Erythrocytes take up carbon dioxide and release oxygen

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

28/12/2022
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 83

This document contains 1 pathway and 8 reactions (see Table of Contents)
Carbon dioxide (CO2) in plasma is hydrated to yield protons (H+) and bicarbonate (HCO3-) by carbonic anhydrase IV (CA4) located on the apical plasma membranes of endothelial cells. Plasma CO2 is also taken up by erythrocytes via AQP1 and RhAG. Within erythrocytes CA1 and, predominantly, CA2 hydrate CO2 to HCO3- and protons (reviewed in Geers & Gros 2000, Jensen 2004, Boron 2010). The HCO3- is transferred out of the erythrocyte by the band 3 anion exchange protein (AE1, SLC4A1) which cotransports a chloride ion (Cl-) into the erythrocyte.

Also within the erythrocyte, CO2 combines with the N-terminal alpha amino groups of HbA to form carbamates while protons bind histidine residues in HbA. The net result is the Bohr effect, a conformational change in HbA that reduces its affinity for O2 and hence assists the delivery of O2 to tissues.

**Literature references**


**CA4:Zn2+ hydrates CO2 to HCO3-**

**Location:** Erythrocytes take up carbon dioxide and release oxygen

**Stable identifier:** R-HSA-1237047

**Type:** transition

**Compartments:** plasma membrane, extracellular region

Carbonic anhydrase IV (CA4) anchored to extracellular face of the plasma membrane (Wistrand et al. 1999) hydrates carbon dioxide (CO2) to yield bicarbonate (HCO3-) and a proton (H+) (Zhu & Sly 1990, Okayuma et al. 1992, Baird et al. 1997, Innocenti et al. 2004). During the reaction a hydroxyl group bound by the zinc ion (Zn2+) of CA4 attacks the CO2 molecule to directly form HCO3- (reviewed in Lindskog 1997). The HCO3- is displaced by water, which is then deprotonated by a histidine residue to recreate the Zn2+-hydroxyl group. Depending on the concentrations of reactants the reaction is reversible.

**Literature references**


**Editions**

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Aquaporin-1 (AQP1) passively transports carbon dioxide (CO2) across the plasma membrane according to the concentration gradient (Nakhoul et al. 1998, Blank & Ehmke et al. 2003, Endeward et al. 2006, Musa-Aziz et al. 2009). The pore in AQP1 that conducts CO2 may be distinct from the pore that conducts water.

Followed by: CA1:Zn2+, CA2:Zn2+ hydrate CO2 to HCO3−, Hemoglobin A is protonated and carbamated causing release of oxygen

Literature references


Editions

2011-03-24 Authored, Edited May, B.
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RHAG transports CO2 from extracellular region to cytosol

**Location:** Erythrocytes take up carbon dioxide and release oxygen

**Stable identifier:** R-HSA-1237069

**Type:** transition

**Compartments:** plasma membrane, extracellular region, cytosol

The Rhesus blood group type A glycoprotein (RhAG) passively transports carbon dioxide (CO2) across the plasma membrane according to the concentration gradient (Endeward et al. 2006, Endeward et al. 2008, Musa-Aziz et al. 2009).

**Followed by:** Hemoglobin A is protonated and carbamated causing release of oxygen, CA1:Zn2+,CA2:Zn2+ hydrate CO2 to HCO3-

**Literature references**


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**CA1:Zn²⁺,CA2:Zn²⁺ hydrate CO₂ to HCO₃⁻**

**Location:** Erythrocytes take up carbon dioxide and release oxygen

**Stable identifier:** R-HSA-1475435

**Type:** transition

**Compartments:** cytosol

Carbonic anhydrase I (CA1, Khalifah 1971, Pesando 1975, Simonsson et al. 1982, Ren & Lindskog 1992) and carbonic anhydrase II (CA2, Tibell et al. 1984, Jones & Shaw 1983, Ghannam et al. 1986) hydrate carbon dioxide (CO₂) to yield bicarbonate (HCO₃⁻) and a proton (H⁺). During the reaction a hydroxyl group bound by the zinc ion (Zn²⁺) attacks the CO₂ molecule in the active site to directly form HCO₃⁻ (reviewed in Lindskog 1997). The HCO₃⁻ is displaced by water, which is then deprotonated by a histidine residue to recreate the Zn²⁺:hydroxyl group. Depending on the concentrations of reactants the reaction is reversible.

**Preceded by:** RHAG transports CO₂ from extracellular region to cytosol, AQP1 tetramer transports CO₂ from extracellular region to cytosol

**Followed by:** SLC4A1 exchanges cytosolic HCO₃⁻ for extracellular Cl⁻

**Literature references**


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CA1:Zn2+,CA2:Zn2+ bind CA inhibitors

Location: Erythrocytes take up carbon dioxide and release oxygen

Stable identifier: R-HSA-9707419

Type: binding

Compartments: cytosol

Erythrocytes take up oxygen and release carbon dioxide in the capillaries of the lung. In other tissues of the body the reverse reaction occurs; erythrocytes take up carbon dioxide from and deliver oxygen to cells. Carbonic anhydrases (CAs) are metalloenzymes that catalyze the interconversion between carbon dioxide (CO2) and water (H2O) and the dissociated ions of carbonic acid, i.e. bicarbonate (HCO3-) and protons (H+). The active site of most CAs contains a zinc ion. CAs maintain acid-base balance and help transport carbon dioxide. Depending on the concentrations of reactants, the reaction is reversible.

Carbonic anhydrase inhibitors have been developed to treat glaucoma via their effect on reducing intraocular pressure and decreasing aqueous humor and in managing seizures in various epileptic conditions (Supuran et al. 2003). In the ocular ciliary processes, the local production of bicarbonate by CAs promotes sodium and fluid transport. CA2 is a key isoenzyme found primarily in red blood cells (RBCs) that regulates aqueous humour production (Balfour et al. 1997, Hasegawa et al. 1994). The inhibition of CA2 in the ciliary process disrupts the formation of bicarbonate ions and reduces sodium and fluid transport, which leads to decreased aqueous humour secretion and reduced intraocular pressure (Sugrue 1996, Sugrue 2000, Iester 2008). Brinzolamide, dorzolamide, diclofenamide, ethoxzolamide and methazolamide are topical carbonic anhydrase (CA) inhibitors that treats elevated intraocular pressure (IOP) associated with open-angle glaucoma and ocular hypertension (Mincione et al. 2008).

Acetazolamide, topirimate, sultiame and zonisamide are effective in the treatment of most types of seizures, including generalized tonic-clonic and focal seizures and absence seizures (Hamidi & Avoli 2015, Aggarwal et al. 2013). They are thought to reduce seizures through the inhibition of CA, thereby increasing CO2 levels in the brain.

Literature references


SLC4A1 exchanges cytosolic HCO3- for extracellular Cl-

**Location:** Erythrocytes take up carbon dioxide and release oxygen

**Stable identifier:** R-HSA-1237038

**Type:** transition

**Compartments:** plasma membrane, extracellular region, cytosol

The band 3 anion exchange protein (AE1, SLC4A1) exchanges chloride (Cl-) for bicarbonate (HCO3-) across the plasma membrane according to the concentration gradients of the anions (Knauf et al. 1996, Dahl et al. 2003). SLC4A1 may be part of a complex ("metabolon") with carbonic anhydrase II (CA2) which would facilitate the transport of HCO3- (Sterling et al. 2001).

**Preceded by:** CA1:Zn2+, CA2:Zn2+ hydrate CO2 to HCO3-

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Hemoglobin A is protonated and carbamated causing release of oxygen

**Location:** Erythrocytes take up carbon dioxide and release oxygen

**Stable identifier:** R-HSA-1237325

**Type:** binding

**Compartments:** cytosol

The Bohr effect refers to the observation that carbon dioxide (CO2) decreases the affinity of hemoglobin (HbA) for oxygen (O2) (Rossi-Bernardi & Roughton 1967, Kwant et al. 1988, Dash & Bassingthwaigthe 2010). The Bohr effect has two components: protonation of histidines in HbA (Chatake et al. 2007, Kovalevsky et al. 2010, Fang et al. 1999) and chemical reaction (carbamation) of the N-terminal valines of HbA by CO2 (Ferguson & Roughton 1934, Forster et al. 1968, Bauer & Schroder 1972, Morrow et al. 1973, Morrow et al. 1976, Mathew et al. 1977, Acharya et al. 1994). The protons (H+) for this reaction are produced by carbonic anhydrase acting on water and CO2 to produce bicarbonate (HCO3-) and H+ (Kernohan & Roughton 1968).

**Preceded by:** RHAG transports CO2 from extracellular region to cytosol, AQP1 tetramer transports CO2 from extracellular region to cytosol

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NADH-Cytochrome b5 reductases (CYB5Rs), flavoproteins consisting of NADH and flavin adenine dinucleotide (FAD) binding domains, catalyse electron transfer from the two-electron carrier NADH to the one-electron carrier ferricytochrome b5 ((Fe(3+)Cb5), forming ferrocytochrome b5 ((Fe(2+)Cb5) (Zhu et al. 1999, Baker et al. 2005, Zhu et al. 2004). CYB5Rs participate in fatty acid synthesis, cholesterol synthesis and xenobiotic oxidation as members of the electron transport chain on the endoplasmic reticulum membrane. In erythrocytes, CYB5Rs participate in the reduction of methemoglobin (MetHb) to hemoglobin A (HbA).

**Literature references**


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