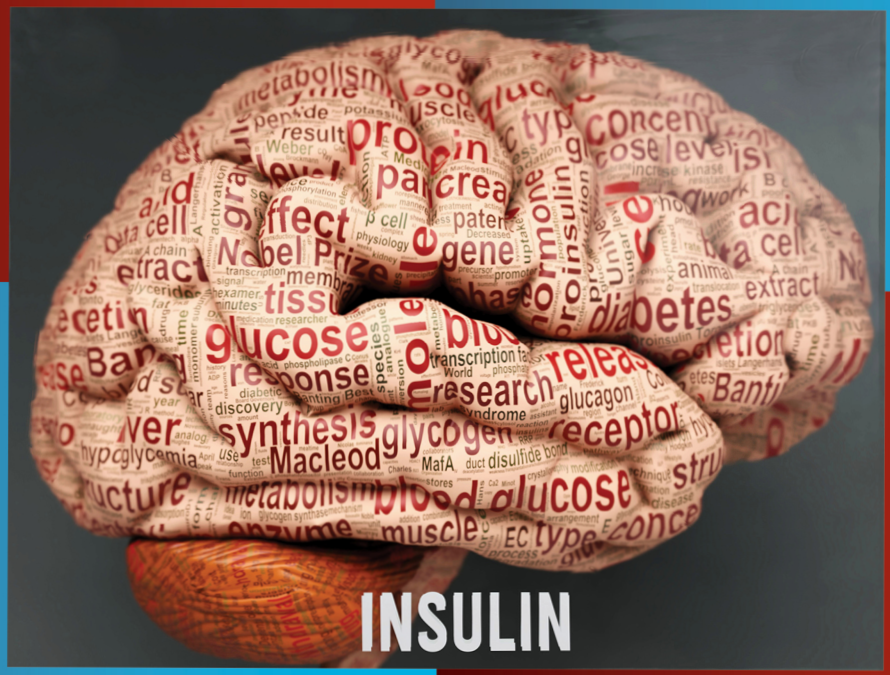
# PHYSIOLOGICAL CONSEQUENCES OF BRAIN INSULIN ACTION




EDITED BY
ANDRÉ KLEINRIDDERS

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# Physiological Consequences of Brain Insulin Action

The brain is crucial for the regulation of whole-body metabolism and behavior. The pancreas-derived hormone insulin modulates brain function and affects energy metabolism as well as cognition. This is partially achieved by modulating several types of brain cell populations including those relevant to satiety and reward. Importantly, brains of Alzheimer's disease patients exhibit a signature of brain insulin resistance with perturbed brain metabolism. This book will cover the basics of insulin signaling in the brain and will describe concepts of insulin resistance, a feature of type 2 diabetes. Moreover, insulin's effect on cognitive function will be pointed out and the association between brain insulin resistance and neurodegenerative diseases discussed. Additionally, potential behavioral and pharmacological concepts which can affect brain insulin signaling will be summarized.

**Key Features**:

- Summarizes insulin and the closely related IGF-1 receptor signaling
- Depicts concepts of insulin resistance
- Highlights the importance of conserved brain insulin signaling for brain function, metabolism, and behavior
- Describes potential behavioral and pharmacological approaches to support brain insulin signaling

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André Kleinridders

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# SERIES PREFACE

# PHYSIOLOGICAL CONSEQUENCES OF BRAIN INSULIN ACTION

*EDITOR: ANDRÉ KLEINRIDDERS*

## THE EDITOR

Dr. André Kleinridders is a Professor for Experimental and Molecular Nutritional Medicine at the Institute of Nutritional Science at the University of Potsdam. Prof. Kleinridders' research programs address the impact of brain insulin signaling on whole body pathophysiology and behavior with implications for diabetes, obesity and neurodegeneration. His studies focus on understanding the mechanisms of central insulin resistance (involving impairment of mitochondrial function) and its consequences on energy homeostasis and neurological alterations associated with aging. Dr. Kleinridders' expertise in endocrinology and genetics expands to areas of high significance for human pathophysiology, including metabolism, insulin signaling, and insulin resistance, the latter an umbrella term with implications for not only diabetes and obesity but also for neurodegenerative disorders, such as Alzheimer's disease. His research focuses on insulin action in the brain and its effect on mitochondrial stress responses and reduction of diet-induced weight gain. His recent publications establish Dr. Kleinridders' unique research focus on the role of brain insulin in human pathophysiology.

## PHYSIOLOGICAL CONSEQUENCES OF BRAIN INSULIN ACTION

PHYSIOLOGICAL CONSEQUENCES OF BRAIN INSULIN ACTION, focuses on different aspects of brain insulin and its regulation of a myriad of systemic effects ranging from starve-feed cycles to behavioral patterns. This book is particularly attractive because it places brain insulin signaling in the physiologic maintenance of whole-body homeostasis as well as impairment of brain insulin signaling in the pathology of diabetes and obesity. Moreover, brain insulin resistance is a critical factor in the pathogenesis of Alzheimer's disease, sometimes termed diabetes type III, hence the significance of brain insulin in modulation of cognitive functions. The book entails mechanistic aspects of brain insulin signaling and that triggered by activation of the insulin-like growth factor receptor (IGF1R), the regulation of neuronal circuits and how insulin modulates metabolism in different brain cell populations. How hypothalamic insulin signaling controls energy metabolism, food intake, and behavior, is viewed among the systemic effects of brain insulin. These chapters expand the effects of brain insulin in terms of insulin resistance as it occurs in type 2 diabetes and Alzheimer's disease as well

as diseases associated with protein misfolding. Pharmacological and dietary interventions that have the potential to overcome insulin resistance are also addressed.

Overall, the major thrust of this book is the recognition of the multifaceted effects of brain insulin and its signaling pathways not only in the brain and in different brain cell populations but how brain insulin modulates systemic tissue functions. This acquires further relevance in terms of brain insulin resistance and its impairment of whole-body homeostasis and association with cognitive deficits.

ENRIQUE CADENAS
HELMUT SIES

*Series Editors*
*Oxidative Stress and Disease*

# PREFACE

The discovery of insulin represents a landmark achievement in medical sciences. Insulin was discovered by Frederick Grant Banting and Charles Herbert Best in the laboratory of John James Rickard McLeod more than 100 years ago and saved millions of lives from a formerly non-curable disease. While type 1 diabetes is characterized by insulin deficiency, which can be treated by the administration of insulin, the majority of patients suffer from type 2 diabetes. These patients exhibit initially reduced sensitivity to insulin, known as insulin resistance. Insulin resistance causes reduced glucose uptake in skeletal muscle and adipose tissue. In the liver, insulin resistance causes deteriorated hepatic glucose production, leading to elevated blood glucose levels overall. Although glucose uptake in the brain is mostly independent of insulin, insulin and its receptor have already been detected in the late 1960s and 1970s in the brain, and research over the last decades has clearly demonstrated that the brain is an insulin-sensitive organ.

Insulin in the brain regulates food intake, affects energy metabolism and glucose handling in peripheral tissues and even modulates fertility. In addition, there is ample evidence that insulin exhibits neuroprotective function. The presence of brain insulin resistance is not only a feature of unhealthy obesity but is also observed in the brains of patients suffering from Alzheimer's disease. Together, these observations highlight the importance of the precise regulation of insulin action in the central nervous system for a healthy metabolism and proper cognitive function.

This book will cover the molecular mechanisms of insulin signaling and the establishment of insulin resistance. As the brain shows region-specific differences in terms of function and cell composition, cell- and region-specific effects of insulin action are discussed. Diabetes-associated disorders including mood disorders and neurodegenerative diseases will be described and associated with brain insulin resistance. The complex interaction of peripheral organs with the brain is characterized to a great extent in this book, as is the hormonal crosstalk of insulin with leptin in the central nervous system. Importantly, novel insights about brain insulin signaling in humans will be explained in addition to behavioral and pharmacological treatment options to counteract insulin resistance. In summary, this book will provide a comprehensive overview about the physiological consequences of brain insulin action.

# ACKNOWLEDGEMENTS

I would like to thank all the people who helped with the preparation of this book. A special thanks goes to all authors and co-authors who dedicated their time and work to contribute to important chapters. Without their efforts, this book would not have been possible.

## EDITOR

**Prof. Dr. André Kleinridders** is a Professor for Experimental and Molecular Nutritional Medicine at the Institute of Nutritional Science at the University of Potsdam, Germany. Dr. Kleinridders' research programs aim at understanding causes and consequences of brain insulin resistance with implications for diabetes, obesity and neurological disorders. His studies focus on the interaction of mitochondrial function and insulin signaling and its consequences on energy homeostasis and behavior. Several publications establish Dr. Kleinridders' unique research focus on the role of brain insulin in metabolic disorders.

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## NOTICE

Scientific knowledge constantly advances. The authors and editor reassessed their sources of information, which they considered as solid to give detailed information about the respective scientific topics. Yet due to possible human error and/or scientific progression, neither the editor nor the authors nor any other party warrants that the presented information of this book is in every aspect accurate and thus disclaims responsibility for any errors or omissions of the provided information in this work.

# ABBREVIATIONS

| | |
|---|---|
| **[Ca2+]i** | Cytosolic $Ca^{2+}$ Concentration |
| **5-HT** | Serotonin |
| **AARE** | Amino Acid Response Element |
| **ACE** | Angiotensin-Converting Enzyme |
| **Acrp30** | Adipocyte Complement-Related Protein of 30 kDa |
| **AD** | Alzheimer's Disease |
| **ADCY** | Adenylate Cyclase |
| **AdipoR** | Adiponectin Receptor |
| **ADP/ATP** | Adenosine Di-/Triphosphate |
| **Ads** | Antidepressants |
| **AGE** | Advanced Glycation End-Products |
| **AgRP** | Agouti-Related Protein |
| **AKT/PKB** | Ak Strain Transforming Kinase/Protein Kinase B |
| **AMPA** | Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid |
| **AMPK** | 5′AMP-Activated Protein Kinase |
| **ANGPTL6** | Angiopoietin-Related Protein 6 |
| **ANLS** | Astrocyte-Neuron Lactate Shuttle |
| **APOE** | Apolipoprotein E |
| **ARC** | Arcuate Nucleus |
| **ASD** | Autism Spectrum Disorder |
| **ATF4** | Activating Transcription Factor 4 |
| **Aβ** | Amyloid Beta (Aβ) |
| **BACE1** | Beta-Secretase 1 |
| **Bad** | BCL2 Associated Agonist Of Cell Death |
| **BAT** | Brown Adipose Tissue |
| **BBB** | Blood–Brain Barrier |
| **BCAA** | Branched-Chain Amino Acids |
| **Bcl-2** | B-cell Lymphoma 2 |
| **BCSF** | Blood–Cerebrospinal Fluid Barrier |
| **BDI** | Beck's Depression Inventory |
| **BDNF** | Brain-Derived Neurotrophic Factor |
| **BHB** | Beta-Hydroxybutyrate |
| **BIR** | Brain Insulin Resistance |
| **BMI** | Body Mass Index |
| **BOLD** | Blood-Oxygen-Level-Dependent Contrast |
| **CART** | Cocaine and Amphetamine-Related Transcript |
| **CBF** | Imaging or Cerebral Blood Flow |
| **CDKAL1** | Cyclin-Dependent Kinase 5 Regulatory Subunit-Associated Protein 1-Like 1 |
| **ChREBP** | Carbohydrate-Response Element-Binding Protein |
| **CNO** | Clozapine-N-Oxyde |
| **CNS** | Central Nervous System |
| **CRE** | Camp Response Element |
| **CREB** | Camp Response Element Binding Protein |
| **CRP** | C-Reactive Peptide |
| **CSF** | Cerebrospinal Fluid |
| **CVD** | Cardiovascular Disease |
| **DA3–CH** | GLP-1/GIP Dual Receptor Agonist |

| | |
|---|---|
| **DAG** | Diacyl Glycerol |
| **DASH** | Dietary Approaches to Stop Hypertension |
| **DAT** | Dopamine Transporter |
| **db/db** | Leptin Receptor-Deficient |
| **DCX** | Doublin or Lissencephalin-X |
| **DHA** | Docosahexaenoic Acid |
| **DIO** | Diet-Induced Obesity |
| **DKK1** | Dickkopf-Related Protein 1 |
| **DM2** | See T2D, T2DM |
| **DMH** | Dorso-Medial Hypothalamus |
| **DPP-4** | Dipeptidyl Peptidase-4 |
| **DRD2** | Dopamin Receptor D2 |
| **DREADD** | Designer Receptor Exclusively Activated by Designer Drug |
| **DRN** | Dorsal Raphe Nucleus |
| **DRP1** | Dynamin-Related Protein 1 |
| **Dvl** | Dishevelled |
| **EEG** | Electroencephalography |
| **EGF** | Epidermal Growth Factor |
| **eIF2α** | Eukaryotic Initiation Factor 2 Alpha |
| **Emx-Cre** | Emx Locus Cre Recombinase |
| **EOAD** | Early-Onset AD |
| **EPA** | Eicosapentaenoic Acid |
| **EPAC** | Exchange Protein Activated by Camp |
| **ER** | Endoplasmic Reticulum |
| **ERK** | Extracellular Signal-Regulated Kinase |
| **ETC** | Electron Transport Chain |
| **F2,6P2** | Fructose-2,6-Bisphosphate |
| **FA** | Friedreich's Ataxia |
| **fa/fa** | Zucker Fatty Rat |
| **FABP2** | Fatty-Acid Binding Protein 2 |
| **FDA** | Food And Drug Administration |
| **FDG** | $^{18}$F Fluorodeoxyglucose |
| **FDG-PET** | 2-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography |
| **FFA** | Free Fatty Acid |
| **FGF-2** | Fibroblast Growth Factor 2 |
| **FGF21** | Fibroblast Growth Factor 21 |
| **FGFR** | Fibroblast Growth Factor Receptor |
| **fMRI** | Functional Magnetic Resonance Imaging |
| **FOXO** | Forkhead Box O |
| **FTO** | Fused-Toes and Obesity |
| **Fzd** | Frizzled |
| **G6P** | Glucose-6-Phosphate |
| **GABA** | Gamma-Amino Butyric Acid |
| **GAD** | Generalized Anxiety Disorder |
| **GCN2** | General Control Nonderepressible 2 |
| **GDF15** | Growth/Differentiation Factor 15 |
| **GDP/GTP** | Guanosine Di-/Triphosphate |
| **GH** | Growth Hormone |
| **GHRH** | Growth Hormone Releasing Hormone |
| **GHSR** | Growth Hormone Secretagogue Receptor |
| **GI** | Glycemic Index |
| **GIP** | Glucose-Dependent Insulinotropic Polypeptide; Gastric Inhibitory Peptide |
| **GIRKO** | Glial Insulin Receptor Knock-Out |
| **GLP1** | Glucagon-Like Peptide 1 |
| **GluA1** | Glutamate Receptor 1 |
| **GLUT** | Glucose Transporter |
| **GPCR** | G-Protein-Coupled Receptor |
| **GRB2, Grb-2** | Growth Factor Receptor-Bound Protein 2 |
| **GRP94** | Endoplasmin |
| **GS** | Glycogen Synthase |
| **GSK** | Glycogen Synthase Kinase |
| **GSK3β** | Glycogen Synthase Kinase-3β |
| **GWAS** | Genome Wide Association Study |
| **Hb** | Habenula |
| **HFD** | High-Fat Diet |
| **HGP** | Hepatic Glucose Production |
| **HMG** | Hemimegalencephaly |
| **HMG-CoA** | B-Hydroxy β-Methylglutaryl-CoA |
| **HMW** | High-Molecular-Weight |
| **HOMA-IR** | Homeostasis Model Assessment of Insulin Resistance |
| **HPA axis** | Hypothalamic–Pituitary–Adrenal Axis |
| **HSGAG** | Heparan Sulfate Glycosaminoglycan |
| **ICV** | Intracerebroventricular |
| **IDE** | Insulin Degrading Enzyme |
| **IDI** | Intranasal Delivery of Insulin |
| **IGF-1, IGF1** | Insulin-Like Growth Factor 1 |
| **IGF-1R, IGF1R** | Insulin-Like Growth Factor 1 Receptor |
| **IGF2** | Insulin like Growth Factor 2 |
| **IGFBP** | Insulin-Like Growth Factor Binding Protein |
| **IKK** | Inhibitor of Nuclear Factor Kappa-B Kinase |

| | |
|---|---|
| **IL** | Interleukin |
| **IL-6** | Interleukin 6 |
| **ILP** | Insulin Peptides |
| **IP3** | Inositol-1,4,5-Triphosphate |
| **IP3R** | Inositol-1,4,5-Triphosphate (IP3) Receptor |
| **IQ** | Intelligence Quotient |
| **IR, InsR, INSR** | Insulin Receptor |
| **IRE1** | Serine/Threonine-Protein Kinase/Endoribonuclease |
| **IRS** | Insulin Receptor Substrate |
| **IRX3** | Iroquois Homeobox Protein 3 |
| **iv** | Intravenous |
| **iv GTT** | Intravenous Glucose Tolerance Test |
| **JAK2** | Janus Kinase 2 |
| **JNK** | C-Jun N-Terminal Kinase |
| **K-ATP** | ATP-Sensitive Potassium Channels |
| **KIR6x** | Inward Rectifier K(+) Channel |
| **Klb-KO** | Bklotho Knockout |
| **KO** | Knockout |
| **LAT1** | L-type Amino Acid Transporter 1 |
| **LDH1/5** | Lactate Dehydrogenase 1/5 |
| **LEF/TCF** | Lymphoid Enhancer Factor/T Cell Factor |
| **LepR b** | Leptin Receptor Isoform b |
| **LH** | Lateral Hypothalamus |
| **LHA** | Lateral Hypothalamic Area |
| **LMW** | Low-Molecular-Weight |
| **LOAD** | Late Onset AD |
| **LPS** | Lipopolysaccharide |
| **LRP6** | Low-Density Lipoprotein Receptor-Related Protein 6 |
| **LTD** | Long-Term (Synaptic) Depression |
| **LTP** | Long Term Potentiation |
| **MAM** | Mitochondrial Associated Membrane |
| **MAO** | Monoamine Oxidase |
| **MAP** | Mitogen-Activated Protein |
| **MAPK** | Mitogen-Activated Protein Kinase |
| **MBH** | Medio Basal Hypothalamus |
| **MC3R** | Melanocortin-3 Receptor |
| **MC4R** | Melanocortin 4 Receptor |
| **MCH** | Melanin Concentrating Hormone |
| **MCI** | Mild Cognitive Impairment |
| **MCRs** | Melanocortin Receptors |
| **MCU** | Mitochondrial $Ca^{2+}$ Uniporter |
| **ME** | Median Eminence |
| **MEG** | Magnetoencephalography |
| **MEK** | Mitogen-Activated Protein Kinase |
| **MFN1/2** | Mitofusin 1/2 |
| **MMSE** | Mini-Mental State Examination |
| **MMW** | Middle-Molecular-Weight |
| **MRI** | Magnetic Resonance Imaging |
| **MRN** | Median Raphe Nucleus |
| **MSR** | Mitochondrial Stress Response |
| **mTNS** | Medial Nucleus of the Solitary Tract |
| **mTOR** | Mechanistic Target of Rapamycin |
| **mTORC** | Mammalian Target of Rapamycin Complex |
| **Munc-18** | Mammalian Uncoordinated 18 Proteins |
| **NAC** | N-Acetylcysteine |
| **NAcc** | Nucleus Accumbens |
| **NAFLD** | Non-alcoholic Fatty Liver Disease |
| **NFT** | Neurofibrillary Tangles |
| **NF-κB** | Nuclear Factor Kappa B |
| **NHID** | National Health Information Database |
| **NIRKO** | Neuronal Insulin Receptor Knock-Out |
| **NLRP3** | Nucleotide-Binding Oligomerization Domain (NOD)-Like Receptor Protein 3 |
| **NMDA** | N-Methyl-d-Aspartate |
| **NPY** | Neuropeptide Y |
| **NRF1/2** | Nuclear Respiratory Factor 1/2 |
| **NRIs** | Norepinephrine Reuptake Inhibitors |
| **NSB** | Non-caloric Sweetened Beverages |
| **NSC** | Neural Stem Cells |
| **NTS** | Nucleus of the Solitary Tract |
| **NTS** | Nucleus Tractus Solitarius |
| **NZO** | New Zealand Obese |
| **ob/ob** | Leptin-Deficient |
| **oGTT** | Oral Glucose Tolerance Test |
| **OPA1** | Optic Atrophy 1 |
| **P** | Postnatal Day |
| **PA** | Physical Activity |
| **PC2** | Prohormone Convertase 2 |
| **PCK-1** | Phosphoenolpyruvate Carboxykinase 1 |
| **PCOS** | Polycystic Ovarian Syndrome |
| **PD** | Parkinson's Disease |

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|---|---|
| **PDK, PDPK** | Phosphatidylinositol Dependent Protein Kinase |
| **PDX-1** | Pancreatic and Duodenal Homeobox 1 |
| **PET** | Positron Emission Tomography |
| **PFC** | Prefrontal Cortex |
| **PFK** | Phosphofructokinase |
| **PFKFB3** | 6-Phosphofructo-2-Kinase/ Fructose-2,6-Bisphosphatase-3 |
| **PGC1α/β** | Peroxisome Proliferator-Activated Receptor Gamma Co-activator 1-α/β |
| **PH** | Pleckstrin Homology Domain |
| **PI3K, PI-3K** | Phosphoinositide 3-Kinase |
| **PiD** | Pick's Disease |
| **PIP2** | Phosphatidylinositol 4,5-Bisphosphate |
| **PIP3** | Phosphatidylinositol 3,4,5-Trisphosphate |
| **PKA** | Protein Kinase A |
| **PKC** | Protein Kinase C |
| **PKR** | Protein kinase |
| **PLCβ** | Phospholipase C Beta |
| **POMC** | Pro-opiomelanocortin |
| **PPAR** | Peroxisome Proliferator-Activated Receptor |
| **PPP** | Pentose Phosphate Pathway |
| **PREDIMED** | Prevention with Mediterranean Diet |
| **PRK** | Interferon-Inducible Double-Stranded RNA-Dependent Protein Kinase Activator A |
| **PSD-95** | Postsynaptic Density Protein 95 |
| **p-Tau** | Hyperphosphorylated Tau |
| **PTB** | Phosphotyrosine-Binding Domain |
| **PTEN** | Dual-Specificity Protein Phosphatase |
| **PTG** | Protein Targeting to Glycogen |
| **PTP1B** | Tyrosine-Protein Phosphatase Non-Receptor Type 1 |
| **PTPN11** | Tyrosine-Protein Phosphatase Non-Receptor Type 11 |
| **PVH** | Para-Ventricular Hypothalamus |
| **PVN** | Paraventricular Nucleus |
| **RA** | Receptor Agonists |
| **Rac** | Ras-related C3 Botulinum Toxin Substrate |
| **RAF** | Rapidly Accelerated Fibrosarcoma |
| **Ras** | Rat Sarcoma Virus |
| **rb-2** | Retinoblastoma Protein 2 |
| **RCT** | Randomized Controlled Trial |
| **Rheb-GTP** | Ras Homolog Enriched in Brain-GTP |
| **ROS** | Reactive Oxygen Species |
| **RPS6** | 40S Ribosomal Protein S6 |
| **RSPO3** | R-Spondin-3 |
| **RTKs** | Receptor Tyrosine Kinases |
| **RYGB** | Roux-en Y Gastric Bypass |
| **RyR** | Ryanodine Receptor |
| **S6K** | Ribosomal S6 Kinase |
| **SERCA** | Sarco-Endoplasmic Reticulum $Ca^{2+}$-ATPase |
| **SERT** | Serotonin Transporter |
| **SES** | Socioeconomic Status |
| **SF-1** | Steroidogenic Factor 1 |
| **SGLT2** | Sodium/Glucose Cotransporter 2 |
| **SH2B1** | SH2 Domain-Containing Adaptor Protein |
| **SHC** | SHC-Transforming Protein |
| **SIDD** | Severe Insulin-Deficient Diabetes Mellitus Type 2 |
| **SIRD** | Severe Insulin-Resistant Diabetes Mellitus Type 2 |
| **si-RNA** | Small Interfering RNA |
| **SIRT1** | Sirtuin 1 |
| **SIX3** | Six Homeobox 3 |
| **SMOC1** | SPARC-Related Modular Calcium-Binding Protein 1 |
| **SNARE** | N-Ethylmaleimide-Sensitive Factor Attachment Protein Receptors |
| **SNP** | Single Nucleotid Polymorphism |
| **SNpc** | Substantia Nigra Pars Compacta |
| **SOCS** | Suppressor of Cytokine Signalling |
| **SOD** | Super Oxide Dismutase |
| **SOS** | Son of Sevenless Homolog |
| **SOX1** | Sry-Box Transcription Factor 1 |
| **SPECT** | Single Photon Emission Computed Tomography |
| **SSB** | Sugar-Sweetened Beverages |
| **SSRIs** | Selective Serotonin Reuptake Inhibitors |
| **STAT3** | Signal Transducer and Activator of Transcription 3 |
| **STZ** | Streptozotocin |
| **SUR** | Sulfonylurea Receptors |
| **T1D, T1DM** | Type 1 Diabetes Mellitus |
| **T2D, T2DM** | Type 2 Diabetes Mellitus |
| **T3DM** | Type 3 Diabetes |
| **TCAs** | Tricyclic Antidepressants |

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|---|---|
| **TCF7l2** | Transcription Factor 7-Like 2 |
| **TCPTP** | T cell Protein Tyrosine Phosphatase |
| **TFAM** | Mitochondrial Transcriptional Factor A |
| **TLR4** | Toll-Like Receptor 4 |
| **TNF** | Tumor Necrosis Factor |
| **TrkB** | Tropomyosin Receptor Kinase B |
| **TSC** | Tuberous Sclerosis |
| **TXNIP** | Thioredoxin-Interacting Protein |
| **TyG** | Triglyceride Glucose |
| **UPR** | Unfolded Protein Reponse |
| **VEGF** | Vascular Endothelial Growth Factor |
| **VMH** | Ventro-Medial Hypothalamus |
| **VMN** | Ventromedial Nucleus |
| **VTA** | Ventral Tegmental Area |
| **WAT** | White Adipose Tissue |
| **WHO** | World Health Organization |
| **WNT** | Wingless-Integration1 |
| **αMSH** | Alpha-Melanocyte stimulating hormone |

CHAPTER ONE

# Molecular Mechanisms of Brain Insulin Signaling[1]

*Simran Chopra, Robert Hauffe, and André Kleinridders*

## CONTENTS



## INTERACTION BETWEEN METABOLISM AND INSULIN

With global type 2 diabetes (T2D) rates on an exponential rise, a major hallmark feature of this metabolic condition is insulin resistance. As a result, the physiological functions and downstream mechanistic actions of insulin are, to this date, being predominantly studied in its main target tissues, including the liver, muscle, and white adipocytes. Although several studies have also demonstrated a correlation between metabolic and neurodegenerative diseases, a higher risk of cognitive decline has been observed in diabetic patients (1–3). This suggests that alterations in brain insulin action can be observed as a pathological feature in both conditions, although other common signaling pathways might additionally be responsible for this, such as inflammation and apoptosis. However, the brain was not considered an insulin-sensitive organ until the late 1970s

[1] Simran Chopra and Robert Hauffe have contributed equally.

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