

# Index

## A

### Absorption

- caffeine, 35–36, 218
- paraxanthine, 73
- theobromine, 66–67, 205, 211
- theophylline, 55, 58

### Abuse potential, 488–490, 492

### Accessory proteins, 272, 293

### ACE inhibitor, 400

### Acetaminophen, 312, 316–318, 323–325, 477

### Acrosome reaction, 355

### Additives, 96, 114, 491, 493, 497, 499

### Adenosine

- and caffeine, sleep, 40, 213, 338–344

- deficiency, 255–257

- receptor, 470, 473, 474

- sleep

  - basal forebrain adenosine concentration, 337

  - circadian variation, 336–338

  - genetic variation, ADA, 338

  - vigilance-state-related variation, 336

### Adenosine deaminase (ADA), 107, 338, 461

### Adenosine receptors, 102, 415–423, 444–449.

*See also* Neurodegeneration

- accessory proteins, 272, 293

- antagonism, 102, 163, 206, 255, 258, 261, 269, 270, 311, 315, 323, 375, 376, 382, 413, 415–417, 419, 439, 444–449, 458, 470, 473, 475, 492, 495, 496, 510, 516, 523, 524, 526, 527, 540

- A<sub>2A</sub>R, 73, 135, 143, 172–177, 206, 207, 257, 270, 311, 315, 316, 318, 320, 325, 336, 338–341, 343, 375, 376, 382, 384, 394, 397, 415–418, 420, 459,

  - 462, 463, 469, 470, 473, 474, 476, 477, 487, 491, 492, 495, 496, 499

- G-protein-coupled receptors, 271–272, 293, 382, 447, 529

- isoforms, 102, 523

- A<sub>1</sub>R, 135, 136, 142, 158–172, 206, 215, 217, 236, 255, 270, 311, 314, 315, 318, 320–322, 325, 339–340, 356, 363, 364, 375, 376, 380, 382–384, 392, 394–398, 401–404, 415–418, 420, 421, 424, 473, 487

- A<sub>2</sub>R, 73, 135, 143, 172–177, 206, 207, 257, 270, 311, 315, 316, 318, 320, 325, 336, 338–341, 343, 375, 376, 382, 384, 394, 397, 399, 15–418, 420, 459, 462, 463, 469, 470, 473, 474, 476, 477, 487, 491, 492, 495, 496, 499, 523

- A<sub>2B</sub>R, 315, 316, 320, 323, 415–417, 446, 447, 458–460, 462

- A<sub>3</sub>R, 216, 375–377, 415–418, 445, 447, 458–460, 473

### ADHD, 383

### Adipose tissue

- FFA mobilization, 525, 527, 537
- lipolysis, 527

### Adjuvant, 235, 312, 313, 316, 318, 323–325, 464, 477

### Adolescence, 376, 384

### Adrenal medulla, 525–526

### Age

- caffeine, 9, 36, 41–42, 46, 48, 51, 253, 286, 363, 365–366, 383, 384, 393, 533–534

- theophylline, 59, 60, 62–63, 65, 253, 379

### Airway smooth muscle (ASM), 105, 439, 442, 444–447

- Alcohol, caffeine, 46–47, 103, 362, 363, 471, 472, 532,
- Alzheimer's disease (AD)  
 A<sub>2A</sub> AR antagonists, 174  
 caffeine-induced beneficial effects, 539–540  
 experimental studies, 282–284  
 human studies, 282–283
- Aminophylline, 60, 145, 252–254, 260, 277, 314, 320, 321, 344, 373, 375, 395, 397, 401, 402, 420, 421, 442, 446, 447, 449, 532
- Amphetamine, 220, 221, 287, 288, 421, 486, 488, 489, 491–494, 501
- Analgesic, 187, 312–314, 316, 318, 321–325, 342, 384
- Anandamide, 202, 222–223
- Angiotensin II, 423, 424
- Antagonists, 143, 144, 151–187, 206, 207, 217, 219, 236, 237, 240, 251, 254, 257, 258, 261, 271, 272, 274, 277, 278, 281–288, 290, 292, 311–313, 315, 316, 318, 320, 322, 340, 356, 380, 392, 395–398, 401–403, 415, 416, 420, 445, 446, 458–460, 464, 474–477, 492, 498–499, 513, 522, 532
- Antiasthmatic, 156, 177, 187, 484
- Antibiotics, fluoroquinolone, 254
- Anticonvulsant, 251, 253–257, 259–261, 313, 322
- Antidepressants, 45, 222, 313, 321–322, 500
- Antioxidants, 202, 203, 260, 427, 511, 521, 530, 535, 537, 538, 540
- Antipsychotics, 45, 271, 500
- Apaxifylline, 163, 164
- Apnea/apnoea, 187, 374–377, 379–385  
 of prematurity, 374, 375, 377, 380–381, 383–385, 450
- Arrhythmias, 167, 253, 417, 421, 449
- Arterial stiffness, 420, 421, 429
- Aspirin, 312, 316–318, 323, 324
- Astemizole, 254
- Asthma, 8, 9, 41, 59, 104, 105, 162, 167, 177, 178, 215, 216, 252, 254, 375, 392, 439–451, 461, 462, 484, 487
- Astrocytes, 237, 240–242, 244–247, 256, 273, 376
- Atherosclerosis, 429
- ATL–802, 158, 178
- ATL–852, 158, 178
- Atropine, 253
- B**
- Barbiturates, 500
- Benzodiazepines, 253, 259, 269, 500
- BG–9719, 163, 164
- BG–9928, 163, 164
- Bioavailability  
 caffeine, 35, 36, 42, 381  
 8-cycloalkylxanthines, 163  
 1,8-disubstituted xanthenes, 179  
 theophylline, 58, 381
- Biotin conjugates, 183, 186
- Birth, 42, 46, 63, 67, 362–366, 374, 376, 378–380, 382, 384, 404
- Blood–brain barrier (BBB), 37, 67, 73, 224, 275–276, 284, 288, 291
- Blood pressure, 219, 220, 268, 332, 376, 396, 399, 414, 417–419, 423–426, 429, 486, 520, 521, 531, 532, 535
- Breast feeding, 379–380, 382, 383
- Bronchitis, 215, 252
- C**
- Cacao (*Theobroma cacao*), 7, 12–15, 18, 25, 204–206, 211
- Café Procope, 4
- Caffeinated energy drinks, 143, 252, 253, 280, 286, 378, 393, 422, 424, 427, 472, 487, 495, 496, 511, 520–532, 535, 538–540
- Caffeine (1,3,7-trimethylxanthine), 152–158, 169, 174, 180, 187, 252–254, 258–261, 470–477. *See also* Neurodegeneration  
 absorption, 35–36, 218  
 animals, 35, 36, 38, 39, 45, 51–53, 56–57, 352, 361, 362, 366  
 biosynthesis, 15, 17–21, 23, 25, 27  
 catabolism, 12, 23–25  
 decaffeinated coffee, 12, 26–27, 40, 342, 378, 421, 422, 424, 427, 472, 518, 520–522, 525, 530, 535, 538, 539  
 degradation, 19, 25  
 discovery, 96  
 distribution, 36–38, 42–45  
 ecological role, 26  
 European multicentre study, 362  
 excretion, 38–39  
 habituation, 520, 535  
 human intake, 268–269  
 humans, 361–363, 366  
 LD50 caffeine, 353, 362  
 long-lasting behavioural effects, 363, 364

- maternal/fetal genotype, 37, 42, 52, 361, 378, 380, 382–384
- metabolism, 41–51
- metabolites and metabolic pathway, 51–57
- molecular targets
  - adenosine receptors, 270–272
  - non-adenosine receptors, 269–270
  - psychostimulant effect, 219, 268, 484, 489,
- neurodegenerative disorder
  - Alzheimer's disease (AD), 281–284, 536, 540
  - Huntington's disease, 289–291
  - multiple sclerosis (MS), 291–292
  - Parkinson's disease (PD), 143, 144, 284–288, 539, 540
  - stroke, 275–279, 281, 293, 532
  - traumatic brain injury, 38, 279–281
- Parkinson's disease, 143, 144, 284–288, 539, 540
- pharmacokinetics, 3–41
- psychopharmacological activity in
  - chocolate, 202–215, 217–219, 225, 226
- risk of developing, 143
- sleep
  - adenosine A<sub>2A</sub> receptors, 340–341
  - adenosine A<sub>1</sub> receptors, 339–340
  - animals, 341
  - CNS and sleep regulation, 338
  - humans, 337, 341–343
  - human sensitivity, 343–344
  - mechanisms, 338–341
  - methylxantines effects, 344–345
  - performance, 343
  - withdrawal syndromes, 344
- sources of variation, pharmacokinetics and metabolism
  - age, 41–42
  - diet and alcohol, 46–47
  - disease, 45
  - drugs, 44–45
  - gender and hormones, 42–43
  - obesity, 43–44
  - physical exercise, 43
  - smoking, 46
- treatment, 365
- Calcineurin inhibitors, 392, 402
- Calcium, 99, 102, 107, 137, 139, 141–144, 206, 217, 237, 238, 260, 268–270, 272–274, 355, 356, 362, 382, 393, 394, 399, 401, 415, 417, 421, 422, 444–447, 460, 523, 539
- Ca<sup>2+</sup> mobilization, 139, 260, 355, 415, 460, 527
- cAMP. *See* Cyclic AMP
- Cancer, 469–477
  - bladder, 538–540
  - breast cancer, 536, 538, 540
  - colorectal cancer, 538, 540
  - liver cancer, 538–540
  - lung, 538–540
- Cannabis, 222, 223, 495, 501
- Capacitation, 355–357, 365
- Carbamazepine, 253, 322–324
- Carbohydrate homeostasis, 512–522, 527, 529–531
- Cardiac function
  - bradycardia, 253, 380
  - cardiac, 257
  - cardiac arrest, 209, 253
  - diabetic cardiac autonomic neuropathy, 253
- Cardiovascular, 378, 383–384
- Cardiovascular disease (CVD)
  - cardiovascular mortality, 421, 428, 532
  - coronary heart disease, 414, 421, 426–429, 532, 535
  - CVD risk, 414, 425–427, 510, 511, 532, 535, 536
  - stroke, 276, 532
- Cardiovascular effects, 215, 350, 362, 384, 413–429, 511
- CD39, 458, 473
- CD73, 291, 458, 473
- CEBPβ, 459
- Cerebral blood flow, 237, 277, 281, 487
- Chemoreceptors, 382, 417, 418
- Child, 59, 60, 63, 64, 76, 174, 258, 324, 362, 375, 381, 384, 402, 446
- China, 1, 2, 5, 6, 50, 96, 511
- Chocolate, 7, 15, 36, 67–69, 71, 201–203, 205, 207–217, 219–226, 345, 365, 366, 380, 424, 484, 488, 489, 511
- Cholesterol, 276, 284, 354, 356, 414, 426, 427, 429, 521, 536
- Cholinergic mechanisms, 316, 334
- Chronic obstructive pulmonary disease (COPD), 104, 105, 215, 458, 461, 462
- Cialis™, 94
- Cirrhosis, 45, 65, 470–472, 475, 477
- Cisplatin, 392, 402–403
- Cizolirtine, 322–324
- Clinical studies, 44, 104, 163, 235, 246, 247, 252, 253, 257, 280, 285–287,

- 312–325, 362, 374, 375, 404, 443, 446, 449, 450, 461, 470, 473–475
- CNS stimulant, 187, 202, 203, 219, 253, 254, 512, 525, 526
- Cocaine wanting, 494
- Cocoa (*Theobroma cocoa*), 201–226
- Coffee, 96, 102, 103, 105, 393, 398, 414, 415, 418, 421, 422, 424–429, 471–473, 475
- acute consumption, 518, 532
- bioactive compounds
- chlorogenic acid (CGA), 427, 475, 521, 522, 528, 530, 535, 537, 538
  - quinides, 521, 522, 529, 535, 537
  - trigonelline, 475, 521
- boiled/unfiltered, 426, 511, 522, 536, 537
- caffeinated, 143, 252, 253, 280, 286, 378, 393, 422, 424, 427, 472, 487, 495, 496, 511, 520–532, 535, 538–540
- Coffea arabica*, 13, 17, 20, 21, 25, 27, 28, 72
- Coffea canephora*, 13, 22, 27, 28
- Coffea eugenioides*, 13, 25
- decaffeinated, 12, 26–27, 40, 342, 378, 421, 422, 424, 427, 472, 518, 520–522, 525, 530, 535, 538, 539
- filtered, 426, 427, 511, 522, 536
- low caffeine coffee, 13, 25, 27, 28, 39
- method of brewing, 426, 521, 536, 537
- regular consumption, 42, 47, 269, 282, 288, 293, 342, 357, 414, 415, 418, 421, 424, 425, 518, 520, 521, 530, 532, 535
- Cognitive dysfunction, 174, 285
- Conditioned place preference (CPP), 488, 493, 499
- Constantinople, 3
- Coronary heart disease, 414, 421, 426–429, 532, 535
- Cortical excitability, 334
- C-peptide, 529, 531
- CPFPX, 185
- CPX, 163, 164
- CREB, 274, 290, 459
- CSC, 167, 175, 186, 274, 278, 287
- Cumulus cell
- DNA methylation pattern, 365
  - nuclear remodelling, 365
  - somatic cell nuclear transfer embryos, 365
- CVD. *See* Cardiovascular disease
- CVT124, 163
- CVT–6883, 157, 178
- Cyclic AMP (cAMP), 393, 472, 473, 475, 523, 525, 527
- Cyclic AMP dependent protein kinase, 96, 109
- Cyclic AMP syn and anti conformations, 109–111
- Cyclic GMP dependent protein kinase, 108, 109, 112
- Cyclic GMP syn and anti conformations, 109–111
- Cyclic nucleotide gated channels, 107–109, 111
- Cycloaddition, 176
- Cyclosporine, 402
- Cytokines, 242–244, 247, 275, 280, 281, 284, 335, 443, 448, 459, 463, 472–476
- D**
- Dantrolene, 141–144
- D2 dopamine receptors, 186, 271, 272, 285, 288
- 9-Deaxanthines, 169, 170, 179
- Diabetes, 45, 65, 178, 414, 427
- Diabetes, Type II (T2D)
- gestational diabetes, 521
  - global health problem, 511
  - lifestyle intervention, 512
  - relative risks, 427, 520, 531, 534, 535
- Diazepam, 253, 254, 259
- Diet
- caffeine, 46–47, 214, 276, 312, 414, 424–429
  - theobromine, 71, 206, 207, 354
- Dihydroimidazo[2,1-*i*]purinones, 170
- Dimethylxanthines
- paraxanthine, 13, 17, 18, 21, 34, 35, 37, 38, 40–42, 44–53, 55–57, 66, 68, 72–76, 96, 102, 136, 140, 143–145, 152, 206, 207, 280, 393, 416, 484, 522
  - theophylline, 9, 13, 35, 96, 136, 152, 206, 237, 252, 277, 314, 340, 353, 375, 392, 415, 440, 458, 484, 516 (see also Theophylline)
- 1,3-Dipropyl-8-cyclopentylxanthine (DPCPX), 162, 163, 169–171, 184, 185, 258, 278, 287, 290, 322, 395, 396, 398, 401, 403
- Disease
- caffeine, 45, 399, 400, 402, 427–429, 471–477, 531–540
  - theophylline, 65, 401
- Distribution
- caffeine, 36–38
  - paraxanthine, 73
  - theobromine, 67–68

- theophylline, 58–59  
 Diuretics, 9, 102, 167, 203, 217, 218, 391, 393, 395, 402, 420, 423, 441  
 DMPX, 153, 155, 157, 174–177, 186  
 Dopamine receptors, 271, 288, 384, 487–489, 491, 492  
 Doxofylline, 155, 395  
 DPCPX. *See* 1, 3-Dipropyl-8-cyclopentylxanthine; 1,3-Dipropyl-8-cyclopentylxanthine  
 DPSPX, 158  
 Drug-discrimination/discriminative, 212, 491, 493, 497, 498,
- Drugs**  
   caffeine, 44–45  
   theobromine, 71  
   theophylline, 64–65  
 Dyskinesia, 175, 284, 286, 288
- E**  
 Ecstasy, 493  
 Electroencephalogram (EEG)  
   homeostatic regulation, 333  
   human vigilance states, 332  
   low EEG frequencies, 333  
 Embryonic development  
   blastocyst rate, 364  
   dibutyl AMP (dbcAMP), 364  
   follicle-stimulating hormone (FSH), 354, 359, 362–364  
   3-isobutyl-1-methylxanthine (IBMX), 360, 361, 364  
   meiotic potential, 364  
 Encapsulated fibroblasts, 257  
 Endothelial dysfunction, 535  
 Energy drinks, 102, 103, 253, 424, 490, 495, 496  
 Enprofylline, 100, 155, 177, 178, 395, 402, 416, 446, 463  
 EPAC, 108, 109, 111, 459  
 Epilepsy, 252–257, 259, 260  
 Epinephrine, 95, 96, 398, 422, 423, 425, 429, 446, 525–528, 531, 532, 537  
 Equilibrative nucleoside transporters, 256, 404, 420  
 Erectile dysfunction, 106  
 Ethanol intoxication, 495, 496, 501  
 Ethiopia (ethiopian), 2–4, 27, 96  
 Euglycemic-hyperinsulinemic clamp, 513, 516–518, 522, 524, 526, 527, 529
- Excretion**  
   caffeine, 38–39  
   paraxanthine, 74  
   theobromine, 68–69  
   theophylline, 59  
 Experimental autoimmune encephalomyelitis (EAE), 291–292
- F**  
 Felbamate, 254  
 Fertility, 352, 353, 355–357, 361–364, 378  
 Fetus, 37, 42, 59, 62, 65, 67, 68, 73, 354, 374, 375, 377–378, 384  
 Flow-mediated dilation, 421  
 Fluorescent conjugate, 184  
 Follicle, 359, 360, 362–364  
 Free radical, 260, 521  
 Furosemide, 398
- G**  
 Gabapentin, 254  
 GAF, 121  
 Gastric emptying, 40, 58, 205, 530  
 Gastrointestinal tract, glucose absorption, 530, 531  
**Gender**  
   caffeine, 42–43  
   theobromine, 70–71  
   theophylline, 63–64  
 Gestational age, 63, 366, 379, 380  
 GIFT  
   IVF/GIFT study, 366  
 Glia, 240, 243, 289, 322  
 Glomerular filtration rate (GFR), 392, 394, 396, 397, 400–404  
 Glomerulosclerosis, 400  
 Glucose tolerance, 513, 518, 520, 526  
 Glutamate release, presynaptic sites, 272–273  
 G-protein-coupled receptors, 271–272, 447, 521  
 Guinea pig spinal cord homogenates (GPSCH), 292  
 Gurana (*Paulinia cupana*), 14, 15, 203
- H**  
 Headache, 187, 214, 219–221, 268, 324, 325, 342, 344, 487, 540  
**Heart**  
   conduction, 421  
   failure, 163, 392, 399, 423, 450, 532  
   inotropic action, 421, 422, 451  
   ischemia-reperfusion injury, 418, 422  
   rate, 223, 332, 342, 376, 414, 416–418, 424, 486  
   rhythm, 421  
 Hemodynamic response, 417, 422, 532

- Hepatitis, 471–477
- Histone deacetylase, 102, 442, 448, 460–461
- Histone deacetylase activity (HDAC), 102, 442, 444, 448–449
- Homocysteine, 16, 20, 282, 414, 426–427, 429, 536, 537
- Hormones
- caffeine, 42–43
  - theobromine, 70–71
  - theophylline, 63–64
- Huntington's disease
- experimental studies, 289–291
  - human studies, 289
- 5-Hydroxytryptamine, serotonergic, 221, 320
- Hyperalgesia, 240, 242–244, 313, 314, 317, 318, 321, 322
- Hypertension, 106, 167, 218, 221, 284, 399, 425, 426, 532, 535
- Hypoxia, 65, 209, 210, 278, 279, 374, 380, 381, 384, 473, 474, 476
- I**
- IL–10, 459, 461, 475, 476
- Incretin
- glucagon-like peptide–1 (GLP–1), 529
  - glucose-dependent insulinotropic peptide (GIP), 529, 530
- Infant, 36, 38, 40–42, 46, 52, 58, 59, 65, 66, 68, 253, 366, 374–376, 379–382, 384, 394, 404, 450
- Inflammation, 105, 215, 274, 275, 289, 292, 400, 403, 417, 442, 443, 447, 451, 462, 464, 469–477, 535
- Insomnia, 219, 253, 342, 540
- Insulin resistance, 513, 516, 520–527, 530, 531, 540
- Insulin secretion, 529, 531
- Intrinsic, 48, 62, 312, 313, 316, 321, 323–325, 418
- Intrinsic antinociception, 313–316, 320, 325
- Intrinsic antinociceptive, 313, 314, 318, 323
- In vitro* fertilization (IVF), 364–366
- In vitro* maturation, 364
- Ischemia, 236–239, 246, 258, 275, 277–279, 417, 418, 422
- Ischemia-reperfusion, 403–404, 418, 422, 474
- Ischemic stroke, 268, 277
- 3-Isobutyl-1-methylxanthine (IBMX), 98–100, 111, 114–122, 141, 156, 341, 344, 360, 361, 395
- Isomerization, 176
- Isoproterenol, 398
- IVF. *See* In vitro fertilization
- K**
- Ketamine, 498, 499
- (E)-KF17837, 177, 186
- Kinase, 96, 107–109, 111–112, 242, 255, 256, 261, 272–276, 278, 313, 356, 359–361, 364, 365, 396, 459, 460, 473, 523
- KW6002, 175, 185, 186, 285, 286, 288
- L**
- L–97–1, 162
- Lactation, 374, 380, 383, 385
- L-dopa-induced motor complications, 288
- Leucoptera coffeella
- coffee leaf miner, 364
  - egg laying, 350, 364
- Levetiracetam, 254, 260
- Levitra<sup>TM</sup>, 106
- Liver, 470–475, 477
- hepatic glucose output, 510, 516, 528, 529, 531, 540
- Locomotor
- depression, 315
  - stimulation, 315, 325
- M**
- Magnesium, 98, 118, 224, 394, 521
- Magnesium, psychopharmacological activity
- in chocolate, 224
- Male gamete
- sperm capacitation, 356, 357, 365
  - spontaneous acrosome reaction, 365
- Mammalian oocytes maturation, 357–361, 364
- Manganese, 98
- MAO-B, 168, 175
- Mast cells, 442, 443, 445–448, 458, 460, 462, 463
- Maté (*Ilex paraguariensis*), 7–8, 14, 15, 25, 203, 484, 487, 511
- Maturation, 63, 351, 352, 355, 364, 375–377
- Mecca, 3
- Medullary blood flow, 397, 401
- Meiosis
- oocytes, 359, 360
  - spermatocytes, 351, 352, 357
- Meiotic competence
- adenylyl cyclase (AC), 359, 360, 364
  - G-protein linked receptor, 359
  - heat shock transcription factor 1, 359
  - oocyte plasma membrane, 359
- Metabolism
- caffeine, 39–51, 498, 536, 537

- paraxanthine, 75–76
- theobromine, 70, 205–206
- theophylline, 25, 61–65
- Metabolites and metabolic pathway
  - caffeine, 51–55
  - paraxanthine, 76
  - theobromine, 71–72
  - theophylline, 65–66
- Methotrexate, 464
- Methylphenidate, 498, 501
- Methyluric acid, theacrine (1,3,7,9-tetramethyluric acid), 13
- Microglia, 237, 240, 242, 246, 247, 278, 317, 318, 325
- Midaxifylline, 163
- Mirodenafil–SLX2101, 100, 106
- Mocha, 3, 5
- Monocytes, 375, 376, 443, 459, 461, 462, 473, 487
- Morphine, 12, 243–244, 312, 316, 318–321, 323, 325, 499
- MRE–2029-F20, 178
- MRS1754, 178
- MSX–2, 175–177
- MSX–3, 176
- MSX–4, 176
- Multiple sclerosis (MS)
  - animal studies, 291–292
  - human studies, 291
- Muscle cells, excitation coupling, 137
- Myocardium, 417, 422
- N**
- Na/HCO<sub>3</sub> cotransport, 396
- Na/H exchange, 396
- Natriuresis, 394–396, 398
- Naxifylline, 163
- Neonatal, 36, 46, 52, 62, 63, 66, 208, 237, 279, 382, 383, 461
- Neurodegeneration. *See also* Caffeine
  - acute degeneration, 268
  - chronic degeneration, 268
  - neuroprotection, caffeine and adenosine receptors
    - blood–brain barrier (BBB), 275–276
    - cellular survival signals, postsynaptic sites, 273–274
    - glutamate release, presynaptic sites, 272–273
  - neuroinflammation control, CNS, 274–275
  - neurotrophic factors, 275
- Neurons
  - release neurotransmitters, 137, 142, 143, 334
  - survival, 137, 143–145, 270, 278, 290
- Neuropathic pain, 240–243, 245, 321, 322
- Neuroprotective, 143, 144, 174, 236, 246, 257, 261, 273, 275, 276, 278–283, 285–287, 292, 293, 380, 381
- Neutrophils, 274, 376, 443, 444, 458–460, 462, 472
- Newborn, 38, 41, 42, 63, 66, 67, 187, 279, 374, 376, 379, 394, 487
- Nicotine, 12, 36, 142, 216, 489, 497–498, 501
- Nitric oxide (NO) synthase, 260, 275
- N*-methyltransferase
  - caffeine synthase (SAM:theobromine *N*-methyltransferase), 12, 16–18, 20–23, 28
  - evolutionary relationship, 21–23
  - 7-methylxanthosine synthase (SAM:xanthosine *N*-methyltransferase), 16, 17, 21, 22, 28
  - theobromine synthase (SAM:7-methylxanthine *N*-methyltransferase), 16–18, 20, 21, 23
- Non-steroidal anti-inflammatory drugs (NSAIDs), 313, 316–318, 323, 325
- Noradrenaline, noradrenergic, 316, 318, 325, 335
- Norepinephrine, 397, 398, 417, 421–423, 525, 528
- NSAIDs. *See* Non-steroidal anti-inflammatory drugs
- 5′-Nucleotidase, 19, 20, 255, 397, 416
- N<sup>ω</sup>-nitro-L-arginine methyl ester, 401
- O**
- Obesity
  - caffeine, 43–44, 512
  - theophylline, 64
- Opioid receptors, 182, 186, 243, 321
- Opioids, 182, 243, 246, 313, 316, 318, 320, 321
- Oral glucose tolerance test, 513
- Osteoporosis, 537, 539, 540
- Ovarian age
  - antral follicle count, 362, 363
  - follicle-stimulating hormone (FSH), 354, 359, 361–364
  - inhibin B, 362, 363
  - oestradiol, 362, 363
- Oxazolo[3,2-*a*]purinone, 172

**P**

- Pain, 178, 214, 235–247, 311–325
- Pancreatic  $\beta$  cells, 516, 529–531
- Paraxanthine, 152
  - absorption, 73
  - demethylated metabolites, 145
  - distribution, 73
  - excretion, 74
  - metabolism, 75–76
  - metabolites and metabolic pathway, 76
  - pharmacokinetics, 74–75
  - RyR channel, 140, 143–145
  - survival, 143, 145
- Parkinson's disease (PD), 172, 175, 268, 539, 540
  - experimental studies
    - A<sub>2A</sub>R antagonists, 286–287
    - L-dopa-induced motor complications, 288
    - MPTP-induced reduction, 287
    - neurotoxicity, 287–288
  - human studies, 268
    - disease modifying effect, 286
    - motor symptoms, 285–286
- PDE4, 100, 116–118, 121, 360, 400
- PDE5, 100, 101, 106–117, 120–122
- PDE6, 99–101, 106
- PDE11, 122
- Pentoxifylline, 100, 105, 236, 344, 400, 402, 414, 416
- Perinatal
  - intrauterine growth restriction, 378
  - spontaneous abortions, 378
- Perinatal caffeine, adenosine A<sub>1</sub> receptors, 356, 363, 364
- Peripheral resistance, 414, 418, 420
- Peroxisome-proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), 444, 448–449
- Pertussis toxin, 396, 460
- PET. *See* Positron emission tomography
- Pharmacokinetics
  - caffeine, 37, 39–47
  - paraxanthine, 74–75
  - theobromine, 69–71, 205–206
  - theophylline, 59–60, 62–65
- Phencyclidine, 498, 499
- Phenobarbital, 253
- Phentolamine, 316
- Phenylethylamine, psychopharmacological
  - activity in chocolate, 202, 220–221
- Phenylethylamines, 220–221, 500
- 8-Phenylethynyl-DMPX, 177
- 8-Phenyltheophylline, 314, 320, 322, 397, 417, 420, 462
- Phenytoin, 253
- Phosphodiesterase (PDE), 93–123, 136, 156, 206, 217, 236, 237, 338, 394, 395, 397–400, 403, 444–445, 447–449, 470, 472, 473, 475
- Phosphodiesterase (PDE) inhibitors, 247, 259, 269, 312, 341, 349, 356, 357, 360, 361, 364, 366, 394, 413, 415, 416, 419, 439, 440, 445, 460, 470, 472, 473, 475
  - cilostamide, 360
  - hypoxanthine, 360
  - 3-isobutyl-1-methylxanthine (IBMX), 98, 114–122, 360, 361, 364
  - milrinone, 360
  - rolipram, 121, 270, 360, 399
- Photoisomerization, 176
- Physical exercise
  - caffeine, 43
  - theophylline, 64
- PKA, cyclin-dependant kinase (Cdk1), 359, 361
- Placenta, 38, 42, 59, 67, 363, 374, 377, 378
- Plasma concentration, 36, 37, 40, 42, 59, 66, 68, 205, 218, 222, 253, 258, 270, 343, 378–381, 461, 511, 526
- Polycystin, 399
- Polymorphism, 47, 49, 52, 61, 76, 281, 286, 289, 338, 340, 343, 344, 532, 535–537, 540
- Porcine oocytes, 360, 361, 364
- Positron emission tomography (PET), 176, 185–186
  - imaging, 185
  - radioligand, 186
- PPAR $\gamma$ . *See* Peroxisome-proliferator-activated receptor  $\gamma$
- Pregnancy, 34, 38, 41, 42, 49, 59, 64, 69–71, 211, 253, 354, 355, 362, 363, 373–385, 521
- Premature, 36, 52, 59, 63, 65, 66, 339, 355, 365, 374, 376, 379–381, 394
- Primidone, 253
- Proconvulsant, 251, 252, 254–259, 261
- Prodrugs, 163, 164, 167, 176, 179
- Propentofylline, 235–247, 283
- Propranolol, 398
- Proteinuria, 400
- PSB–10, 180, 181
- PSB–11, 180, 181
- PSB–50, 179



- PSB-53, 157, 179  
PSB-55, 157, 179  
PSB-63, 171, 172  
PSB-298, 157, 179  
PSB-601, 157, 160  
PSB-603, 157, 179  
PSB-1115, 157, 179, 316, 318  
Psychostimulant effect, 268, 269, 271, 486, 499  
Pulmonary hypertension, 94, 106  
Puromycin, 400  
Pyrimido[1,2,3-*cd*]purinediones, 170  
Pyrimido[2,1-*f*]purinediones, 171, 176
- R**
- Regulation, sleep  
  induction mechanisms, 334–338  
  waking mechanisms, 334  
Renal sympathetic nerve, 397  
Renin, 219, 398–400, 423  
Renin-angiotensin system, 398, 400, 414, 418, 419, 422–424  
Reperfusion, 418, 473  
Respiration, 219, 376, 381, 383–384, 450–451  
Respiratory drive, 380, 382  
Revatio<sup>TM</sup>, 94, 106  
Rheumatoid arthritis, 240, 464  
Rolipram, 121, 270, 360, 399  
Roscovitine, 360  
Ryanodine, 135–146, 260, 394, 399  
Ryanodine receptors (RyR), 446–447  
  endoplasmic reticulum (ER), 136, 138, 141–142  
  sarcoplasmic reticulum (SR), 136, 137, 139–141  
RyR channels  
  activation site, 138, 140  
  desensitization, 140  
  dopamine, 141–145  
  endogenous modulators, 145  
  neurotransmitter release, 137, 142, 143  
  pore region, 138  
  quantal Ca<sup>2+</sup> release, 140, 447  
  receptor subtypes, 137  
  sensitize, 141, 145  
  somatodendritic, 142  
RyR1, congenital myopathy, 138
- S**
- S-adenosyl-L-methionine (SAM)  
  SAM cycle, 19, 20  
  SAM route for caffeine biosynthesis, 19, 20  
Salsolinol, psychopharmacological activity in chocolate, 223–224  
SCH58261, 273–275, 278, 283, 286, 287, 290, 316, 318  
Second meal, 518  
Seizures  
  epilepsy, 252–255  
  febrile seizures, 253  
  sudden unexplained death in epilepsy (SUDEP), 258–259  
  Theophylline-associated seizures (TAS), 253, 258, 259  
Self-administration, 488, 489, 493, 494, 497, 499  
Self-medication, 496, 500  
Serotonin, psychopharmacological activity in chocolate, 219, 221–223  
Sildenafil, 98–100, 105–107, 111, 114, 117, 120–122  
Silk-based polymers, 257  
Skeletal muscle  
  carbohydrate storage, 525  
  glucose uptake, 523–526, 529  
  glycogen synthesis, 524, 525, 528  
Sleep  
  caffeine (*see* Caffeine, sleep)  
  chocolate, 213, 345  
  circadian component, 333  
  homeostatic regulation, 333, 341  
  in humans, 332  
  induction mechanisms, 334–336  
  in mammals, 332  
  non-REM sleep, 332, 337, 339, 342  
  regulation, 333–338  
  REM sleep, 332, 337, 341  
  tea, 345  
  two-process model, 333  
  waking mechanisms, 334  
Sleep apnea  
  central, 450  
  obstructive, 450  
Smoking, 41, 48–50, 143, 286, 362, 363, 378, 497, 498, 532, 539  
  caffeine, 46  
  theobromine, 71  
  theophylline, 65  
Smooth muscle relaxation, 111, 112, 216  
SNS. *See* Sympathetic nervous system  
Species dependence, 169, 174, 319  
Spermatids, 352, 354, 355  
Spermatogenesis  
  spermatidogenesis, 351, 352  
  spermatocytogenesis, 351  
  spermiogenesis, 351, 352

- Spermatozoa, 351, 352, 355–357  
 Sperm capacitation, 356–357  
 Spin labels, 184–185  
 8-SPT, 158  
 Stem cells, 257, 351  
 Stroke  
   experimental studies, 277–279  
   human studies, 276–277  
 Styrylxanthines, 175, 176, 186  
 8-Styrylxanthines, 167, 168, 175–177,  
   185, 186  
 Substance P, 186  
 Sympathetic nerve activity, 418, 422, 423  
 Sympathetic nervous system (SNS), 417, 418,  
   512, 525–527, 531  
 Synthetic methylxanthines, 141, 236
- T**
- Tadalafil, 100, 117, 121, 122  
 T cells, 137, 291, 376, 444, 448, 470–474,  
   476, 487
- T2D  
   gestational diabetes, 521  
   global health problem, 511  
   lifestyle intervention, 512  
   relative risks, 427, 520, 531, 534, 535
- Tea, 2, 3, 5–9, 19–23, 25, 26, 28, 96, 103, 203,  
   205, 212, 219, 226, 283, 345, 365,  
   366, 424, 472, 484, 511, 520, 538  
   *Camellia irrawadiensis*, 14, 18, 22  
   *Camellia sinensis*, 13, 14, 17, 21, 25  
   kekecha (cocoa tea, *Camellia*  
   *ptilophylla*), 14  
   kucha (*Camellia sinensis assamica* var.  
   *kucha*), 14
- Teratogenic/sperm injuring potential  
   caffeine, 352, 378  
   0.5 caffeine, 353  
   male gamete maturation, 355  
   male rats, 354  
   rats, 353  
   roosters, 352  
   theobromine, 353–355  
   theophylline, 353–355  
   ubiquitin-proteasome pathway (UPP), 355
- Testes, 350–352, 354, 355
- Tetrahydro- $\beta$ -carbolines,  
   psychopharmacological activity in  
   chocolate, 223–224
- Tetraplegia, 526, 527
- T helper (Th), 459
- Theobromine (3,7-dimethylxanthine), 12–18,  
   20, 21, 23–25, 27  
   absorption, 66–67  
   angiogenesis inhibition, 209  
   animal poisoning, 209–210, 225  
   cardiovascular effects, 214–215  
   characteristics, 203  
   dental effects, 217–218, 225  
   distribution, 67–68  
   doping in animal racing, 211, 225  
   excretion, 68–69  
   metabolism, 70  
   metabolism in man, 205–206  
   metabolites and metabolic pathway, 71–72  
   natural occurrence, 203  
   pest control, 210  
   pharmacokinetics, 69–70  
   pharmacokinetics in man, 205–206  
   psychopharmacological activity in  
   chocolate, 201–226  
   renal effects, 217  
   respiratory effects, 215–217  
   sources of variation, pharmacokinetics and  
   metabolism, 70–71  
   synthesis and catabolism in *Theobroma*  
   *cacao*, 203–206  
   teratogenesis, 209  
   testicular atrophy, 208  
   thymus gland atrophy, 208  
   toxicity in animals, 208–210  
   uptake in man, 205–207  
   use as medicine, 216, 218
- Theophylline (1,3-dimethylxanthine), 13, 15,  
   23–25, 152–158, 169, 174, 180,  
   187, 252–255, 258, 260, 261, 314,  
   319–321, 440–451  
   absorption, 55, 58  
   distribution, 58–59  
   excretion, 59  
   metabolism, 61–62  
   metabolites and metabolic pathway, 65–66  
   pharmacokinetics, 59–60  
   sources of variation, pharmacokinetics and  
   metabolism, 62–65
- Thermogenesis, 537
- Tolerance, 113, 209, 211, 243–244, 246, 312,  
   342, 343, 400, 418, 422, 424, 429,  
   441, 484, 486–487, 491, 496, 498,  
   513, 518, 520, 526
- Toponafylline, 163
- Traumatic brain injury (TBI), 38, 256, 268, 293  
   experimental studies, 280–281  
   human studies, 280
- Tryptophan, psychopharmacological activity in  
   chocolate, 219, 221–223

Tubuloglomerular feedback (TGF), 397, 398, 420  
Tumor, 237, 244, 274, 291, 418, 459, 470, 476–477  
Tyramine, psychopharmacological activity in chocolate, 219, 221, 223

**U**

Udenafil, 100, 106  
8-Unsubstituted xanthine, 153–156

**V**

Vardenafil, 98–100, 106, 107, 116, 117, 121, 122  
Vascular resistance, 531, 532  
Vascular tone, 396, 397, 414, 417, 419, 420  
Vasoconstriction, 276, 324, 378, 392, 397, 401–403, 420  
Vasodilation, 215, 274, 417–420  
Vasomotor action, 419  
Vasopressin, 393, 394, 399

Venice, 3, 4  
Viagra<sup>TM</sup>, 105  
Vienna, 4  
Volatile solvents, 500

**W**

Water solubility, 156, 158, 163, 170, 174–177  
Water-soluble prodrugs, 176  
Weight-loss, 208, 537, 538, 540  
Withdrawal, 214, 219, 252, 258, 259, 274, 324, 342, 344, 382, 441, 484, 486–488, 498, 500, 520, 540

**X**

XAC, 158, 162, 169, 174, 181, 182, 184–186  
Xanthosine, 15–20, 27, 28, 204

**Z**

Zaprinast, 98–101, 107  
Zinc, 98, 118