Plasma Level of Brain Derived Neurotrophic Factor in a sample of Egyptian Chronic Heroin Users; Impact on Cognitive Functions

Thesis

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قَالُوا سُبْحَانَكَ
لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ
صدق الله العظيم
سورة البقرة الآية (٣٢)

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Mahmoud Farag Mohamed Soliman

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LIST OF ABBREVIATIONS

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
BBB	Blood brain barrier
BDNF	Brain derived neurotrophic factor
BNST	Bed neucleus of stria terminalis
CPP	Conditioned place preference
CREB	cAMP response element binding protein
GABA	Gamma aminobutyric acid
GDNF	Glial cell derived neurotrophic factor
KA	Kainic acid
LTM	Long term memory
LTP	Long term potentiation
MAM	Mono acetyl morphin
mGLU	Metabotropic glutamate
MOPr	μ-Opiod peptide receptors
mPFC	Medial prefrontal cortex
NA	Neucleus accumbens
NGF	Nerve growth factor
NMDA	n-methyl-d-aspartayl acid
P-75	Protin 75 receptor
PI3K	Phosphatidyl inositol-3-kinase
PLC	Phospholipase c
rTMS	Repetitive transcranial magnetic stimulation
SGZ	Sub-granular zone
SNP	Single neucleotid polymorphism
SUD	Substance use disorder
TLR	Tall like receptor protein
TrK-B	Tropomyosin receptor kinase B
VTA	Ventral tegmental area
WAIS	Wechsler adult intelligence scale
WCST	Wisconsin card sorting test
WHO	World health organization
WMS	Wechsler memory scale

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Abstract

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Addiction is a chronic and progressive condition associated with such symptoms as compulsion, uncontrollable craving, drug seeking behaviors and continual drug use, which brings harmful social, mental, physical, familial and economic consequences. World Health Organization (1996) defines addiction as any substance that enters an organism and causes adaptation or variation in the quality and function of the organism. Addiction symptoms as sorted out by World Health Organization (WHO) include: need for using a chemical substance the abstention from which causes abnormal physical disorders which is unbearable by the addict, tendency towards gradual increase in drug use for pleasure and comfort, physical and mental dependency on drug, and a sense of ecstasy after drug use. Human addiction is a complicated disorder process affecting about 1.2 % of population, in which cognitive factors including inability to control personal behavior against the compulsion to take the preferred substance are involved. A newly-proposed hypothesis emphasizes the role of executive dysfunctions in continuation of drug addiction. Therefore, in information processing approach a cognitive factors contribute to the drug use leads to relapse in addicts. Accordingly, from among the factors contributing to drug dependency neuropsychological factors plays a crucial role, this is because drug dependency causes damages to cognitive functions including problem solving, planning, working memory, organization, learning new material, visuospatial abilities, cognitive flexibility and retention skills.

Key words:
AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CREB :cAMP response element binding protein NMDA: n-methyl-d-aspartayl acid P-75:Protin 75 receptor

Introduction

Addiction is a chronic and progressive condition associated with such symptoms as compulsion, uncontrollable craving, drug seeking behaviors and continual drug use, which brings harmful social, mental, physical, familial and economic consequences ***(Dawe, 2004).***

World Health Organization (1996) defines addiction as any substance that enters an organism and causes adaptation or variation in the quality and function of the organism. Addiction symptoms as sorted out by World Health Organization (WHO) include: need for using a chemical substance the abstention from which causes abnormal physical disorders which is unbearable by the addict, tendency towards gradual increase in drug use for pleasure and comfort, physical and mental dependency on drug, and a sense of ecstasy after drug use ***(Noël, 2007).***

Human addiction is a complicated disorder process affecting about 1.2 % of population, in which cognitive factors including inability to control personal behavior against the compulsion to take the preferred substance are involved. A newly-proposed hypothesis emphasizes the role of executive dysfunctions in continuation of drug addiction.

Therefore, in information processing approach a cognitive factors contribute to the drug use leads to relapse in addicts ***(Fereshteh, 2012).***

Accordingly, from among the factors contributing to drug dependency neuropsychological factors plays a crucial role, this is because drug dependency causes damages to cognitive functions including problem solving, planning, working memory**,** organization, learning new material, visuospatial abilities, cognitive flexibility and retention skills ***(Ardila, 2007; Chan, 2008).***

Heroin is characterized as one of the most frequently abused illegal drugs (nearly 7.3 % of addict are using heroin), and addiction to this drug is linked to significant attention deficits and inadequate performance on memory tasks. Furthermore, chronic exposure to opiates is also shown to affect brain regions related to learning and memory, such as the frontal cortex and the hippocampus ***(Lu et al., 2010; Soyka et al., 2011).***

Brain-derived neurotrophic factor (BDNF) is a secreted protein that, in humans, is encoded by the BDNF gene. BDNF is a member of the "neurotrophin" family of growth factors that are found in the brain and the periphery.

BDNF acts on certain neurons of the central nervous system helping to support the survival of existing neurons, and encourage the growth and differentiation of new neurons and synapses. In the brain, it is active in the hippocampus, cortex, and basal forebrain which are areas vital to learning, memory, and higher thinking ***(Bekinschtein, 2008).***

Experimental and clinical data suggested that BDNF plays an important role in the pathogenesis of Alzheimer's disease and Amnestic mild cognitive impairment and many other psychiatric disorders which are characterized by declined cognitive functions. Serum concentrations of BDNF was significantly lower than those of healthy controls in these diseases in various studies which suggested that reduced BDNF levels may play a role in the pathophysiology of cognitive impairment ***(Yu, 2008).***

BDNF level in plasma can reflect brain-tissue BDNF levels as supported by data ***(klein, 2011),*** and this plasma BDNF was found to be decreased in chronic heroin users ***(Francesco, 2007).***

Rationale of the study

Heroin use disorder is a wide spread phenomenon. In Egypt it is about 0.5 million persons addicted on heroin as reported in The National Review of Drug Abuse and Addiction, so in a glance we can find out to what extend heroin use resemble a real problem in our country. Western studies suggested negative effect of chronic Heroin use on brain tissues and subsequently cognitive functions. Also proved that one of the pathophysiological mechanisms is through affection of neurotrophic factors of the brain. Yet similar Egyptian studies that explain effect of heroin use on cognitive function and brain neurotrophic factors are scanty that is why find it worthy to study these effects in Egyptian patients. As knowing the pathophysiological mechanisms beyond addiction opens new horizons in its management.

Hypothesis of the study

Heroin use is known to affect cognitive functions especially with chronic use that will affect plasma BDNF level with permanent cognitive dysfunctions.

Aims of the study

1- To recognize impact of chronic heroin use on the cognitive functions.

2- To describe the impact of chronic heroin use on BDNF plasma level.

3- To identify the relationship between the degree of severity of heroin use on both BDNF plasma level and corresponding cognitive dysfunction.

Chapter (1):

Impact of Substance Use specifically Heroin on Cognitive Functions

World Health Organization (1996) defines addiction as any substance that enters an organism and causes adaptation or variation in the quality and function of the organism. Addiction symptoms as sorted out by World Health Organization (WHO) include: need for using a chemical substance the abstention from which causes abnormal physical disorders which is unbearable by the addict, tendency towards gradual increase in drug use for pleasure and comfort, physical and mental dependency on drug, and a sense of ecstasy after drug use ***(Noël, 2007).***

Human addiction is a complicated neurological process affecting about 7-15% of population, in which cognitive factors include inability to control personal behavior against the compulsion to take the preferred substance are involved. A newly-proposed hypothesis emphasizes the role of damage of executive functions in addiction to drugs. Therefore, in information processing approach, cognitive factors contribute to repeated drug use and relapse in the addicts ***(Fereshteh, 2012).***

Unfortunately substance use is a hydrophobic disorder that preys youth starting from their early adolescent period leading to grievous consequences on their entire life including negative effect on their brain tissues and subsequently cognitive functions which then brings harmful social, mental, physical, familial and economic consequences ***(Dawe, 2004)***. Moreover substance use disorder (SUD) is a wide spread phenomenon. In Egypt, one of the studies that was done in five districts to estimate the percentage of substance use showed results as follow: 14,8% polysubstance use, 26% tetrahydrocannabinoid (THC) use, 9% opioid use, 10% alcohol use, 7% sedative hypnotics use and 0.5 % stimulants use -reported in The National Review of Drug Abuse and Addiction- so in a glance we can find out to what extent substance use resemble a real problem in our country ***(Khoweiled, 2012).***

It is now clear that substance use disorder is a chronic relapsing disease, and the tendency to relapse are caused by a combination of environmental, biological, and genetic factors, where processes during early stages of drug use is suggested to promote strong maladaptive connections between use of drugs and environmental input that serves the