Micronutrients and the Human Brain

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By

Mrinal Kanti Poddar,
Soumyabrata Banerjee,
and Apala Chakraborty

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DEDICATED

To
My departed **Parents** and my **Family** for their continuous support and patience **and** my beloved teacher, late **Prof. Jagat Jiban Ghosh, Ph.D.; D.Sc.** for his unparallel, and pathbreaking multidisciplinary research, innovative teaching, motivation, and inspirational guidance to reach the success.
-Mrinal Kanti Poddar

To
My Parents, **Sabita Banerjee** and **Bijoy Banerjee**
for their love and immense support
and my philosopher and guide, **Prof. Mrinal Kanti Poddar, Ph.D.; D.Sc.**
For his constant motivation, active support, and guidance.
-Soumyabrata Banerjee

To
My Parents, late **Mrinal Chakraborty** and Mrs. **Parna Chakraborty** for their great support and continuous care throughout my academic journey.
-Apala Chakraborty

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PREFACE

The human brain is a unique inner mirror universe, through which all external events are processed and perceived. In fact, in the realm of living systems, the brain represents the pinnacle of sophistication. But it is an imperfect organ, whose variable performance in the healthy state contributes in undetermined degree to the world's social problems. There is every reason to believe the future holds even greater promise.

It is well known that brain research took root near the end of the century before last when Ramon y' Cajal proved that neuron is the basic functioning unit of the brain and Sherrington revealed its method of transmitting impulses. It is only in the past four decades that brain science as "neuroscience" has been established as a recognized discipline where the anatomical, cellular, physiological, chemical and molecular aspects of neuronal function are considered in a unified fashion. It is not unreasonable to assume that this logical advancement allows brain research to reach new levels of modern sophistication and that led to the development of different branches of neuroscience including **micronutritional neuroscience**. Needless to mention that already it has resulted in the establishment of graduate and postgraduate programs at several universities, and the founding of numerous journals devoted to reports of inter disciplinary research in the brain.

This book consists different aspects of micronutrients' (minerals and vitamins) involvement in mammalian including human brain functioning.

Each chapter is well designed with updated information as research outcome. The clinical as well as experimental evidence are focused for clear and better understanding. Nutrition is a popular topic to discuss, and it is known to be crucial for our biochemical, physiological and even psychological activity. So many books on nutrition as a whole as well as macronutrients are available in this field, but very limited books are there, emphasizing the effects of micronutrients on different aspects of the brain and its functions. Any such book, describing on the importance of micronutrients on different aspects of the human brain, such as its development to neural function to behavior as well as different pathological

conditions related to the brain, even how intelligence depends upon the micronutrients is very rare. With these perspectives, the present book carries an immense value and priority to reach a broader range of readers. This book possesses those chapters whose importance of knowledge in present day's research is undoubtedly valuable and thought provoking. The information incorporated in each of these chapters is very relevant to understand the potency of vitamins and minerals related to different aspects of brain functions including its development.

In addition to the role of micronutrients, another new and flourishing aspect is introduced for the readers as modern concept which includes gut-microbiota / microbiome in relation to the availability of micronutrients in the gut and its transportation to the body's systems including the nervous system (both central and peripheral). This thought in fact, has long been believed to be linked with the different brain functioning. This new approach is thought to be beneficial to the readers in their thought-provoking critical thinking on this topic and will be considered as a value-added approach as a whole. Few schematic representations are there for easy and better understanding of the topic in brief. The general physiological aspects are also discussed to get an essence of the topic of a particular chapter.

The authors are tried to simplify the expression of their thoughts to reach a broader spectrum of readers. The students of various biological backgrounds, even researchers can also get their clues of further investigations by going through this book. Each chapter of this book will provide a huge input to the philosophers, scientists, teachers, students, and above all the readers.

This book is very special to each of us. Numerous emotions are attached with it. The preparatory phase of this book has passed through one of the toughest times, the COVID-19 pandemic situation while many lives, who were close to the heart were lost during this time frame. The Editors of this book deeply mourn for those losses and convey heartfelt condolences to those families.

Mrinal K. Poddar,
Soumyabrata Banerjee &
Apala Chakraborty

ABBREVIATIONS

μM = micromolar
25-(OH)D = 25-hydroxyvitamin D
25-(OH)D3 = 25-hydroxyvitamin D3
1,25-$(OH)_2$D = 1,25-dihydroxy vitamin D
1,25-$(OH)_2$D3 = 1,25-dihydroxy vitamin D3
3XTg-AD = Triple transgenic-AD
5-hmc = 5-hydroxymethylcytosine
5-HT = 5-hydroxy tryptamine (Serotonin)
5-HTP = 5-Hydroxy tryptophan
5-MTHF = 5-methyltetrahydrofolate
AADC = Aromatic L-amino acid decarboxylase
AAV5 = Adeno-associated Virus type 5
Ach = Acetylcholine
AchE = Acetylcholine esterase
AchT = Ach transferase
ACTH= Adrenocorticotropic hormone
AD = Alzheimer's disease
ADAM-10 = A Disintegrin and Metalloproteinase Domain-containing Protein 10
ADHD = Attention deficit hyperactivity disorder
AGE = Advanced glycation end products
AIM = Amsterdam Initiative for Malnutrition
AKAP12 = A-kinase anchoring protein 12
AKD = α-ketoglutarate dehydrogenase
Akt = Protein kinase B (PKB)
Al = Aluminium
ALA = Alpha-linolenic acid
ALC = Child's ability to actively learn
ALDH1A1= Aldehyde dehydrogenase 1a1
ALK = Anaplastic lymphoma receptor tyrosine kinase
ALS = Amyotrophic lateral sclerosis
AMP = Adenosine monophosphate
AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPA-Rs = AMPA receptors
Ang = Angiopoietin

Ang-1 = Angiopoietin-1
Ang-2 = Angiopoietin-2
ANGPTL4 = Angiopoietin-like 4
AP-1 = Activator protein-1
ApaI = One of the three gene polymorphisms of VDR
ApoE = Apolipoprotein E
APP = Amyloid precursor protein
APP/PSEN1= APP/ Presenilin-1
As = Arsenic
ATF4 = Activating transcription factor 4
ATP = Adenosine triphosphate
ATP7A = ATPase copper transporting alpha
ATP7B = ATPase copper transporting beta
ATRA = All-*trans* retinoic acid
ATRX = Alpha-thalassemia/mental retardation syndrome, X-linked
AVED = Ataxia with vitamin E deficiency
Aβ = Amyloid beta peptide
Aβ-40 = Amyloid beta peptide (1-40)
Aβ-42 = Amyloid beta peptide (1-42)
BACE1 = Beta-secretase APP-cleaving enzyme 1
BARD1 = BRCA1-associated RING domain 1
BBB = Blood-brain barrier
BCAA = Branched-chain amino acid
BCAT = Branched-chain amino acids aminotransferase
BCKA = Branched-chain α-keto acid
BCKDC = Branched-chain α-keto acid dehydrogenase complex
BDNF = Brain derived neurotrophic factor
bFGF = basic fibroblast growth factor
Bi = Bismuth
BMI = Basal metabolic index
BRCA1 = Breast cancer type 1 gene
BSN = Bio-Engineered supplements and nutrition
BuChE = Butyl choline esterase
Ca = Calcium
Ca^{2+}= Calcium ion
CA = Cornu Ammonis
CA1 = Cornu Ammonis 1
CA3 = Cornu Ammonis 3
CAC = Citric acid cycle
CAG = Cytosine-adenine-guanine
CaM = Calmodulin

CaMKII = Calcium/calmodulin-dependent protein kinase II
cAMP = cyclic adenosine monophosphate
CAMTA1 = Calmodulin-binding transcription activator 1
CaN = Calcineurin
CASZ1 = Castor zinc finger 1
CAT = Choline acetyltransferase
cblC = Cobalamin C
CBP = CREB binding protein
Cd = Cadmium
CD31 = Cluster of differentiation 31
CDC42 = Cell division cycle 42
CDK4 = Cyclin-dependent kinase 4
CDKN3 = Cyclin-dependent kinase inhibitor 3
CDP-choline = Cytidine diphosphate-choline
cGMP = Cyclic guanosine monophosphate
ChAT = Choline acetyl transferase
CHERP = Calcium homeostasis endoplasmic reticulum protein
CHME3 = Cultured human microglial clone 3
CI = Confidence interval
CNS = Central nervous system
CO_2 = Carbon di-oxide
CoA = Coenzyme A
Cox2 = Cyclooxygenase-2
CREB = cAMP response element-binding protein
CREB/CBP = cAMP response element-binding protein/ CREB binding protein
CRP = C reactive protein
CSF = Cerebrospinal fluid
CSMD1 = CUB (for complement C1r/C1s, Uegf, Bmp1) and sushi multiple domains 1
CT= Computed tomography
CT1 = Cardiotrophin1
CTE = Chronic traumatic encephalopathy
Ctr1= Copper transporter1
Cu = Copper
Cu^{+} = Cuprous ion
Cu^{2+}= Cupric ion
CUB = complement C1r/C1s, Uegf, Bmp1
Cx36 = Connexin 36
Cyp27B1 = Cytochrome P450 family 27 subfamily B member1
Cyp2R1= Cytochrome P450 family 2 subfamily R member 1

DBH = Dopamine beta- hydroxylase (Dopamine β-hydroxylase)
DBPs = Vitamin D binding proteins
DDX4 = DEAD (Asp-Glu-Ala-Asp)-box helicase 4
Delta-T3 = Vitamin E delta-tocotrienol
DH = Deoxyhaemoglobin
DHA = Docosahexaenoic acid
DIO1 = Iodothyronine deiodinase 1
DIO2 = Iodothyronine deiodinase 2
DLC1 = Deleted liver cancer 1
DMT1 = Divalent metal transporter 1
DNA = Deoxyribonucleic acid
DOPA = 3,4 dihydroxy phenylalalnine
DUSP12 = Dual-specificity phosphatase 12
DV= Dorso-ventral
E. coli = *Escherichia coli*
E1 = Ependymal cells 1
E2 = Ependymal cells 2
E3 = Ependymal cells 3
EC = Endothelial cell
ECF = Extracellular fluid
ECM = Extracellular matrix
EC-SOD = Extracellular-superoxide dismutase
EDTA = Ethylenediamine tetraacetic acid
EGF = Endothelial growth factor
EGF-1 = Endothelial growth factor-1
EGF-2 = Endothelial growth factor-2
eNOS = Endothelial NOS
ENS = Enteric nervous system
EPA = Eicosapentanoic acid
EPC = Endothelial progenitor cells
Eph = Erythropoietin-producing-hepatocellular carcinoma receptors
Ephrins = Eph receptor-interacting signals
EPSP = Excitatory postsynaptic potential
ER = Endoplasmic reticulum
ERK = Extracellular signal-regulated kinase
ERK1 = Extracellular signal-regulated kinase 1 (Isoform) (MAPK3)
ERK1/2 = Extracellular signal-regulated kinase 1/2
ERK2 = Extracellular signal-regulated kinase 2 (Isoform) (MAPK1)
EVOO = Extra virgin olive oil
FA = Fatty acid
FABP4 = Fatty acid-binding protein-4

FABP5 = Fatty acid-binding protein type-5
FAD = Flavin adenine dinucleotide
FAs = Fatty acids
FBF = Family benefit fund
Fe = Iron
Fe^{2+}= Ferrous ion
Fe^{3+} = Ferric ion
fEPSP = Field excitatory postsynaptic potential
fEPSPs = Field excitatory postsynaptic potentials
FGF = Fibroblast growth factor
FGF2 = Fibroblast growth factor 2
FMN = Flavin mononucleotide
FMS = Feline McDonough Sarcoma
FokI = One of the three gene polymorphisms of VDR
foxD3 = Forkhead box protein D3
FR = p-Src-FA receptor
FTF = Feed the Future
FTY720 = Fingolimod hydrochloride
FXN = Frataxin
G-6-P = Glucose-6-Phosphatase
GABA = Gama-Aminobutyric acid
$GABA_AR$ = GABA-A receptors
GAC = Global Agenda Council
GAIN = Global Alliance for Improved Nutrition
GCN2 = General control nonderepressible 2
GCN2/ATF4 = general control nonderepressible 2/activating transcription factor 4
GF = Germ free
GFAP = Glial fibrillary acidic protein
GI = Gastro intestine
GLS = Glutaminase
GluR1 = Glutamate receptor 1
GluR2 = Glutamate receptor 2
GPR109A = G protein-Coupled Receptor 109A
GPR39 = Zn^{2+} activated G protein-Coupled Receptor 39
GPX4 = Glutathione peroxidase
GS = Glutamine synthetase
GSH = Reduced glutathione
GTP = Guanosine triphosphate
GWAS = Genome-wide association studies
H_2O_2 = Hydrogen peroxide

H_2S = Hydrogen sulfide
HACE1 = HECT Domain and ankyrin repeat-containing E3 ubiquitin-protein ligase 1
HAWIVA Scale = Hannover-Wechsler intellihenztest für das Vorschulalter
HAWIVA-III = Hannover-Wechsler intelligence test for pre-school children, third edition German version.
Hcy = Homocysteine
HD = Huntington's disease
HDL = High density lipoprotein
HECT = Homologous to the E6-AP carboxyl terminus
Hg = Mercury
HIF = Hypoxia-induced factor
HIF-1 = Hypoxia-induced factor-1
His = Histidine
HK2 = Hexokinase 2
HO-1 = Heme oxygenase-1
Hoxa1 = HomeoboxA1
Hoxb2 = HomeoboxB2
HPA = Hypothalamic-pituitary-adrenal cortex
HT = Hydroxytyrosol
HTT = Huntingtin
HUVEC = Human umbilical vein endothelial cell
HUVECs = Human umbilical vein endothelial cells
HVLT = Hopkins Verbal Learning Test
IBS = Irritable bowel syndrome
ICF = Intracellular fluid
IDD = Iodine deficiency disorder
IDE = Insulin-degrading enzyme
IDO = Indoleamine-2,3-dioxygenase
IDO1 = Indoleamine 2,3-dioxygenase 1
IDO2 = Indoleamine 2,3-dioxygenase 2
IGF-1 = Insulin-like growth factor 1
IIS = Insulin/insulin-like growth factor-1 signalling
IL1 = Interleukin-1
Il-1α = Interleukin-1 alpha
IL-1β = Interleukin-1 beta
IL6 = Interleukin-6
iNOS = inducible nitric oxide synthase
INPC = International Neuroblastoma Pathology Committee
INRG = International Neuroblastoma Risk Group

INSS = International Neuroblastoma Staging System
IPSP = Inhibitory postsynaptic potential
IQ = Intelligence quotient
IREs = Iron regulatory elements
IRP1 = Iron regulatory protein1
IRPs = Iron response proteins
IU = International unit
JAK3 = Janus kinase 3
K = Potassium
K^+ = Potassium ion
KALRN = Kalirin RhoGEF Kinase
KAP = Kinase-associated phosphatase
KIF1B = Kinesin family member 1B
LC = Locus coeruleus
LCPUFA = Long chain polyunsaturated fatty acid
LCPUFAs = Long chain polyunsaturated fatty acids
LCω-3PUFA = Long-chain omega-3 polyunsaturated fatty acids
LDH = Lactate dehydrogenase
L-DOPA = Levodopa /L-3,4dihydroxyphenylalanin
LIN28B = Lin-28 Homolog B
LMO1 = LIM domain only 1
LPS = Lipopolysaccharide
LTD = Long-term depression
LTP = Long-term potentiation
L-VGCC = L-type Voltage-gated calcium channel
LY86 = Lymphocyte antigen 86
LycT = Lycopene-enriched tomato extract
M = Molar
MAO = Monoamine oxidase
MAPK = Mitogen-activated protein kinase
MAPK8 = Mitogen-activated protein kinase 8
Mash-1 = Mammalian achaete-scute homolog-1
MCI = Moderate or mild cognitive impairment
MDG = Millenium Development Goals
MEF2 = Myocyte enhancer factor 2
Mfn2 = Mitofusin 2
Mg = Magnesium
mg = milligram
Mg^{2+}= Magnesium ion
mGluRs = metabotropic glutamatergic receptors
MgT = Mg-L-threonate

MiADMSA = Monoisoamyl -2,3-dimercaptosuccinic acid (a C5-branched-chain alkyl)
MIBG = Metaiodobenzylguanidine
miRNA = microRNA
MISIC = Malin's Intelligence Scale
MitoVES = Mitochondrially targeted vitamin E succinate
MMP = Matrix metalloprotienase
MMP-2 = Matrix metalloproteinase-2
MMP-2/9 = Matrix metalloprotienase-2 and -9
MMP-9 = Matrix metalloproteinase-9
MMSE = Mini-mental state examination
MMTV = Mouse mammary tumor virus
Mn = Manganese
Mn^{2+} = Manganous ion
Mn^{3+} = Manganic ion
MNP = Metabolic nutrition program
Mn-SOD = Manganese-superoxide dismutase
Mn-SOD/SOD2 = Manganese-superoxide dismutase/superoxide dismutase 2
MRI = Magnetic resonance imaging
mRNA = messenger RNA
MS = Methionine synthase
MS = Multiple sclerosis
MTHFR = 5,10-methylenetetrahydrofolate reductase
MT-III = Metallothionein-III
mTOR = mammalian target of rapamycin
MTRR = Methionine synthase reductase (MSR)
MTs = Metallothioneins
MYC or myc = Myelocytomatosis
MYCN = Mutation in the N-myc proto-oncogene
MZF1 = Myeloid zinc finger 1
MZF1-AS1 = MZF1 antisense RNA 1
Na = Sodium
Na^{+}= Sodium ion
NAD = Nicotinamide adenine dinucleotide
NAD^{+} = Nicotinamide adenine dinucleotide (Reduced)
NADP = Nicotinamide adenine dinucleotide phosphate
NADPH = Reduced nicotinamide adenine dinucleotide phosphate
NCC = Neural crest cells
NEFL = Neurofilament light
NEPSY = Neuropsychological Assessment

NeuroD-1 = Neurogenic differentiation 1
NEWSUP = New food supplement (it is a fortified vitamin supplementation)
NF1 = Nuclear Factor I
NF-kB = Nuclear factor Kappa B
NFT = Neurofibrillart tangle
NG2-glia = Nerve/glial antigen 2
NGF = Nerve growth factor
Ngn-1 = Neurogenin 1
$-NH_2$= Amino group
NHANES = National Health and Nutrition Examination Survey
Ni = Nickel
nM = nanomolar
NMDA = N-methyl-D-aspartate
NMDA-R = NMDA receptor
NMDA-Rs = NMDA receptors
nNOS = neuronal NO synthase
NO = Nitric oxide
NOS = Nitric oxide synthase
NOS3 = Nitric oxide synthase 3
NR2B or NMDAR2B = N-methyl D-aspartate receptor | Subtype 2B
Nrf2 = Nuclear factor erythroid2- related factor
NTBI = Non-transferrin bound iron
OAA = Oxaloaceticacid
$OH^{\bullet}$ = Hydroxyl radical
OXPHOS = Oxidative phosphorylation
P2X7 = Purinergic receptors
p38 = mitogen-activated protein kinase
p53= Tumor suppressor protein
PA = Protocatechuic acid
PAI-2 = Plasminogen activator inhibitor-2
pAkt = phosphorylated Akt
PAM = Peptidyl glycine α-amidating monooxygenase
PARP1 = Poly (ADP-ribose) polymerase 1
PAs l = Plasminogen activators
Pb = Lead
Pbx = Pre-B cell leukaemia transcription factor
p-CaMKII/CaMKII = phospho-CaMKII/CaMKII
p-CREB/CREB = phospho-CREB/CREB
PD = Parkinson’s disease
PDGF = Platelet-derived growth factor

PDGFR-alpha = Platelet-derived growth factor receptor-alpha
PDH = Pyruvate dehydrogenase
PDK = Phosphoinositide-dependent kinase
pERK1/2 = phosphorylated extracellular signal-regulated kinase 1/2
PFA = Potent functional analysis
PGF = Placental growth factor
PGM = Peptidyl glycine monooxygenase
pH = Negative logarithm of H^+ concentration
PHGDH = Phosphoglycerate dehydrogenase
PHOX2B = Paired like homeobox 2b
PI3K = Phosphoinositide 3-kinase
PI3K Akt = phosphoinositide 3-kinase-protein kinase B/Akt
PIB-PET Method = Positron emission tomography method with N-methyl [11C] 2-(4'-methyla|inophenyl)-6- hydroxy-benzothiazole
PIP2 = Phosphatidyl inositol bisphosphate
PKA = Protein kinase A
PKC = Protein kinase C
PKC-δ = Protein kinase C-delta
PKD = Polycystic kidney disease
PLC = Phospholipase C
PLGA = Polylactic-co-glycolic acid
PLP = Pyridoxal 5'- phosphate
pM = picomolar
PMAT-FC = Primary Mental Abilities Test for Filpino Children
PMP = Pyridoxamine 5′-phosphate
PNP = Pyridoxine 5′-phosphate
PNS = Peripheral nervous system
POGs = Paediatric oncology groups
PP2A = Protein phosphatase 2A
PPARs = Peroxisome proliferator-activated receptors
PPI3K = Active PI3K (pPI3K)
PPPARβ/δ = Peroxisome proliferator-activated receptor β/δ
Prl2c2 = Proangiogenic prolactin 2c2/proliferin
Prl7d1 = antiangiogenic prolactin 7d1/proliferin-related protein
proNGF = pro-nerve growth factor
PS = Presenilin
PS1 = Preseniline1
PS2 = Preseniline2
PSD93 = Post synaptic density protein 93
PSD95 = Postsynaptic density protein 95

p-Src = phosphorylated Src
p-tau = phosphorylated tau
PTPRD = Protein tyrosine phosphatase receptor type D
PUFA = Polyunsaturated fatty acids
RA = Retinoic acid
RAR = RA receptor
Rarb = RA receptor beta
RARs = RA receptors (isoforms)
RAVLT = Rey Auditory Verbal Learning Test
Rb = Retinoblastoma tumour suppressor protein
RCT = Randomised control trial
RCTs = Randomised control trials
RDA = Recommended daily allowance
RDAs = Recommended daily allowances
RDI = Recommended daily intake
RDIs = Recommended daily intakes
RFC = Reduced folate carrier
RNA = Ribonucleic acid
RNS = Reactive nitrogen species
ROS = Reactive oxygen species
RSC96 = Rat Schwann Cell line 96
RTT = Real-time test
RXR = Retinoid X receptor (an endogenous ligand- dependent nuclear receptor transcription factor)
Rxrg = Retinoid X receptor gamma
RXRs = Retinoid X receptors
SAM = S-adenosylmethionine
SA-NCC = Sympathoadrenal-NCC
sAPP = soluble / secreted Amyloid precursor protein
sAPPα = soluble Amyloid precursor protein α
Se = Selenium
Sec = Selenocysteine
SELENOF = Selenoprotein F
SELENOH = Selenoprotein H
SELENOI = Selenoprotein I
SELENOK = Selenoprotein K
SELENOM = Selenoprotein M
SELENOO = Selenoprotein O
SELENOP = Selenoprotein P
SELENOR = Selenoprotein R
SELENOS = Selenoprotein S

SELENOT = Selenoprotein T
SELENOU = Selenoprotein U
SELENOV = Selenoprotein V
SELENOW = Selenoprotein W
Se-Met = Seleno-L-methionine
SePP = SELENOP, Selenoprotein P
SFK = Src family kinase
sFLT1 = soluble FMS-like tyrosine kinase-1
SG = Sympathetic ganglion
SHMT = Serine-hydroxymethyl transferase
siRNA = small interfering RNA
SIRT = Sirtuin
SN= Sensory neuron
SNCA = Synuclein alpha
SNPs = Single nucleotide polymorphisms
SOD1 = Superoxide dismutase1
SOD2 = Superoxide dismutase2
Sox10 = SRY-Box transcription factor 10
Sox6 = SRY-box transcription factor 6
sp1 = specificity protein1 (transcription factor)
SPHS2 = Selenophosphate synthetase 2
SRY = Sex determining region Y
SSeCKS = Src-suppressed C-kinase substrate
sSPP β = soluble Amyloid precursor protein β
STAT1 = Signal transducer and activator of transcription 1
STAT3 = Signal transducer and activator of transcription 3
STZ = Streptozotocin
SUN = Scaling Up Nutrition
SVCT2 = Sodium-dependent vitamin C transporter 2
T3 = Tocotrienol
TACE = TNF-α converting enzyme
TCA = Tricarboxylic acid
TDEC = Tumour-derived endothelial cells
TDO2 = Tryptophan 2,3-dioxygenase
TDP = Thiamine diphosphate
TENM = Teneurin transmembrane protein
TENM 2 = Teneurin transmembrane protein 2
TENM 3 = Teneurin transmembrane protein 3
TERT = Telomerase Reverse Transcriptase
Tg-AD = Transgenic-AD
TGF = Transforming growth factor

TGF-β = Transforming growth factor-beta
THF = Tetrahydrofolate
THFA = Tetrahydrofolic acid
THP-1 = Human leukaemia monocytic cell line
TIAM1 = T-cell lymphoma invasion and metastasis 1
TIE = Tyrosine kinase with immunoglobulin-like and EGF-like domains
TIE-1 = Tyrosine kinase with immunoglobulin-like and EGF-like domains-1
TIE-2 = Tyrosine kinase receptors with immunoglobulin-like loops and epidermal growth factor homology domains-2
TIMP2 = Tissue inhibitor of metalloproteinase 2
TK = Transketolase
TLR4 = Toll-like receptor 4
TNF = Tumor necrosis factor
TNF-α = Tumor necrosis factor-alpha
TPH2 = Tryptophan hydroxylase 2
TPP = Thiamine pyrophosphate
TrkB = Tropomyosine receptor kinase B
TRPM7 = Transient receptor potential Melastatin 7
TrxR1 = Thioredoxin reductase1 (selenoprotein)
TS = Thymidylate synthase
TSP = Thrombospondins
TTP = Thiamine pyrophosphate
USA= United States of America
UTR = Untranslated region
UV = Ultraviolet
VAchT = Vesicular acetylcholine transporter
VDCC = Voltage-dependent Ca^{2+} channels
VDR = Vitamin D receptor
VDR-FokI= Vitamin D receptor-FokI
VE-cadherin = Vascular endothelial-cadherin
VEGF = Vascular endothelial growth factor
VEGF-A = Vascular endothelial growth factor-A
VEGFR = Vascular endothelial growth factor receptor
VEGFR1 = Vascular endothelial growth factor receptor1
VEGFR2 = VEGF receptor 2
VEGF-VEGFR = Vascular endothelial growth factor receptor system
VEM = Verbal episodic memory,
VGCC = Voltage-gated calcium channels
Vit A = Vitamin A
Vit B1 = Vitamin B1 (thiamine)

Vit B2 = Vitamin B2 (riboflavin)
Vit B3 = Vitamin B3 (niacin)
Vit B5 = Vitamin B5 (pantothenic acid)
Vit B6 = Pyridoxine (vitamin B6)
Vit B7 = Vitamin B7 (biotin)
Vit B9 = Vitamin B9 (folate)
Vit B12 = Vitamin B12 (cobalamin)
Vit C = Vitamins C (ascorbic acid)
Vit D = Vitamin D
Vit D3 = 1,25-dihydroxyvitamin D3 [1alpha,25-$(OH)_2$D3] or calcitriol
Vit E = Vitamin E (tocopherol)
Vit K = Vitamin K
VK3-OH = Hydroxyl analog of Vitamin K3 derivatives
WHO = World Health Organization
WISC = Wechsler Intelligence Scale for children
WISC-III = Wechsler Intelligence Scale for children- IIIrd edition
WISC-IV = Wechsler Intelligence Scale for children- IVth edition
WISC-R = Wechsler Intelligence Scale for children- Revised
Wnt = Wingless integrated
Wnt-1 = wingless-type MMTV integration site family member 1
WPPSI-R = Wechsler preschool and primary school of intelligence-Revised
ZIP = Zinc-regulated, and iron-regulated transporter-like protein
Zn = Zinc
Zn^{2+} = Zinc ion
ZnT3 = Zinc transporter 3
ZnTs = Zinc transporters
ZO = Zonula occludens
α = Alpha
α-KG = α-ketoglutarate
α-KGD = α-ketoglutarate dehydrogenase
α-TTP = Alpha-tocopherol transfer protein
β = Beta
β-CM = β-carotene 15, 15'-monoxygenase
γ = Gama
δ = Delta
ε = Epsilon
ω = Omega
ω-3 DHA = Omega-3 docosahexaenoic acid
ω-3 FA = Omega-3 fatty acid
ω-6 FA = Omega-6 fatty acid

CHAPTER 1

ROLE OF MICRONUTRIENTS IN BRAIN DEVELOPMENT

MRINAL KANTI PODDAR,
APALA CHAKRABORTY,
SOUMYABRATA BANERJEE

Contents

Abstract

Micronutrients, such as vitamins and minerals, are necessary building blocks that the body needs in minute amounts to generate enzymes, hormones, neurotransmitters, and other vital substances for growth and development. Micronutrient deficiencies during pregnancy and lactation can result in improper brain development since they are necessary for the division of neurons, the synthesis of DNA, the production of neurotransmitters, and the metabolism of neurohormones, among other

processes. Micronutrients are necessary for the primary stages of neural development, including synaptogenesis, synaptic pruning, neuronal migration and division, and connection development. Additionally, micronutrients have the ability to alter gene expression, which then affects how the developmental processes work. Micronutrients play an important role in all stages of cell growth, either as cell signalling molecules (e.g., retinoic acid) or as cofactors of enzymatic reactions (e.g., copper, zinc, Vit B6), which is the focus of this chapter. Micronutrient deficiencies can be caused by a variety of factors, including a lack of dietary intake, genetic variation, micronutrient interaction, or exposure to certain stressors. Thus, it is critical to understand and prevent micronutrient deficiency, particularly during the early stages of brain development, by implementing proper planning and action to ensure the effective consumption of micronutrients enrich balance diet, particularly by women and children, as well as their development globally.

1. Introduction

Micronutrients, such as vitamins and minerals, are critical for individual development and growth, as well as for healthy living. According to the World Health Organization (WHO), "Micronutrients" are "magic wands", or substances that are required in small amounts by the body but play an important role in the production of enzymes, hormones, neurotransmitters, and other important components that are directly involved with the body's developmental processes [1]. Malnutrition is frequently associated with a lack or excess of essential micronutrients such as, vitamins and minerals, and it has been identified as the leading cause of child mortality (around 45%) worldwide [2]. The importance of micronutrients on health outcomes has been recognised, and awareness of malnutrition-related health severity, prevention, and control have been considered in recent decades [3]. In this context, it is worth noting that iron, Vit A, and iodine are the three most common micronutrient deficiencies addressed globally among pregnant women and children, according to a WHO report [4]. These micronutrient deficiencies are responsible for some severe health issues, as well as a lack of energy and developmental capacities, which leads to a reduction in work productivity, particularly in children under the age of five and expectant mothers [4]. These micronutrient deficiencies are responsible for some severe health issues, as well as a lack of energy and developmental capacities, which leads to a decrease in work productivity, particularly in children under the age of five and expectant mothers [4]. Maternal malnutrition is strongly linked to problems with brain development, growth