} \rightarrow H_2O_2 \rightarrow OH^{\cdot} \rightarrow H_2O_2$

“The Great Oxygen Event”

- Oxygen partial pressure was about 10^{-12} lower than it is now
- Almost 1 billion years later, large life forms became possible.
- Resulted in protective ozone layer and hence biology expanded exponentially
- Other than chlorine and fluorine, the reduction of oxygen yields the largest free energy per electron transferred
- Since O_2 is stable perfect terminal electron acceptor in high energy metabolism

More than 1000 biochemical reactions were added to aerobic life forms compared to anaerobic life forms.

Oxidative Phosphorhylation



Redox Factors and Antioxidant Molecules

- Ascorbate
- Carotenoids
- Tocopherols
- Lipoic acid
- Ubiquinone
- Flavonoids
- NAD
- Flavin
- Quinones
- Pterins and Molybpterins
- Folic Acid

Energy

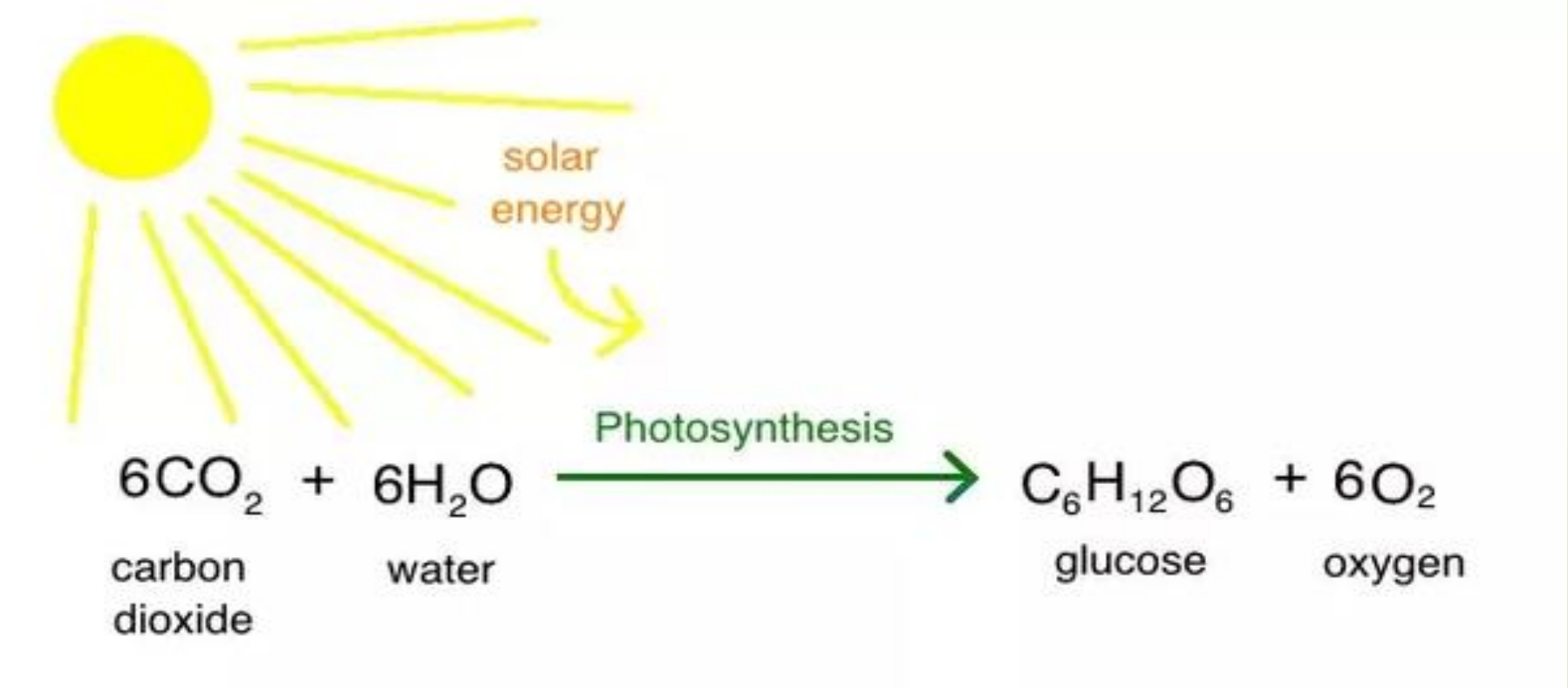
Old age – Youth

Sickness – Health

When you run out of energy,
the game is over

Plants Produce Exactly What We Need

Byproducts of photosynthesis are the fundamental constituents for oxidative phosphorylation



$\Delta G'_{ATP}$ is tightly regulated in all cells between -53 to -60 kJ/mol

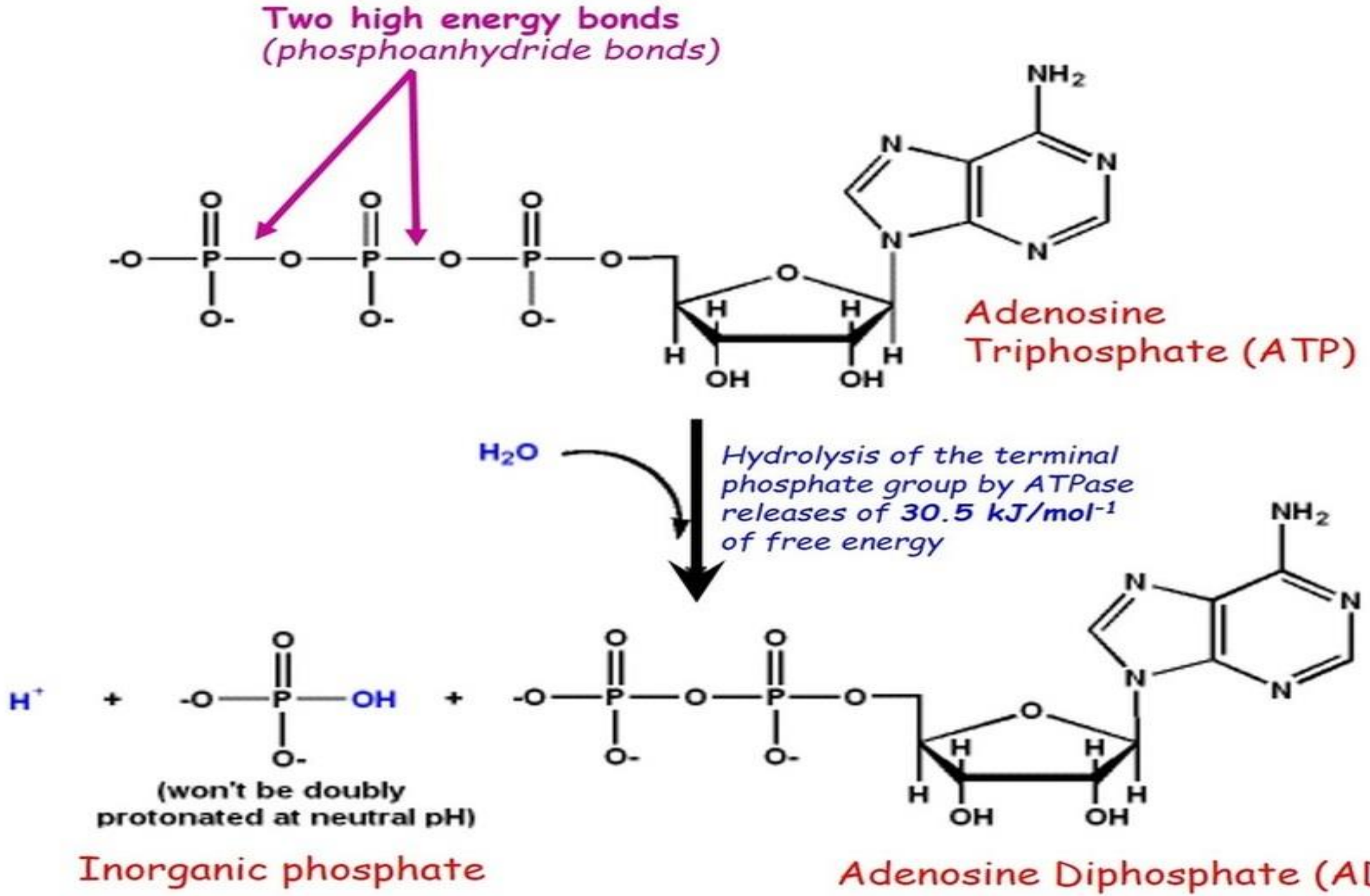
94% of energy is produced in mitochondria (ox-phos)
6% of energy is produced in the cytoplasm (glycolysis)

Most of this energy for ionic membrane pumps … maintain viability

- 56 kJ/mol heart, liver and RBCs

Warburg showed that energy production in kidney and liver cells is the same as that produced in proliferating cancer cells

$\Delta G'_{ATP}$ = standard energy of hydrolysis under physiological conditions


Two high energy bonds
(phosphoanhydride bonds)
Adenosine Triphosphate (ATP)
H2O
Hydrolysis of the terminal phosphate group by ATPase releases of 30.5 kJ/mol-1 of free energy
H+
(won't be doubly protonated at neutral pH)
Inorganic phosphate
Adenosine Diphosphate (ADP)

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Intravenous vitamin C in the supportive care of cancer patients ...

https://www.ncbi.nlm.nih.gov › pmc › articles › PMC5927785

by E Klimant - 2018 - Cited by 12 - Related articles

Apr 30, 2018 - This **article** reviews **intravenous vitamin C** (**IV** C) in **cancer** care and offers a rational ... Is it safe to administer **IV** C to **cancer** patients during and after chemotherapy? ..... 2012;7:e29794. doi: 10.1371/**journal**.pone.0029794.

METHODS · RESULTS · DISCUSSION · CONCLUSIONS

Intravenous Vitamin C for Cancer Therapy – Identifying the ...

https://www.ncbi.nlm.nih.gov › pmc › articles › PMC6115501

by AC Carr - 2018 - Cited by 5 - Related articles

Jump to **Article** information - This **article** was submitted to Clinical and Translational Physiology, a section of the **journal** Frontiers in Physiology. Received ...

Abstract · Q4. Does IVC Interfere With ... · Q6. What Are the Relevant ... · Conclusion

Systematic Review of Intravenous Ascorbate in Cancer ...

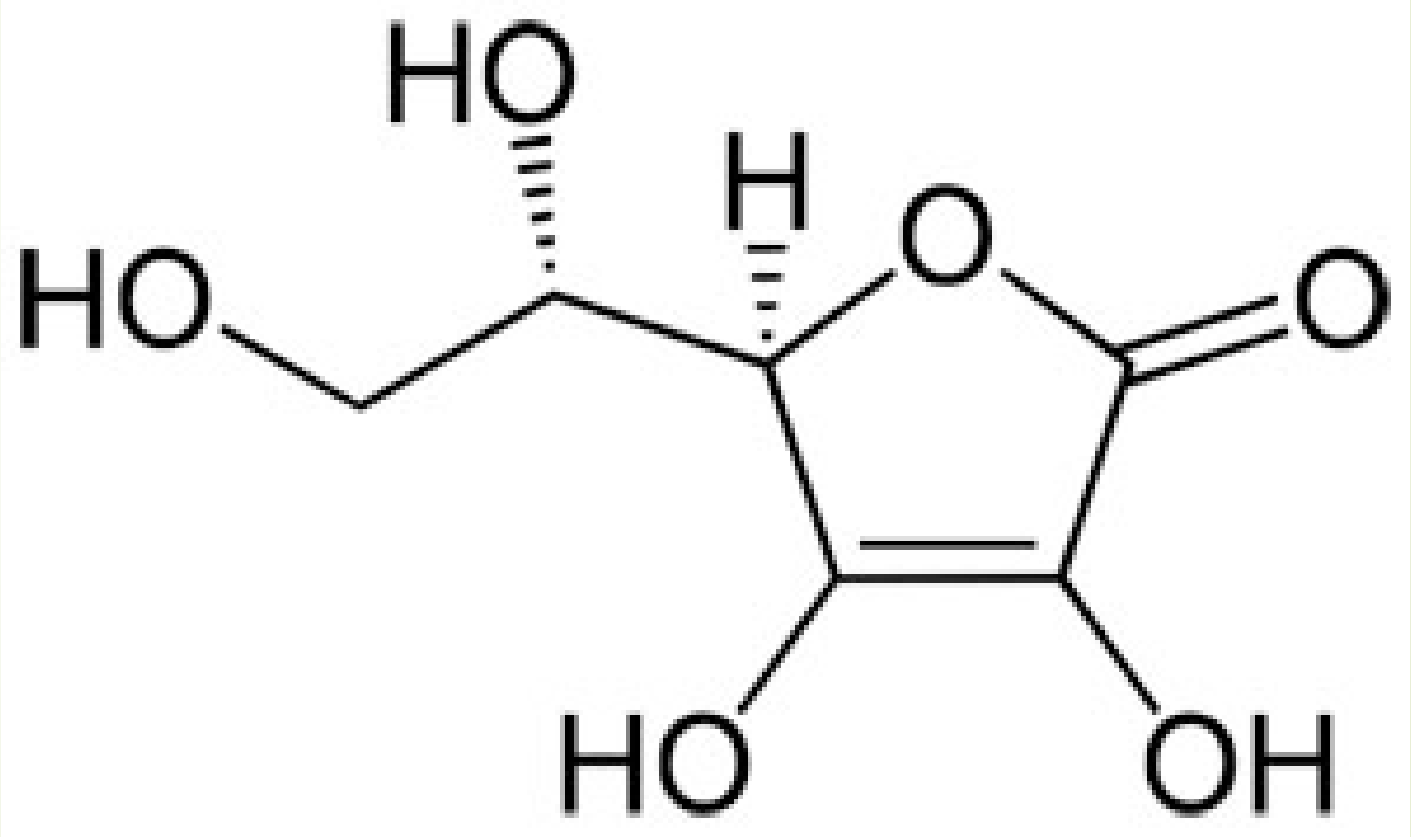
https://www.ncbi.nlm.nih.gov › pmc › articles › PMC6071214

by G Nauman - 2018 - Cited by 13 - Related articles

Jul 12, 2018 - Background: Ascorbate (**vitamin C**) has been evaluated as a potential treatment for **cancer** as an independent agent and in combination with ...

Introduction · Materials and Methods · Results · Future Directions

Ascorbic Acid

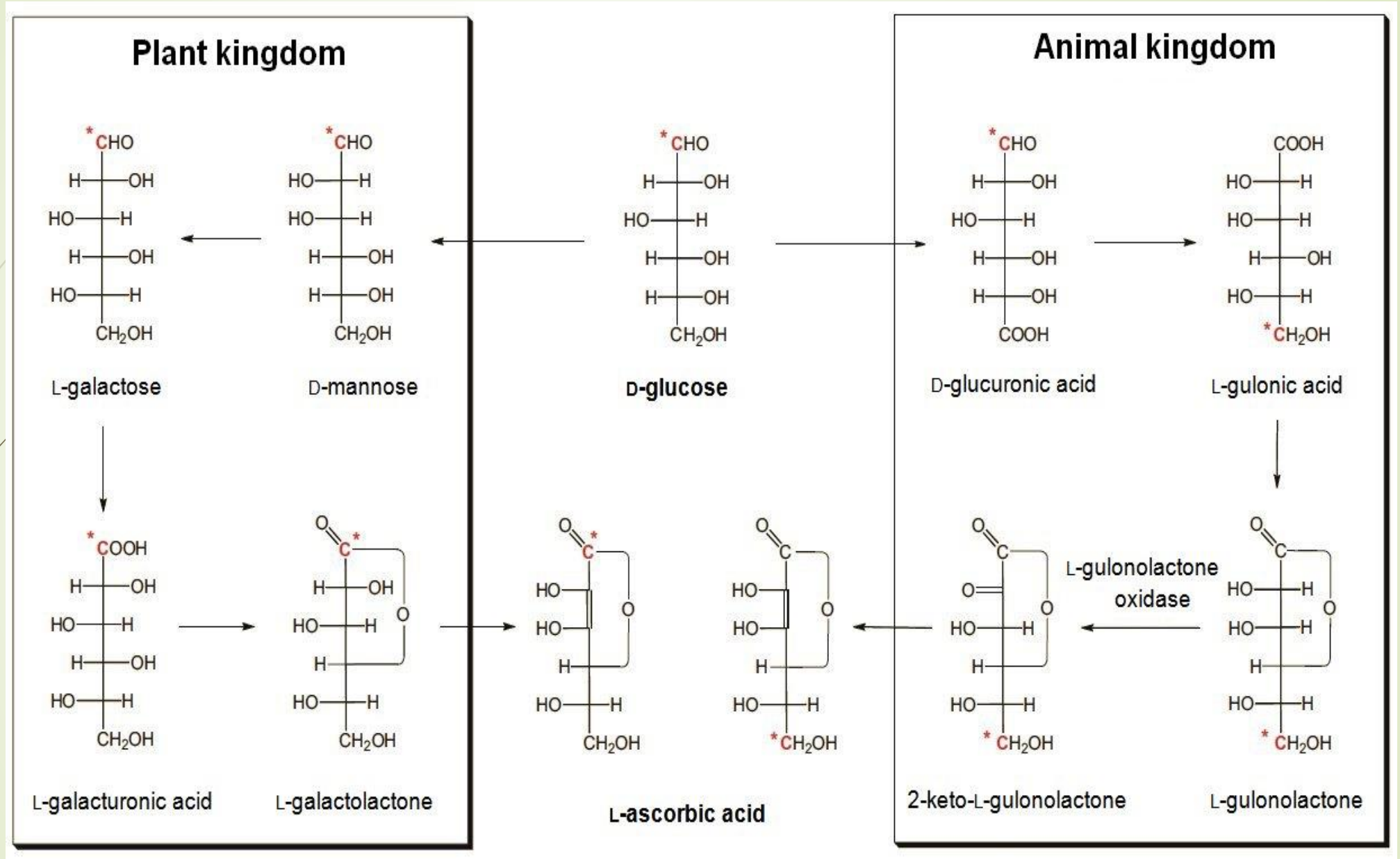


Essential to Biology

Ascorbate is required for a range of essential metabolic reactions in ALL animals and plants

- Only the L-enantiomer is found in Nature
- Almost all organisms can produce it as needed
- **Exceptions:**
  - Bats – guinea pigs – capybaras and Haplorrhini, a primate suborder with tarsiers, monkeys and apes (humans)

All species that do not synthesize ascorbate require it in their diet….it is essential for life


Plant kingdom
Animal kingdom
L-galactose
D-mannose
D-glucose
D-glucuronic acid
L-gulonic acid
L-galacturonic acid
L-galactolactone
L-ascorbic acid
L-gulonolactone oxidase
2-keto-L-gulonolactone
L-gulonolactone

“Vitamin” C

- Ascorbic acid is produced by plants and animals from monosachharides
- Humans lack the enzyme - ***L-gulonolactone oxidase***
- Hence it is an essential nutrient that must be obtained through diet = ***“vitamin”***

Dietary Sources

Vitamin C: in citrus fruits, green peppers, red peppers, strawberries, tomatoes, broccoli, brussels sprouts, turnip, Indian gooseberry and other leafy vegetables.

Animal sources usually <30–40 mg/100 g.

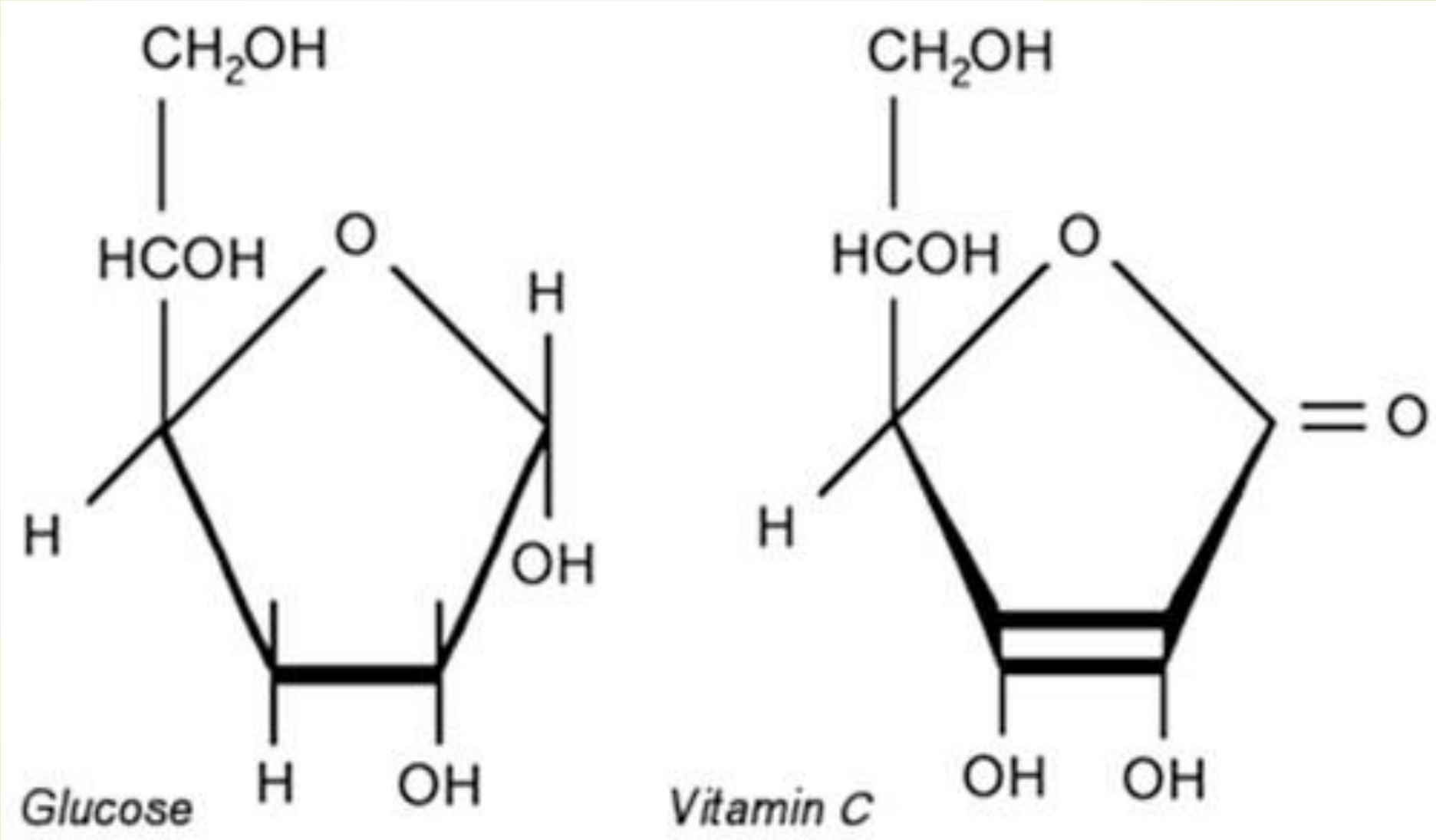
Plant sources up to 5,000 mg/100 g.

Absorption:

Buccal cavity = passive diffusion

Gastrointestinal tract = active sodium dependent vitamin C transporters ($SVCT_1$ & $SCVT_2$)

Similar Structures



Vitamin C

Functions and Mechanisms of Action

- Antioxidant and Pro-oxidant Activity
  - Reducing agent (antioxidant) (AH^-)
    - Donate electrons and hydrogen ions
    - AH^- may react with free radicals and reactive oxygen species
  - Reactive oxygen species
    - OH (hydroxy radical), O_2^- (superoxide radical), H_2O_2 (hydrogen peroxide), and HO_2 (hydroperoxyl radical)
    - Attack phospholipids and protein embedded in membranes
    - Oxidize LDL and red blood cells

Redox Cycling

The one- and two-electron oxidized forms of vitamin C

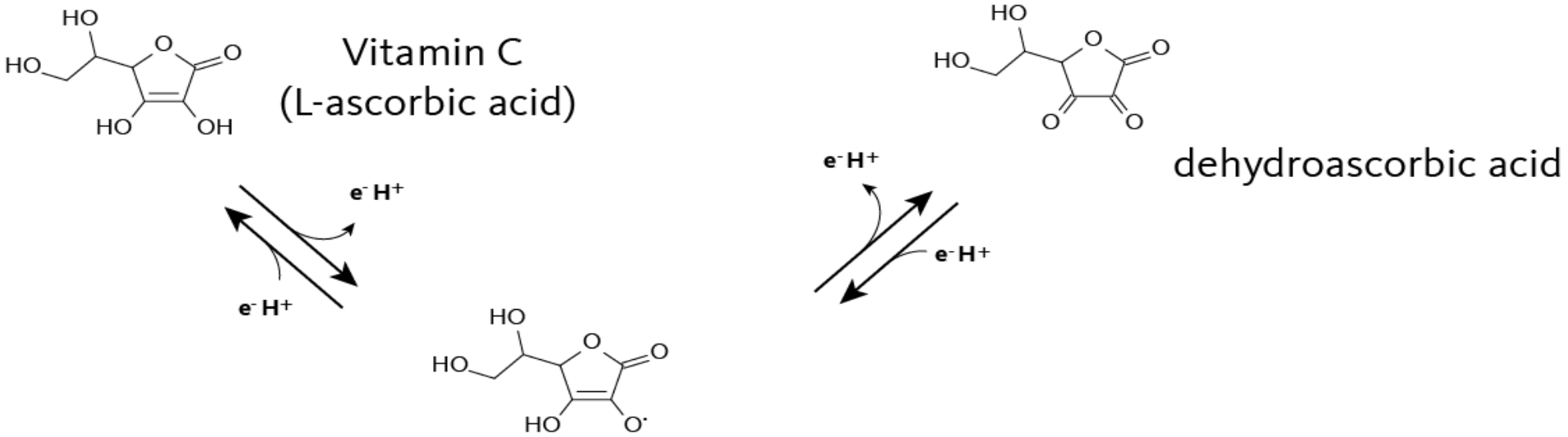
*semidehydroascorbic acid

*dehydroascorbic acid

Reduced in the body by glutathione and NADPH-dependent enzymatic mechanisms

The presence of glutathione in cells and extracellular fluids maintains ascorbate in a reduced state

Figure 1. Vitamin C



Vitamin C (L-ascorbic acid) is an electron donor. Vitamin C can sequentially donate two electrons. Vitamin C can donate electrons to reactive free radicals, which then become reduced. The loss of one electron results in vitamin C being oxidized to the ascorbate free radical, which is relatively unreactive compared to other free radicals. The ascorbate free radical can be reduced to vitamin C by gaining one electron or be further oxidized to dehydroascorbic acid by losing another electron. Dehydroascorbic acid is only stable for a few minutes and is then either irreversibly hydrolyzed to form 2,3-diketogulonic acid or reduced to semidehydroascorbic acid and vitamin C (not shown here). However, the efficacy of the *in vivo* reduction reactions that yield vitamin C from dehydroascorbic acid and semidehydroascorbic acid appears to be low as vitamin C deficiency occurs in 30 days when vitamin C is removed from the diet of healthy people. Thus, most of the vitamin C is likely oxidized to dehydroascorbic acid, which is irreversibly metabolized.

Functions

Ascorbate is the cofactor for Cu+–dependent monooxygenases and Fe2+–dependent dioxygenases.

• Maintenance of normal connective tissue, wound healing and bone remodeling

• Forms epinephrine from tyrosine

• Synthesis of L-carnitine, peptide hormone amidation, and the synthesis of bile acids, cholesterol metabolism, cytochrome P-450 activity, and neurotransmitter synthesis

• Steroidogenesis - the adrenal cortex contains high levels of vitamin C which are depleted upon adrenocorticotropic hormone (ACTH) stimulation of the gland.

• **Dietary ascorbate:**

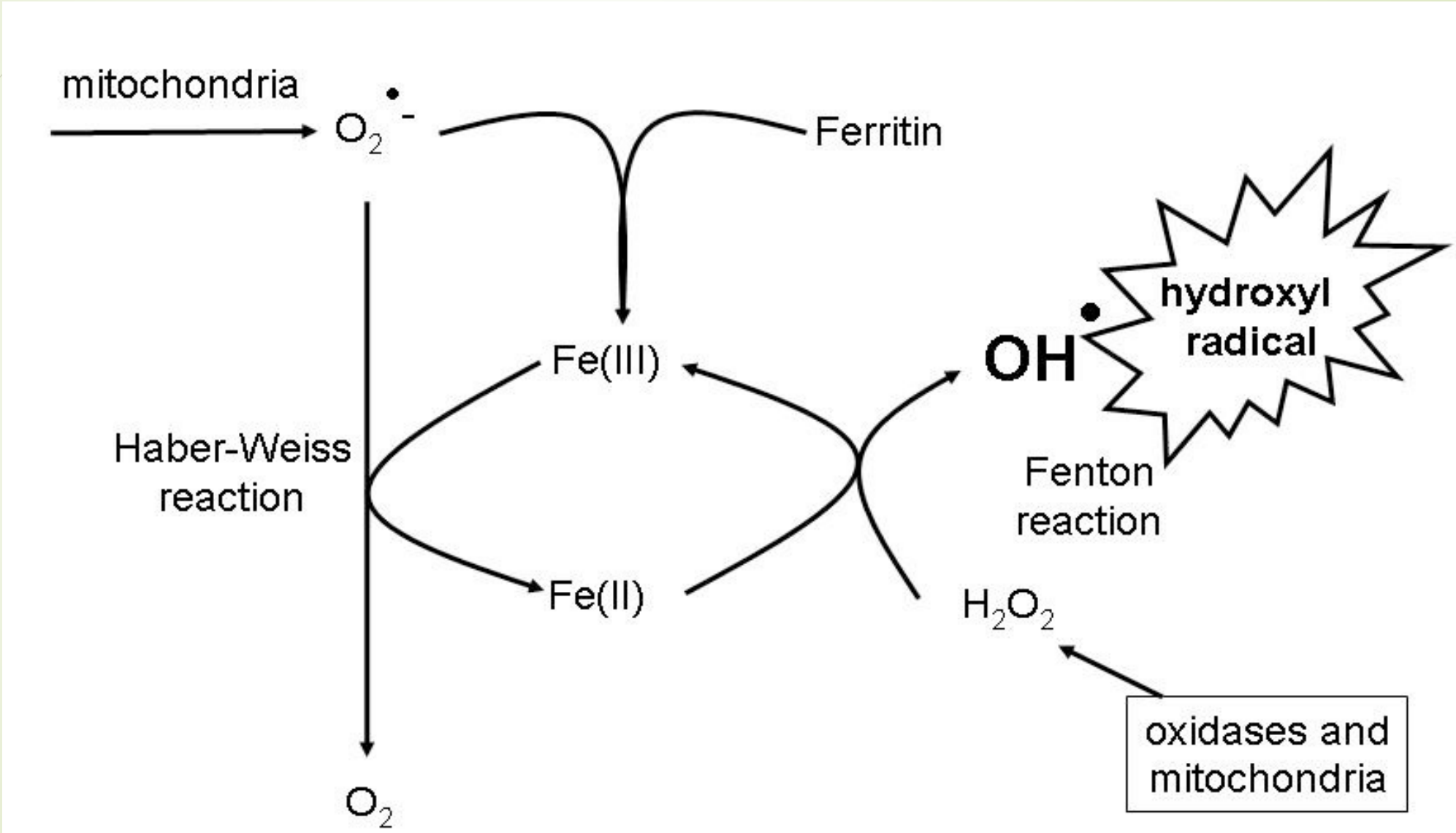
*non-heme iron absorption in the small intestine

*overall regulation of iron homeostasis

*reduce cytochromes a and c

*reduce molecular oxygen.

Fenton Reaction



Early Scurvy

Generally feeling unwell

- Fatigue
- Loss of appetite
- Nausea
- Diarrhea
- Fever
- Painful joints and muscles
- Small ‘pinpoint’ bleeding around hair follicles visible in the skin.

Late Symptoms of Scurvy

- Swollen, spongy and purplish gums that are prone to bleeding
- Loose teeth
- Bulging eyes (proptosis)
- Bleeding into the skin (severe and easy bruising)
- Scaly, dry and brownish skin
- Very dry hair that curls and breaks off close to the skin
- Slow or non-healing wounds
- Opening of previously healed scars
- Bleeding into the joints and muscles
- Premature cessation of bone growth (in babies and children).

CSS Syndrome

Chronic Subclinical Scurvy (the CSS Syndrome) is our most widespread disease (Stone, 1972).

- 45 mg of ascorbate will prevent the appearance of the terminal symptoms of the disease
- To correct Chronic Subclinical Scurvy requires at least 10 grams of ascorbate a day depending upon the incident stresses (Stone, 1977).
- Under heavy stresses the daily ascorbate requirement may be 200 grams or 300 grams to keep ahead of the CSS Syndrome.
- The long term biochemical results of Chronic Subclinical Scurvy set the stage for the development of the serious medical problems of later life; the heart attacks, the cancer, the collagen diseases and many more.
- Preliminary clinical tests indicate that mega levels of ascorbate are useful in the prevention and treatment of cancer (Stone, 1974, 1976), heart disease, and many others (Stone 1972).
- In the case of viral diseases (Pauling, 1978, Stone, 1972), research of the past

30 years indicates that no one should succumb to a viral infection any more.

Dr. Irwin Stone (1907-1984) was an American biochemist , chemical engineer and author

Contraindications IV Vitamin C

- G6PD deficiency is an inherited enzyme deficiency

  (If positive can cause hemolysis)
- Hemochromatosis will produce high levels of peroxides in the liver and other organs.
- Oxalate nephropathy or with severe preexisting renal dysfunction (?)
- Caution with Congestive Heart Failure, ascites and edema

Cancer Patients are Deficient

Most cancer patients are found to be ascorbate deficient when measurements have been made

(Anthony and Schorah, 1982; Ray and Husain, 2001; Mayland et al., 2005; Shah et al., 2009; Badid et al., 2010; Nagamma et al., 2014).

Cancer Patients are Deficient in Ascorbic Acid

- As reviewed by McGregor and Biesalski**, numerous inflammatory** conditions including gastritis , diabetes, pancreatitis, pneumonia, osteoporosis, rheumatoid arthritis , are all associated with marked reduction in plasma AA levels as compared to healthy controls.
- **There is a correlation between tumor aggressiveness and low AA**
- Kuiper et al. found that the pro-angiogenic transcription factor HIF-1 alpha is negatively correlated with tumor AA content.
- Correlations where also made between low AA content, high VEGF, and levels of the anti-apoptotic protein bcl-2.
- Cancer patients have a general state of chronic inflammation
- Elevation in the level of classical inflammatory markers such as fibrinogen, CRP, ESR, NfKB, ferritin, neopterin, homocysteine, IL-6], and free radical stress have been well-documented in cancer patients

Numerous studies demonstrating that elevation of inflammatory markers is associated with poor survival.

In several studies it was found that decreasing inflammatory markers by IVC correlated with decreases in tumor marker levels.

Ascorbate Transport & Uptake

- Transported to the tissues via the circulation.
- Most cells concentrate ascorbate much higher than plasma levels (average ~50 µM) via sodium-dependent vitamin C transporters SVCT1 and SVCT2 (Tsao, 1997; May and Qu, 2005; Savini et al., 2008; Harrison and May, 2009; Mandl et al., 2009; Nualart et al., 2014).
- Red blood cells do not express SVCT2 and accumulate ascorbate by uptake of dehydroascorbate (DHA) via the GLUTs (Tu et al., 2017). (***same as cancer cells***)
- Brain, adrenals, liver, and white cells maintain concentrations up to 20 mM (Tsao, 1997).

Oral vs Intravenous

- Vitamin C is toxic to cancer cells at extracellular concentrations greater than 1,000 µM.
- 3 grams every 4 hours (6 times daily) > 220 µM. Padayatty SJ, Sun H, Wang Y, et al. Vitamin C Pharmacokinetics: Implications for Oral and Intravenous Use. Annals of Internal Medicine 2004;140:533-537
- IV vitamin C - plasma concentrations around 15,000 µM.

Liposomal Vitamin C = Peyer's Patches

- The lymphatic capillaries of the small intestine drain directly into the general circulation.
- Dr. Hickey's group investigated oral liposomal doses (5 to 36 grams)
- Plasma ascorbate levels greater than 400 µM from large single 36-gram oral dose of liposomal vitamin C
- Accordingly, we can speculate that steady-state blood ascorbate levels of at least 500 µM could be achieved and sustained through repeated oral liposomal doses. O'Driscoll CM. Lipid-based formulations for intestinal lymphatic delivery. Eur. J. Pharm. Sci 2002;15(5):405-15.

Not a “New Therapy”

- Klenner FR. The treatment of poliomyelitis and other virus diseases with vitamin C. J. South. Med. and Surg. **1949**;111:210-4.

- McCormick, WJ. Ascorbic acid as a chemotherapeutic agent. Archives of Pediatrics of New York. **1952**;69:151-155 C.

Vitamin C “Debunked” ?

- Pauling and Cameron treated people with advanced cancers in the 1970’s (1976, 1978)
  10 grams IV / day - ***significantly longer survival rates***.

- The Mayo clinic “debunked” these findings 10 years later with 2 studies showing that “there were no clinical benefits”.Creagan ET, Moertel CG, O’Fallon JR, Schutt AJ, O’Connell MJ, Rubin J, Frytak S. Failure of high-dose vitamin C (ascorbate) therapy to benefit patients with advanced cancer: A controlled trial. N Engl J Med. 1979;301:687-690. 38.Moertel CG, Fleming TR, Creagan ET, Rubin J, O’Connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy: A randomized
- These studies included 200 patients who were treated with 10 grams of vitamin C ***orally once per day.***
- There is a maximum amount of ascorbate that can be absorbed via GI tract therefore these studies are not comparable….apples vs oranges.

- A dynamic flow model for vitamin C (dual-phase pharmacokinetics) by Hickey, Roberts and Cathcart (Hickey DS, Roberts HJ, Cathcart RF. Dynamic Flow: A New Model for Ascor).

1st phase when blood levels < 70 µM (0.123 mg/dl)… the kidney’s SVCT reabsorb ascorbate.

2nd phase plasma ascorbate > 70 µM - **kidneys excrete ascorbate**

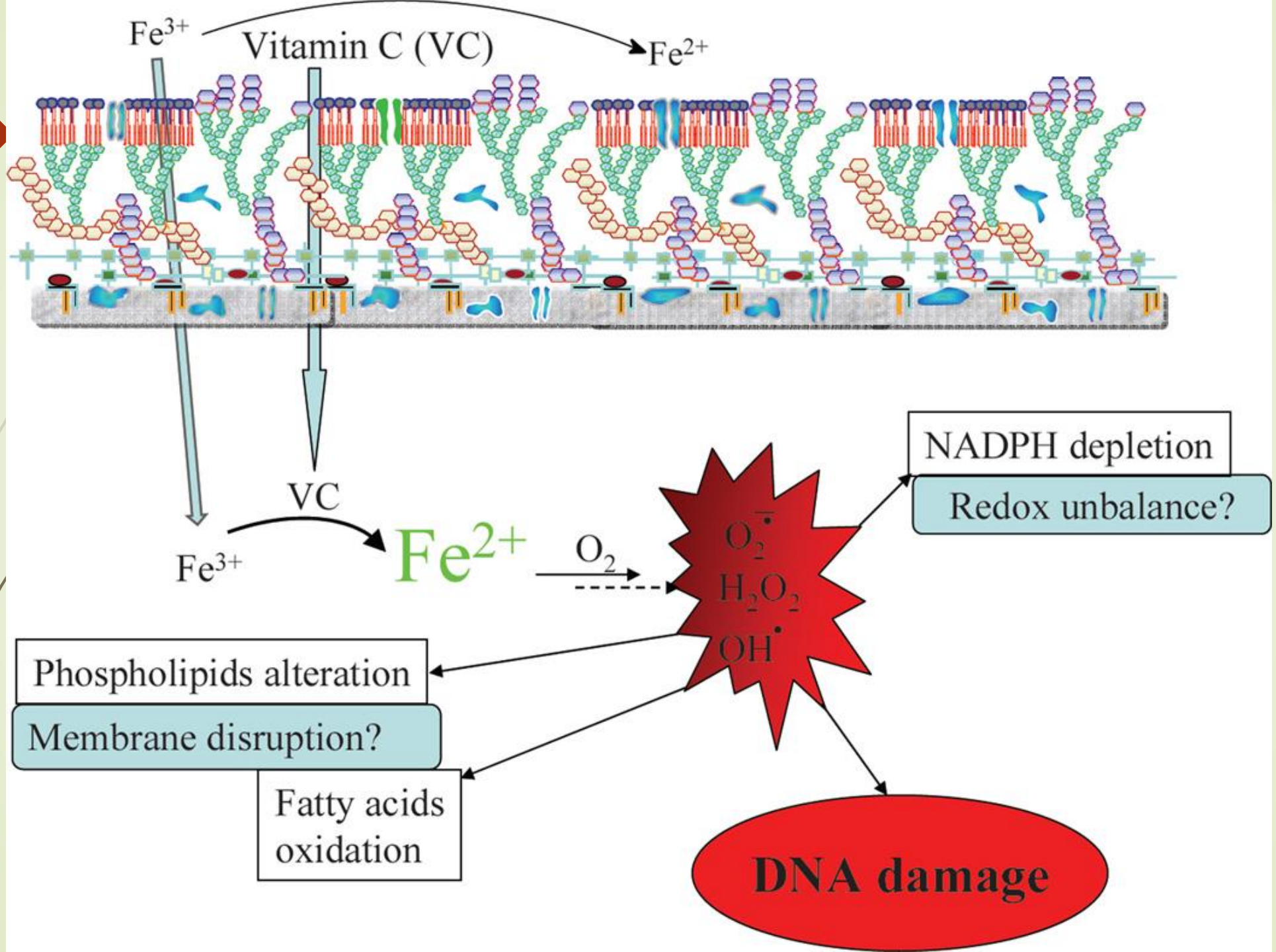
RDA has been Debunked !

- Plasma levels >70 µM have ½ life of 30 minutes –
- Large doses taken several hours apart must be considered independent, as should be their bioavailability.
- Hence splitting a single large dose into several smaller ones, taken a few hours apart, increases the effective bioavailability of the large dose
- Cathcart's bowel tolerance method - individual bioavailability varies by a factor of at least two and variation depends upon the person's health status.

"Bioavailability is not a static property of ascorbate, but is subject to individual differences and varies with the timing of the dose."

Anti-Cancer Activities of AA

- Pro-oxidant Effect
- DHA – Oxidative stress
- Down Regulation of Hypoxic Phenotype (HIF-1)
- Epigenetic Mechanisms of Action


Fe3+
Vitamin C (VC)
Fe2+
VC
Fe3+
Fe2+
O2
O2•−
H2O2
OH•
NADPH depletion
Redox unbalance?
Phospholipids alteration
Membrane disruption?
Fatty acids oxidation
DNA damage

Ascorbate for Cancer

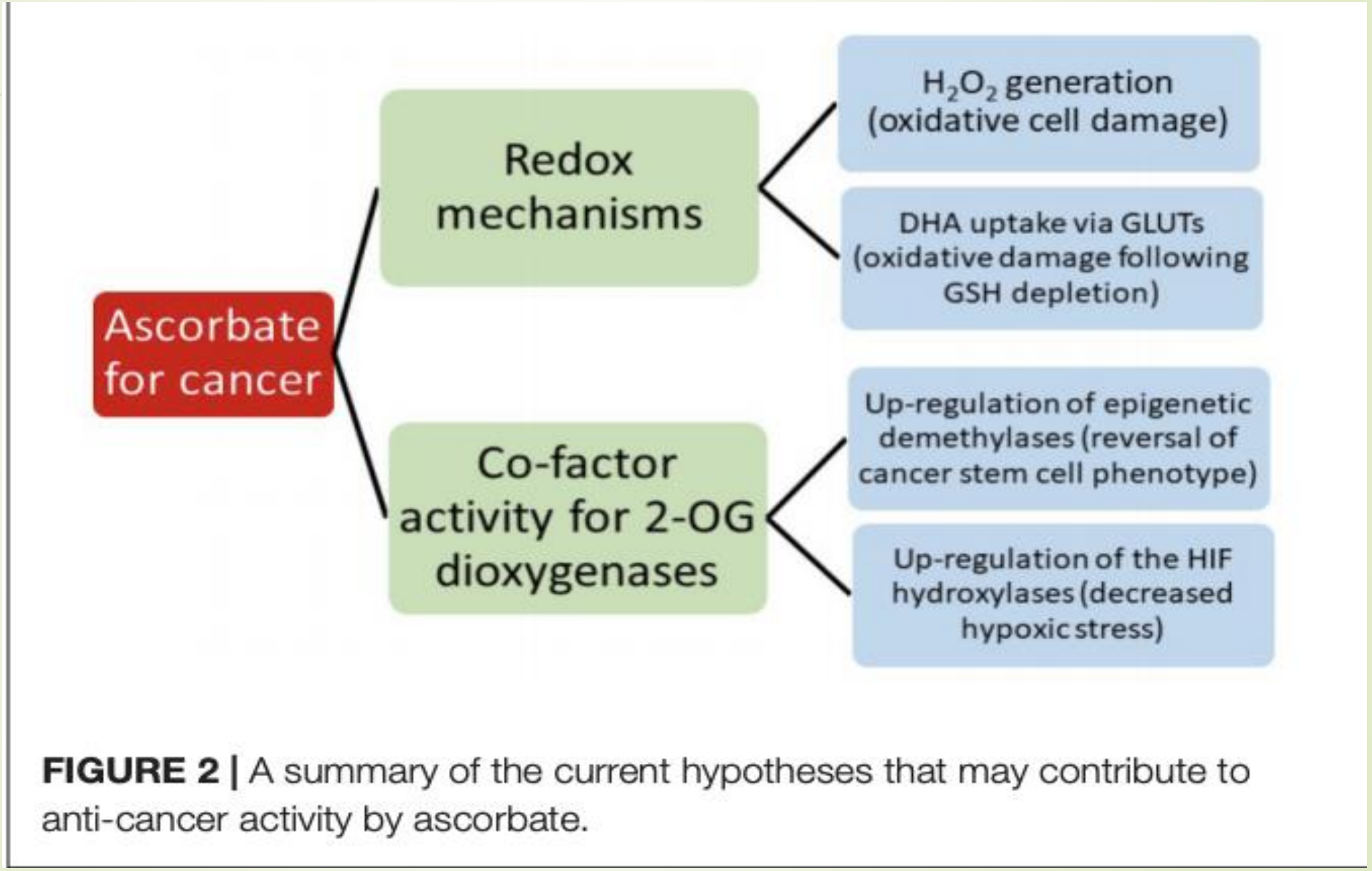


FIGURE 2 | A summary of the current hypotheses that may contribute to anti-cancer activity by ascorbate.

Pro-Oxidant Effect

H2O2 is generated when ascorbate is present at concentrations of 1 mM or above (Wells et al., 1995; Reddy et al., 2001; Pathak et al., 2002; Wozniak and Anuszewska, 2002; Guerriero et al., 2006; Kassouf et al., 2006; Chen et al., 2007, 2012; Martinotti et al., 2011; Verrax et al., 2011; Ma et al., 2014; Cieslak et al., 2015; Xia et al., 2017) or radiation (Herst et al., 2012; Castro et al., 2014).

1) Increased cell cycle arrest
2) p53 upregulation
3) Decreased ATP levels
4) Compromised mitochondrial function
5) Suppression of antioxidant gene expression NrF-2
6) Cell death by apoptosis

(Tarumoto et al., 2004; Fromberg et al., 2011; Rouleau et al., 2016; Yang et al., 2017).

DHA – Oxidative Stress

- DHA is structurally similar to glucose and is taken up via GLUTs.
- DHA is reduced by GSH, NADH and NADH-dependent enzymes - ***depletes cells of antioxidant molecules.***
- KRAS and BRAF mutated cells upregulate GLUT1, hence increased uptake of DHA leading to anti-oxidant enzyme depletion.
- Therefore, many cancers including NSCLC , colon, hairy cell leukemia, melanoma, papillary thyroid and papillary craniophyrngeomas.
- "Our findings address this fundamental question, suggesting that the oxidized form of vitamin C, **DHA**, is the **pharmaceutically active agent**, and that the selective toxicity of vitamin C to tumor cells stems from high GLUT1 expression combined with *KRAS* or *BRAF* oncogene-induced glycolytic addiction." (Yun et al., 2015)

Down Regulation of Hypoxic Phenotype

- HIFs are activated by hypoxia and nutrient deprivation in tumor environment
- HIFs: successful tumor adaptation to a stressful microenvironment via transcription of glycolytic genes, glucose transport, angiogenesis, metastases and resistance to chemo/radiation.
- High HIF activity promotes the expression of a stem cell phenotype in breast cancer (De Francesco et al., 2015; Semenza, 2015, 2016) and is associated with a poor prognosis in a number of cancers
- Activation of the HIFs is controlled by proline and asparaginyl hydroxylases (the HIF hydroxylases) that modify the regulatory HIF-α subunit (Bishop and Ratcliffe, 2014; Pugh and Ratcliffe, 2017), targeting the protein for proteasomal degradation and ***preventing the formation of an active transcriptional complex.***
- HIF hydroxylases are iron containing dioxygenases that use oxygen and 2-oxoglutarate, ***which require ascorbate as a co-factor.***
- ***Increasing ascorbate supply to cancer cells stimulates the activity of the HIF hydroxylases and decreases the activation of the HIFs, thereby slowing tumor growth rates.***

Strong association between ascorbate content, HIF activation and tumor growth in vivo.

Epigenetics

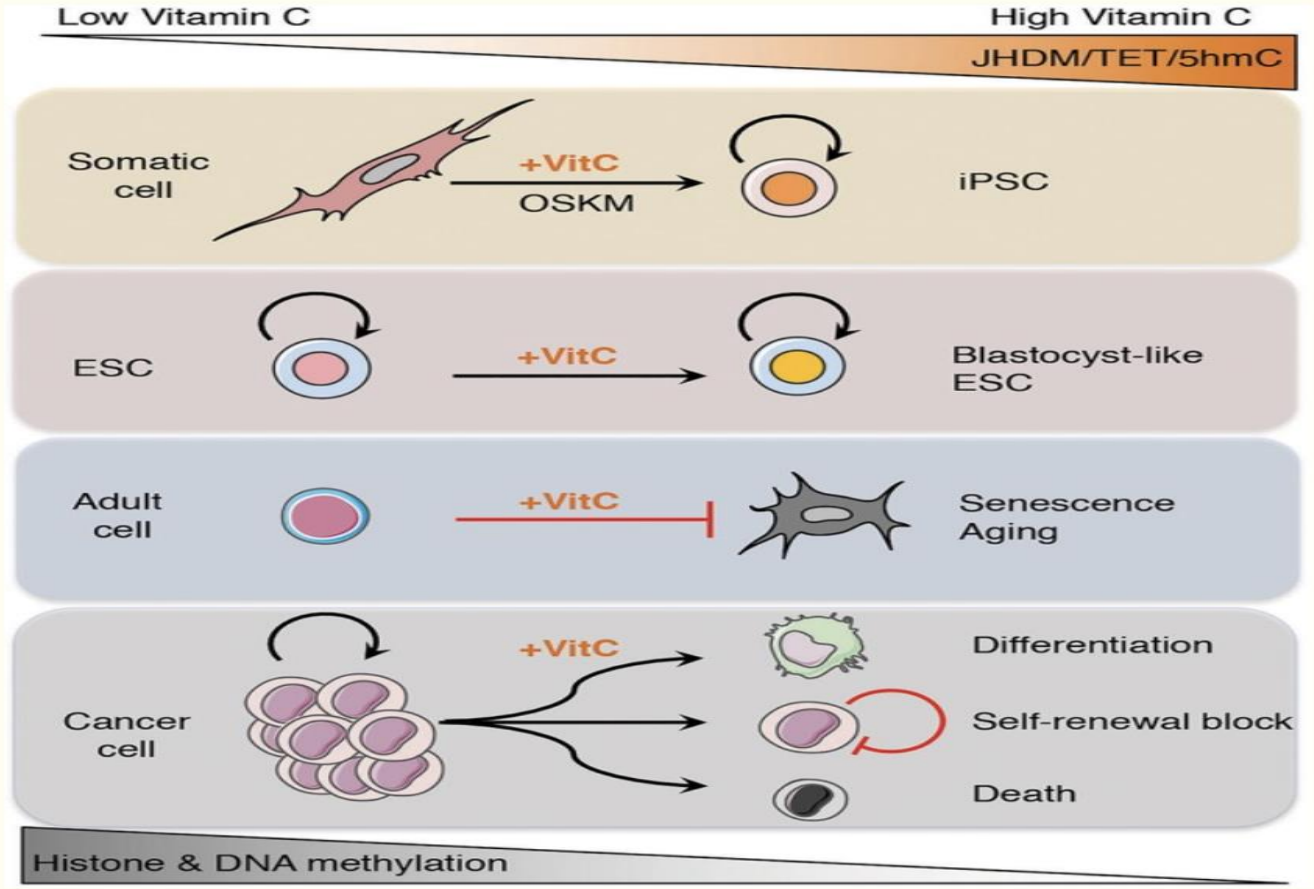


FIGURE 3

Vitamin C reprograms the epigenome to reverse commitment, prevent senescence and restore differentiation potential. Under growth conditions with low levels of vitamin C, the epigenome of cells becomes hypermethylated, most likely due to suppressed activity of α-ketoglutarate dependent dioxygenases (α-KGDDs) including Jumonji-C domain-containing histone demethylases (JHDMs) and ten-eleven translocation (TET) proteins. By increasing the levels of vitamin C, JHDM, and TET enzymatic activity is enhanced, leading to the loss of histone and DNA methylation, respectively, that promotes somatic cell reprograming, increased differential potential of ESCs toward a blastocyst-like state, protects adult cells from senescence and aging, and can drive the differentiation or death of cancer cells.

Role of Ascorbate in Epigenetics

- By adding vitamin C to the culture media of somatic cells during reprogramming improves the efficiency and quality of iPSC formation (Esteban et al., 2010; Wang et al., 2011; Stadtfeld et al., 2012)
- Ascorbate is a critical cofactor of Fe2++ and α-ketoglutarate-dependent dioxygenases (α-KGDDs) maintaining and enhance the activity of these enzymes.
- **Impaired α-KGDD function** leads to histone and DNA hypermethylation that is **a hallmark** of several cancers including hematologic malignancies, such as AML (Figueroa et al., 2010a, b), glioma (Lu et al., 2012; Turcan et al., 2012) and epithelial tumors (Xiao et al., 2012; Killian et al., 2013).
- Enhances activity of JHDMs and TETs drive histone and DNA demethylation in somatic cells that allow **pluripotency genes to turn on while simultaneously erasing the epigenetic memory** of the adult cell
- These **epigenetic erasers** are **often mutated** in cancer, **resulting** in histone and DNA hypermethylation that block tumor cells from responding to differentiating cues and provide protection from chemotherapy.

Vitamin C at high-doses is being explored as a therapeutic approach to overcome metabolic or epigenetic dysregulation and reprogram the cancer epigenome, allowing cells to regain their ability to differentiate and improve their responsiveness to standard chemotherapies.

Epigenetic Reprograming

- Low plasma vitamin C levels are associated with poor dietary intake and shorter survival in cancer patients (Anthony and Schorah, 1982; Mayland et al., 2005
- The majority of patients with hematologic malignancies (up to 58%) are vitamin C deficient compared to normal healthy controls (Huijskens et al., 2016; Liu et al., 2016) and **chemotherapy or HSC transplantation causes vitamin C levels to decrease further** (Nannya et al., 2014)
- Restoring TET function in cancer cells by vitamin C administration, in combination with other targeted epigenetic therapies and hypomethylating agents, may help to erase the epigenetic memory of the cancerous cell state and reprogram the epigenome of these cells that allows them to re-acquire normal differentiation potential and tumor suppressive gene expression programs.

The same mechanisms underlying the erasure of epigenetic memory during reprogramming can also be harnessed in cancer therapy to reverse aberrant epigenetic signatures and allow tumor cells to regain their potential to differentiate or die.

Epigenetic Reprograming in Cancer

“ In addition to improving the quality of stem cells used for regenerative medicine, vitamin C represents a natural, non-toxic, epigenetic therapy that can be used in the prevention and treatment of cancer. Given that loss of function in epigenetic regulators is a hallmark of malignant transformation and a driver of cancer progression, the ability of vitamin C to enhance the activity of epigenetic erasers such as JHDM and TET proteins suggest that future research into the efficacy of vitamin C as an epigenetic therapy should focus on improving the bioavailability and uptake of vitamin C and its general applicability as an adjuvant to existing chemotherapy.”

Reprogramming the Epigenome With Vitamin C Taylor Lee Chong,[1,†] Emily L. Ahearn,[1,†] and Luisa Cimmino[1,2,*]Front Cell Dev Biol. 2019; 7: 128.

Ascorbates with Chemotherapeutics

- Anti-cancer effects have also been demonstrated with ascorbate levels well below 1 mM: levels as low as 100 µM or even 1 µM in the culture medium enhanced the susceptibility of cancer cells to etoposide, cisplatin, or doxorubicin (Kurbacher et al., 1996; Reddy et al., 2001; Tarumoto et al., 2004; An et al., 2011). The mechanism of action at these low concentrations remains unclear, but potentially involves modification of cell survival pathways involving p53
- There is significant consensus that ascorbate can act synergistically with gemcitabine (Kassouf et al., 2006; Espey et al., 2011; Martinotti et al., 2011; Volta et al., 2013; Cieslak et al., 2015), and treatment with a combination of the two agents did not result in any adverse events in recent phase I/II trials (Monti et al., 2012; Welsh et al., 2013)

Phase I study of high-dose ascorbic acid with mFOLFOX6 or FOLFIRI in patients with metastatic colorectal cancer or gastric cancer

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Feng Wang, Ming-Ming He, Zi-Xian Wang, Su Li, Ying Jin, Chao Ren, Si-Mei Shi, Bing-Tian Bi, Shuang-Zhen Chen, Zhi-Da Lv, Jia-Jia Hu, Zhi-Qiang Wang, Feng-Hua Wang, De-Shen Wang, Yu-Hong Li, and Rui-Hua Xu

A total of 36 patients were enrolled in this phase I mCRC 30 and mGC 6.

Among the 30 patients with mCRC, 26 patients were assayed for KRAS, NRAS and BRAF status.

Results

Partial response 14 patients (objective response rate, 58.3%)

Stable disease in nine (37.5%),

Disease control rate of 95.8%.

Among 22 patients with mCRC receiving first-line therapy, the **objective response rate was 59.1% and the disease control rate was 95.5%.**

Conclusions

- In summary, the combination of AA at 1.5 g/kg once daily for three consecutive days with mFOLFOX6 or FOLFIRI with or without bevacizumab every 14 days exhibits a favorable safety profile and potential clinical efficacy in patients with mCRC or mGC.
- As a result, a randomized phase III study is ongoing investigating the additional efficacy of treatment when AA is combined with mFOLFOX6 ± bevacizumab **as first-line therapy for patients with mCRC**

Vitamins C and K3 Sensitize Human Urothelial Tumors to Gemcitabine

Wassim Kassouf, Ralph Highshaw, Gina M. Nelkin, Colin P. Dinney, Ashish M. Kamat https://doi.org/10.1016/j.juro.2006.06.042

- Vitamins C plus K3 induced cytostasis and caused apoptosis to a greater degree than either vitaminC or K3 alone ($p < 0.05$).
- Vitamins C plus K3 also substantially augmented the effects of gemcitabine in vitro.
  Gemcitabine + Vitamins C + K3 = 32.3% apoptosis
  Gemcitabine = 5.3%
  Vitamins C + K3 = 15.8%
- **In vivo tumor growth was substantially inhibited by gemcitabine plus vitamins C plus K3 compared with that in the control or for either agent alone.**
- Mean tumor weight and growth rate in the and 11.3 mm 3 daily) were decreased compared with those in the control (530 mg and 34.3 mm 3 daily), and those for vitamins C plus K3 alone (490 mg and 25.2 mm 3 daily) and gemcitabine alone (400 mg and 21.3 mm 3 daily) ($p < 0.05$).

Vitamins C and K3 have significant antiproliferative and apoptotic effects when used in combination. This combination enhances the efficacy of gemcitabine against bladder cancer in vivo.

Future Directions

- Most effective and safest way to administer ?

- **LADME:**

Liberation of the active substance from the delivery system

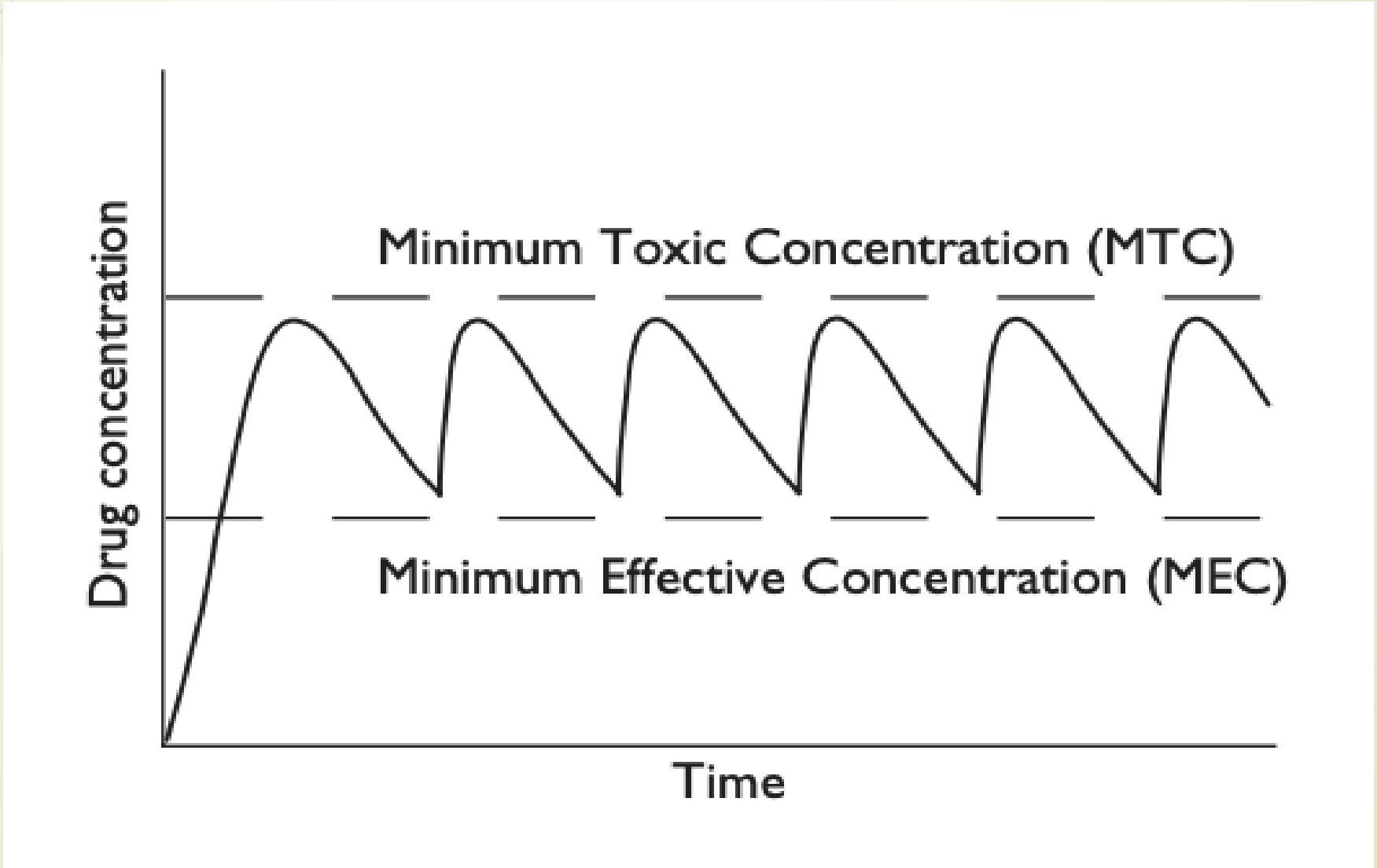
Absorption of the active substance

Distribution through the blood plasma and different body tissues

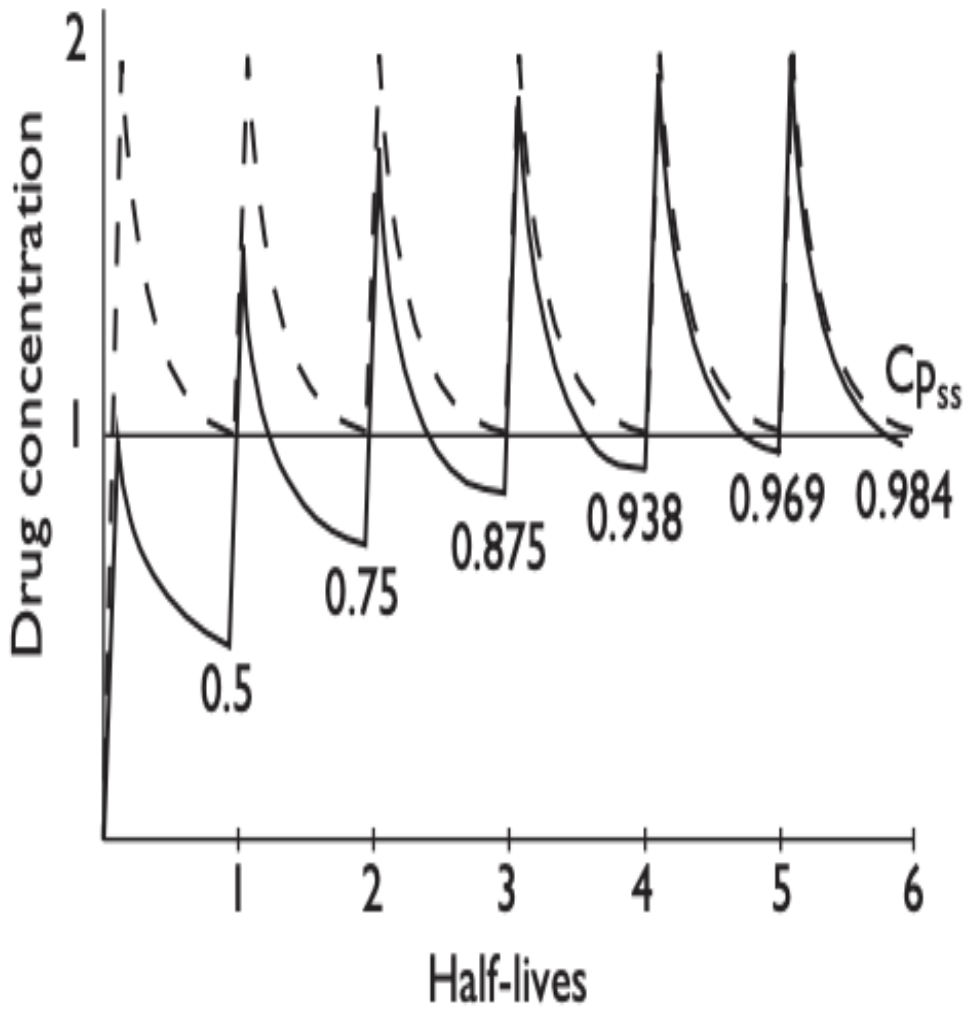
Metabolism inactivation of the xenobiotic substance

Excretion or elimination of the substance or the products

Pharmacokinetics



Pharmacokinetics



LD enables steady-state concentrations to be achieved quickly

Top curve – LD followed by maintenance dosing every t½

Bottom curve – maintenance dosing every t½ (i.e. no LD)