**Table 1 Effects of hypoxia on CYP expression**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Family | Cytochrome | Xenobiotic substrate | Endogenous substrate | Effects | Method | Refs |
| CYP1 | CYP1A1 | Benzo[a]pyrene | Hormones (17β-estradiol ),  Melatonin ,  Arachidonic acid,  Eicosapentoic acid | Protein ↓ | Rabbits placed in a Plexiglas chamber (0.75× 1.20 × 1.25 m3) with a FiO2 of 8% for 48 h | (Fradette et al., 2007) |
| Protein ↓ , mRNA ↓ , | HepG2 and HaCaT cells were incubated at 1% O2 for 8 h or 16 h | (Vorrink et al., 2014) |
| CYP1A2 | Phenacetin,  Caffeine,  Clozapine,  Tacrine,  Propranolol,  Mexiletine,  Aflatoxins,  Mycotoxins,  Nitrosamines | Hydrocarbons，  Steroids | Protein ↓ | Rabbits placed in a Plexiglas chamber (0.75× 1.20 × 1.25 m3) with a FiO2 of 8% for 48 h | (Fradette et al., 2007) |
| mRNA ↑ | Threespine stickleback were exposed to hypoxia (24-28% air saturation) for 48 h and microarray measurements were performed | (Leveelahti et al., 2011) |
| Activity ↓ , Protein ↓ , mRNA ↓ | Rats were modeled in high-altitude hypoxia and divided into AMH, CMH, AHH, and CHH | (Li et al., 2014) |
| Activity ↓ , Protein ↓ | Rats were exposed to high-altitude hypoxic environment at 4,300 m for 3 d | (Wang et al., 2017) |
| CYP1B1 | Aromatic amines,  Polycyclic aromatic,  Hydrocarbons | Eicosanoids,  Fat-soluble vitamins,  Steroids,  Bile acids | Protein ↑ , mRNA ↑ | SERT+ (overexpressing the serotonin transporter) mice were exposed to hypobaric hypoxia (10% O2) for 14 d | (White et al., 2011) |
| Protein ↑ , mRNA ↑ | AC16 cell were cultured in a hypoxic (1% O2) incubator for 24 h | (Chen et al., 2024) |
| CYP2 | CYP2B6 | Efavirenz,  Cyclophosphamide,  Bupropion,  Methadone | Arachidonic acid,  Lauric acid,  17β-estradiol,  Estrone,  Ethinylestradiol,  Testosterone | Protein ↓ | Rabbits placed in a Plexiglas chamber (0.75 × 1.20 × 1.25 m3) with a FiO2 of 8% for 48 h | (Fradette et al., 2007) |
| Protein ↓ | DAOY medulloblastoma cells were exposed to moderate (1% O2) or severe (0.1% O2) hypoxic conditions for 24 h | (Valencia-Cervantes et al., 2019) |
| CYP2C8 | Paclitaxel,  Amodiaquine,  Troglitazone,  Amiodarone,  Verapamil,  Ibuprofen, | Arachidonic acid,  Retinoids | Protein ↑ , mRNA ↑ | HUVEC incubated in hypoxia (1% O2) for 1,4,12, and 24 h | (Michaelis et al., 2005) |
| Protein ↑ | Human hepatoma cells, Hep3B, and HUAEC were cultured in hypoxia (1% O2) for 12 h | (Suzuki et al., 2008) |
| mRNA ↑ | Human retinal astrocytes, Mu ̈ller cells, and HRMEC were exposed to hypoxia (0.1% O2) for 24 h | (Capozzi et al., 2014) |
| CYP2C9 | Tolbutamide,  Glyburide,  Diclofenac,  Celecoxib,  Torasemide,  Phenytoin losartan,  S-warfarin | Steroids,  Melatonin,  Retinoids,  Arachidonic acid | mRNA ↑ , Protein ↑ | Primary cultured astrocytes were incubated under normoxic or hypoxic conditions for 1, 3, 6, 24, or 48 h | (Liu et al., 2005) |
| Protein ↓ | Rabbits placed in a Plexiglas chamber (0.75 × 1.20 × 1.25 m3) with a FiO2 of 8% for 48 h | (Fradette et al., 2007) |
| mRNA ↑ | Huh-7 cells incubated under hypoxic culture conditions (1% O2) | (Myung et al., 2012) |
| Protein ↓ | Rats were exposed to simulated altitude of 7,620 m (∼25,000 ft) for AHH exposure (6 and 24 h) in a decompression chamber | (Gola et al., 2013) |
| Activity - , Protein - | Rats were modelled in high-altitude hypoxia and divided into AMH, CMH, AHH, and CHH | (Li et al., 2014) |
| Protein ↑ | Rats rapid arrival at 4,010 m plateau hypoxia 24 h | (Huang et al., 2022) |
| CYP2C19 | Omeprazole,  Clopidogrel,  Citalopram | Arachidonic acid | Protein ↓ | Rabbits placed in a Plexiglas chamber (0.75 × 1.20 × 1.25 m3) with a FiO2 of 8% for 48 h | (Fradette et al., 2007) |
| Activity ↑ (AHH) , Protein ↓ | Rats were modelled in high-altitude hypoxia and divided into AMH, CMH, AHH, and CHH | (Li et al., 2014) |
| CYP2D6 | Tamoxifen,  Gefitinib,  Cyclophosphamide,  Bufuralol | Arachidonic acid | Activity ↓ | Healthy subjects who lived at sea level were exposed to altitude-induced hypoxia for 7 days at 4,559 m above sea level | (Jürgens et al., 2002) |
| Activity ↑ (CMH, CHH) , Protein ↑ (CMH, CHH) , mRNA(AMH ↓ ,AHH, CHH ↑ ) | Rats were modelled in high-altitude hypoxia and divided into AMH, CMH, AHH, and CHH | (Li et al., 2014) |
| CYP2E1 | Chlorzoxazone,  Acetaminophen,  Isoniazid,  Chlorzoxazone,  Prilocaine,  Lidocaine | Arachidonic acid | Activity ↓ (CMH, CHH) , Protein ↓ (CHH) , mRNA ↓ (CMH, CHH) | Rats were modelled in high-altitude hypoxia and divided into AMH, CMH, AHH, and CHH | (Li et al., 2014) |
| CYP2S1 | Benzo[a]pyrene-7,8-diol,  Naphthalene,  AQ4N | Eicosanoids,  Retinoic acid,  Retinoid,  Arachidonic acid,  Linoleic acid,  Eeicosapentaenoic acid | Protein ↑ , mRNA ↑ | HepG2 and Hep3B were incubated in a hypoxic chamber at 1% of O2 and 5% CO2 during 0, 6, 12, 18, and 24 h | (Cabrera-Cano et al., 2021) |
| CYP2R1 |  | Vitamin D3 | mRNA ↑ | Nonpregnant ewes, near-term pregnant ewes, and their fetuses exposed to normoxia (low altitude) or hypoxia (3,820 m) for 100 d | (Goyal et al., 2016) |
| CYP2J2 | Astemizole,  Terfenadine | Arachidonic acid,  Vitamin D3 | Protein ↓ , mRNA ↓ | HRVECs were stimulated with hypoxia (1% O2) for 24 h | (Zhang et al., 2021) |
| CYP3 | CYP3A4 | Midazolam,  Rivaroxaban,  N-nitrosonor-nicotine | Steroid,  Bile acid,  Cholesterol,  Lipid,  Hormones,  Vitamin D3 | Activity ↓ | Healthy subjects who lived at sea level were exposed to altitude-induced hypoxia for 7 days at 4,559 m above sea level | (Jürgens et al., 2002) |
| Protein ↑ | Rats placed in a Plexiglas chamber (0.75× 1.20 × 1.25 m3) with a FiO2 of 8% for 48 h | (Fradette et al., 2007) |
| mRNA ↓ | HFL cells were exposed to 3% O2 for 72 h | (Suzuki et al., 2012) |
| Activity ↓ (CMH, CHH) , Protein ↓ (CMH, CHH) , mRNA ↓ (CMH, CHH) | Rats were modelled in high-altitude hypoxia and divided into AMH, CMH, AHH, and CHH | (Li et al., 2014) |
| Activity ↓ （CHH）, Protein ↓ （CHH）, mRNA ↓ （CHH） | Rats were modelled in high-altitude hypoxia and divided into CMH and CHH | (Zhang et al., 2016) |
| Activity ↑ , Protein ↓ | Rats were exposed to high-altitude hypoxic environment at 4,300 m for 3 d | (Wang et al., 2017) |
| Protein ↓ | DAOY medulloblastoma cells were exposed to moderate (1% O2) or severe (0.1% O2) hypoxic conditions for 24 h | (Valencia-Cervantes et al., 2019) |
| Protein ↓ , mRNA ↓ | Rats were modelled in high-altitude hypoxia and divided into AHH, CHH and CH-N | (Zhu et al., 2022) |
| CYP3A5 | Diltiazem,  Cyclosporine,  3-acetyl-11-keto-b  boswellic acid (AKBA) | Steroid,  Bile acid,  Progesterone,  Rostenedione | Protein ↓ | DAOY medulloblastoma cells were exposed to moderate (1% O2) or severe (0.1% O2) hypoxic conditions for 24 h | (Valencia-Cervantes et al., 2019) |
| CYP4 | CYP4A11 |  | Arachidonic acid,  Fatty acid,  Lauric acid | Protein ↑ , mRNA ↑ | EPC cells were exposed to 2% O2 | (Chen et al., 2014) |
| Other | CYP7A1 |  | Bile acid biosynthesis | mRNA ↓ | HepG2 cells were incubated in hypoxia (0.1% O2) for 8 or 16 h | (Moon et al., 2016) |
| CYP24A1 |  | Vitamin D | Protein ↑ , mRNA ↑ | HepG2 and Hep3B were incubated in a hypoxic chamber at 1% of O2 and 5% CO2 during 0, 6, 12, 18, and 24 h | (Cabrera-Cano et al., 2021) |
| CYP19A1 |  | Androgens | Protein ↓ , mRNA ↓ | Atlantic croaker exposed to hypoxia (dissolved oxygen, DO: 1.7 mg/L) for 4 w | (Rahmanet al., 2021) |

Note: CYP: Cytochrome; AMH: acute moderate-altitude hypoxia group, 2 800 m, 24 h; CMH: chronic moderate-altitude hypoxia group, 2 800 m, 30 d; AHH: acute high-altitude hypoxia group, 4 300 m, 24 h; CHH: chronic high-altitude hypoxia group, 4 300 m, 30 d; AH: acute hypoxia group, 4 300 m, 3d, CH: chronic hypoxia group, 4 300 m, 30d; CH-N: chronic hypoxia to normoxia groups, 390 and 4 300 m; FiO2: fraction of inspired oxygen; HaCaT: human keratinocyte cells; HepaRG: human hepatoma cell line; HepG2: hepatoma G2; AC16: human cardiomyocytes; HUVEC: Human umbilical vein endothelial cells; HRMEC: retinal microvascular endothelial cells; HFL: Human fetal liver cells; Huh-7: human hepatocellular carcinoma cell line; EPC: Circulating endothelial progenitor cells; O2: oxygen; ↑: Increase; ↓: Decrease

**Table 2 Effects of high-altitude hypoxia on drug metabolis**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug classification | Drug | Clinical use | Method | Species | Changes in pharmacokinetic parameters | | | | | | | Refs |
| t 1/2 | Ke | MRT | Vd | AUC | Cmax | CL |
| Drugs for the prevention and treatment of highland hypoxic diseases | | | | | | | | | | | | |
| Nervous System  Cardiovascular System  Respiratory system | Ibuprofen | High altitude headaches | Exposed to 7,620 m for 6 h or 24 h | Rat | ↑ | - | ↑ | - | - | - | - | (Gola et al., 2013) |
| Exposed to 7,620 m for 7 d or 14 d | Rat | ↑ | - | ↑ | ↑ | ↓ | ↓ | ↓ | (Gola et al., 2016) |
| Acetaminophen | High altitude headaches and acute altitude sickness | Exposure to hypoxia for 4 or 30 d in a low-pressure oxygen chamber at 5,000 m altitude | Rat | ↑ | ↓ | ↑ | ↓ | ↑ | ↑ | ↓ | (Zhu et al., 2021) |
| Nifedipine | Treatment and prevention of HAPE | Modelled in high-altitude hypoxia and divided into AHH, CHH, and CH-N | Rat | ↑ | - | ↑ | ↓ | ↑ | ↑ | ↓ | (Zhu et al., 2022) |
| Sildenafil | Treatment and prevention of HAPE | Modelled in high-altitude hypoxia and divided into AHH, CHH, and CH-N | Rat | - | - | - | ↓ | ↑ | ↑ | ↓ | (Zhu et al., 2022) |
| Dexamethasone | Treatment of moderate and severe progressive altitude sickness, HACE | Exposed to a FiO2 of 9.0% | Rat | ↑ | ↓ | ↑ | - | - | ↓ | - | (Gong et al., 2015) |
| Furosemide | First aid for HACE and HAPE | Acute expose to high altitude at 4,300 m | Rat | ↑ | - | ↑ | - | ↑ | ↑ | ↓ | (Luo et al., 2018) |
| Acetazolamide | Prevention of high altitude headache, acute altitude sickness, central sleep apnea | Exposed to 429 mmHg equivalent to 15,000 feet | Rabbits | ↑ | ↓ | - | - | - | - | - | (Ritschel et al., 1998) |
| Other commonly used drugs | | | | | | | | | | | | |
| Respiratory drugs | Theophylline | Treatment of symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases | Exposed to hypoxia (12% O2 corresponding to the ambient PO2 at an altitude of 4,500 m) | Human | - | - | - | - | - | - | - | (Streit et al., 2005) |
| Salbutamol | Treatment of respiratory diseases with bronchospasm, such as bronchial asthma or wheezing bronchitis | Exposed to hypoxia (10% O2) for 4 d | Rabbits | ↑ | - | - | ↑ | - | - | - | (Perreault et al., 1994) |
| Mosapride | Improvement of gastrointestinal symptoms in non-ulcerative dyspepsia | Acute exposure to a plateau at 4,300 m | Rat | ↑ | - | ↑ | ↑ | ↑ | ↑ | ↓ | (Zhang et al., 2013) |
| Cardiovascular system drugs | Verapamil | Angina pectoris, tardive dyskinesia, essential hypertension, hypertrophic cardiomyopathy | Exposed to hypoxia (12% O2 corresponding to the ambient PO2 at an altitude of 4,500 m) | Human | ↑ | - | - | ↑ | ↑ | ↑ | ↑ | (Streit et al., 2005) |
| Propranolol | Hypertension, exertional angina, arrhythmias, hypertrophic cardiomyopathy, thyroid crisis, migraines | Acute exposure to high altitude at 4,010 m | Rat | ↑ | - | ↑ | ↓ | ↑ | ↑ | ↓ | (Wenbin et al., 2015) |
| Boshentan | pulmonary arterial hypertension | Modelled in high-altitude hypoxia and divided into AHH, CHH, and CH-N | Rat | - | - | ↑ | ↓ | ↑ | ↑ | ↓ | (Zhu et al., 2022) |
| Simvastatin | Secondary prevention of hyperlipidaemia and coronary heart disease | Modelled in high-altitude hypoxia and divided into AHH, CHH, and CH-N | Rat | ↑ | - | ↑ | - | ↑ | ↑ | ↓ | (Zhu et al., 2022) |
| Metoprolol | Hypertension, angina pectoris, myocardial infarction, heart failure, arrhythmia, hypertrophic cardiomyopathy, hyperthyroidism | Acute exposure to high altitude (4,010 m) | Rat | ↑ | - | ↑ | ↓ | - | - | - | (Zhang et al., 2014) |
| Diltiazem | Hypertension, angina pectoris, supraventricular arrhythmia, hypertrophic cardiomyopathy | Exposed to a FiO2 of 0.08 for 1h or 120 h | Dog | - | - | - | ↓ | ↑ | - | ↓ | (du Souich et al., 1993) |
| Clopidogrel | Acute coronary syndrome, peripheral artery disease | Acute exposure to high altitude at 4,100 m | Rat | - | - | - | - | ↑ | ↓ | ↑ | (Zhang et al., 2023) |
| Atorvastatin | Hypercholesterolaemia, coronary heart disease | Exposed for 14 d at an altitude of 5,500 m | Rat | - | - | ↓ | ↓ | ↑ | ↑ | - | (Huang et al., 2023) |
| Amlodipine besylate | Hypertension and stable angina | Plateau-dwelling Tibetan healthy subjects | Human | - | - | - | - | - | ↓ | - | (Zhang et al., 2023) |
| Losartan potassium | Hypertension, heart failure, diabetic nephropathy | Modelled in high-altitude hypoxia and divided into AHH, CHH, and CH-N | Rat | ↓ | ↑ | ↓ | ↑ | ↓ | ↓ | ↑ | (Zhou et al., 2021) |
| Nervous system drugs | Diazepam | Psychiatric or neurological disorders such as anxiety, fear, insomnia, epilepsy and convulsions, anaesthesia | Exposed to a fractional concentration of inspired O2 (FiO2) of 9.0% | Rat | - | - | ↑ | - | ↑ | ↑ | - | (Gong et al., 2015) |
| Phenytoin | Antiepileptic, antiarrhythmic | Acute hypoxia (exposure to hypoxia at 48 mmHg barometric pressure) | Rabbits | - | - | - | - | ↑ | - | ↓ | (du Souich et al., 1986) |
| Phenobarbital | Sedative-hypnotic, anticonvulsant, pre-anaesthetic administration, antihyperbilirubinaemia | Exposed to 429 mm Hg equivalent to 15,000 feet altitude for 5 h/d for 7 d | Rabbits | ↑ | ↓ | - | - | - | - | - | (Vij et al., 2012) |
| Buspirone | Anxiolytic | Acute exposure to high altitude (4,010 m) | Rat | ↑ | - | ↑ | - | ↑ | ↑ | ↓ | (Zhang, 2013) |
| Caffeine | Primary apnea in premature neonates, paediatric hyperactivity disorder | Exposure to high altitude (4,300 m) for 16 d | Human | ↓ | - | - | - | ↓ | - | ↑ | (Kamimori et al., 1995) |
| Lithium carbonate | Mania | Exposure to high altitude (4,360 m) for 24 h or 10 months | Human | ↑ | - | ↑ | ↑ | - | - | ↓ | (Arancibia et al., 2003) |
| Endocrine system drugs | Gliquinone | Type 2 diabetes | Acute exposure to high altitude (4,010 m) for 24 h | Rat | ↑ | ↓ | ↓ | ↓ | - | ↑ | - | (Huang et al., 2022) |
| Metformin | Type 2 diabetes | Exposure to hypoxia for 4 or 30 d in a low-pressure oxygen chamber at 5,000 m altitude | Rat | ↑ | ↓ | ↑ | - | - | ↓ | - | (J. B. Zhu et al., 2021) |
| Prednisolone | Treatment of allergic and autoimmune inflammatory diseases | Exposure to high altitude (3,600 m) for 15 h and 6 months | Human | - | - | - | ↓ | ↑ | ↑ | ↓ | (Arancibia et al., 2005) |
| Miglito | Type 2 diabetes | Acute exposure to high altitude (4,010 m) for 24 h | Rat | ↑ | - | ↑ | - | ↑ | ↑ | ↓ | (Zhang et al., 2023) |
| Antibiotic | Gentamycin | Infections caused by various sensitive bacteria, recurrent mouth sores, traumatic mouth ulcers, conjunctivitis, blepharitis, blepharitis | Exposed to 429 mmHg equivalent to 15,000 feet altitude for 5 h/d for 7 d | Rabbits | ↑ | ↓ | - | - | - | - | - | (Vij et al., 2012) |
| Norfloxacin | Respiratory, urinary and gastrointestinal tract infections caused by sensitive organisms | Acute exposure to high altitude 4,300 m for 3 d | Rat | ↓ | ↓ | ↑ | ↑ | ↓ | ↓ | ↑ | (Luo et al., 2017) |
| Sulfamethoxazole | Broad-spectrum antimicrobials, suitable for the treatment of infections caused by sensitive bacteria | Exposure to high altitude (3,800 m) for 16 h or 1 year | Human | ↑ | - | - | - | ↑ | - | ↓ | (Li et al., 2009) |
| Amoxicillin | Against Gram-positive and Gram-negative organisms | Acute exposure to high altitude 4,300 m for 24 h | Rat | ↑ | - | ↑ | - | ↑ | ↑ | ↓ | (Luo et al., 2017) |
| Metronidazole | Infections caused by anaerobic bacteria | Acute exposure to a plateau at 4,300 m | Rat | - | - | - | ↑ | ↓ | ↓ | ↑ | (Xie, 2021) |
| levofloxacin | For the treatment or prevention of infections caused by sensitive bacteria | Acute exposure to a plateau at 4,300 m | Rat | - | - | ↑ | - | ↑ | ↑ | ↓ | (Wang et al., 2017) |
| Others | Methazolamide | For chronic open-angle glaucoma, secondary glaucoma, preoperative treatment of acute closed-angle glaucoma | Acute exposure to high altitude (4,010 m) | Rat | - | - | - | - | - | - | - | (Zhang, 2013) |
| Indocyanine green | Diagnostic medication | Exposure to high altitude (4,300 m) for 16 d | Human | - | - | - | ↑ | ↓ | - | ↑ | (Kamimori et al., 1995) |
| Meperidine | Analgesic, sedative | Exposure to high altitude (4,360 m) for 1 d or 10 months | Human | - | - | ↑ | - | - | - | ↓ | (Ritschel et al., 1996) |
| Lidocaine | Local anaesthesia, antiarrhythmic, anticonvulsant | Chinese and Tibetan volunteers living at an altitude of 2,200 ~ 4,500 m | Human | ↑ | - | ↑ | ↑ | - | - | ↓ | (Zhang et al., 2016) |
| Propofol | Anaesthetic | Exposure to high altitude (3,831 m), mid altitude (2,270 m) and plains (400 m) for 1 month | Rat | ↑ | - | ↑ | - | ↑ | ↑ | ↓ | (Li et al., 2024) |

*Cmax*: peak plasma concentration; *t1/2*: plasma half-life; AUC: area under the concentration-time curve from the time of dosing to the end of the observation period; CL: clearance; *Vd*: volume of distribution; MRT: mean residence time; *Ke*: elimination rate constant; AHH: acute high-altitude hypoxia group, 4 300 m, 24 h; CHH: chronic high-altitude hypoxia group, 4 300 m, 30 d; CH-N: chronic hypoxia to normoxia groups, 390 and 4 300 m; FiO2: fraction of inspired oxygen.