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Role of cyclic adenosine monophosphate as a key regulator of energy homeostasis in rats

A Thesis Submitted By

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Declaration

I declare that this thesis has been composed by myself and that this work, which has been recorded here in after has been done by myself. It has not been submitted for a degree at this or any other university.

Aya M. M. Farahat

Dedication

I would like to dedicate this thesis with all my love to my family and for all my friends and those from whom I have learned, whenever and wherever they are.

Aya M. M. Farahat

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Aya Farahat

Role of cyclic adenosine monophosphate as a key regulator of energy homeostasis in rats

Abstract

Energy homeostasis refers to the balance between energy intake, including the intake through the form of food and drinks, and energy expenditure, including resting energy expenditure (basal metabolism) and physical activity over a prolonged period in adult animals.

Obesity results from an imbalance between food intake and energy expenditure which leads to accumulation of body fats resulting in cardiovascular and metabolic disorders. Weight lowering and antihyperlipidemic agents from medicinal plants are extensively used recently due to their safety and efficacy. To evaluate the effect of black pepper and coffee extracts on chronic and acute experimental induced obesity and energy homeostasis, rats were divided into ten groups including control, high-fat diet (HFD), triton, HFD+triton, black pepper+HFD, black pepper+HFD+triton, coffee+HFD, coffee+HFD+triton, mixture+HFD and mixture+HFD+triton groups. Body mass index (BMI), food efficiency intake (FEI) and body weight gain (BWG) were calculated. Blood glucose, plasma insulin, and insulin resistance were estimated. Lipid profile, liver, and kidney functions were measured, serum and brain cyclic adenosine monophosphate (cAMP) was estimated by enzyme-linked immunosorbent assay (ELISA) and brain

neurotransmitters were measured by high-performance liquid chromatography (HPLC). Also, histopathology of the liver was performed.

The findings showed that blood glucose, insulin, lipid profile, kidney and liver functions as well as brain cAMP and neurotransmitters were significantly increased, concomitant with a significant decrease in serum cAMP in both high-fat diet and triton induced obesity groups compared to control. Supplementation with black pepper extract, coffee extract and a mixture of both significantly improved these findings. In conclusion, cAMP has a great impact in obesity treatment by elevating serum cAMP and using black pepper and coffee extracts are overlooked as promising weight reduction and antihyperlipidemic agents by increasing serum cAMP. Black pepper and coffee also have an impact on brain levels of cAMP and neurotransmitters, decrease food intake, and stimulate of thermogenesis, bringing a net effect of decreasing fat accumulation throughout the body and lowering body weight.

KEY WORDS: Energy homeostasis, obesity, black pepper extract, coffee extract, cAMP, neurotransmitters.

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LIST OF Abbreviations

5-HT	Serotonin
A2AR	Adenosine receptors
ABCA1	ATP-binding cassette transporter A1
AC	Adenylyl cyclase
Ach	Acetylcholine
ACTH	Adrenocorticotropic hormone/or adrenocorticotropin
AdipoQ	Adiponectin
AdipoR1	Adiponectin receptor 1
ADP	Adenosine diphosphate
AGRP	Agouti-related protein
AI	Atherogenic Index
Akt	Protein kinase B (PKB)
ALT	Alanine amino transaminase
AMPK	5' adenosine monophosphate-activated protein kinase
AP	Area postrema
APOA1	Apolipoprotein A1
ARC	Arcuate nucleus
AS	Atherosclerosis
AST	Aspartate amino transaminase
ATP	Adenosine triphosphate
b.w.	Body weight
BAT	Brown adipose tissue
BBB	Blood–brain barrier
BCL2	B-cell lymphoma 2
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BWG%	Body weight gain%
C2R2	2 catalytic and 2 regulatory units

Ca^{+2}	Calcium ion
cAMP	3'-5'-cyclic adenosine monophosphate/ or cyclic AMP
CART	Cocaine and amphetamine regulated transcript
CCK	Cholecystokinin
cGMP	Cyclic guanosine monophosphate
CHE	Cholesterol esterase
CHOD	cholesterol oxidase
Cm	Centimeter
CNS	Central nervous system
CREB	cAMP response element
CRH	Corticotropin-releasing hormone
CRI	Coronary Risk Index
CVD	Cardiovascular disease
DA	Dopamine
DAG	Diacylglycerol/or Diglyceride
DARPP-32	cAMP-regulated phosphoprotein
DMN	Dorsomedial nucleus
DNA	Deoxyribonucleic acid
DS	Dorsal striatum
DVC	Dorsal vagal complex
DVN	Dorsal motor nucleus of vagus
ELISA	Enzyme linked immunosorbent assay
ENPP1	Ectonucleotide pyrophosphatase/ phosphodiesterase1
EPAC	exchange factor (protein) directly activated by cAMP
ERK	Extracellular signal–regulated kinases
FA	Fatty acid
FAD	Food and Drug Administration
FER	Feed efficiency ratio

FFA	Free fatty acid
FTO	Fat mass and obesity associated gene
G	Gram
GABA	γ-aminobutyric acid
GHSRs	Secretagogue receptors
GI	Gastrointestinal
G_i	Inhibitory G
GIRK	G-protein-gated inwardly rectifying K^+ channels
GLP-1	Glucagon-like peptide-1
GLUT4	Transporter type-4
GOD	Glucose Oxidase Enzyme
GPCRS	G -protein-coupled receptors
GPO	glycerol-3-oxidase
G_s	Stimulatory G
HDL	High density lipoprotein
HFD	High Fat Diet
HOMA-IR	homeostasis model assessment of insulin resistance
HPLC	High-performance liquid chromatography
HSL	Hormone-sensitive lipase
HSL-P	phosphorylates HSL
i.p.	Intraperitoneally
IL-6	Interleukin-6
IP3	Inositol trisphosphate/ or Inositol 1,4,5-trisphosphate
IR	Insulin resistance
IRS-1	Insulin receptor substrate-1
LDL	Low density lipoprotein
LEP	Leptin

LEP-R	Leptin receptor
LHA	Lateral hypothalamic area
LPL	Lipoprotein lipase
MAG	Monoacylglycerol/or Monoglyceride
MAPK	Mitogen-activated protein kinases
MC3R	Melanocortin 3 receptor
MC4R	Melanocortin 4 receptor
MCH	Melanin-concentrating hormone
ME	Median eminence
mg/dL	Milligrams per deciliter
mmol/L	Millimole per liter
MRP	Multidrug associated resistance protein
MSH	Melanocyte-stimulating hormone
mTOR	Mechanistic target of rapamycin/or mammalian target of rapamycin
mTORC2	mechanistic target of rapamycin complex 2
NA	Norepinephrine/or Noradrenaline
NAc	Nucleus accumbens
NFkB	nuclear factor kappa- activated B cells
NHE3	Sodium–hydrogen antiporter 3
NIFAs	Non-esterified fatty acids
NLD	Normal Laboratory Diet
nmol/L	Nanomoles per liter
NPY	Neuropeptide-Y
NTRK2	neurotrophic tyrosine kinase receptor type 2
NTS	Nucleus of the tractus solitaries
PAP	Phosphatidate phosphatase