Effect of Methamphetamine Addiction on Brain Chemistry Through the Adoption of Fractalkine as an Indicator

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Abstract

Methamphetamine (METH), a highly addictive drug and a strong stimulant of the central nervous system. METH abuse is increasing, especially among young people and adolescents, and therefore we wanted in this research to shed light on some of the problems resulting from meth use, especially its effect on the central nervous system, the blood-brain barrier, and Fractalkine (CX3CL1).

CX3CL1 is the only member of the CX3C subcategory of chemokines, which have a major role in the central nervous system by regulating interactions between neurons, glial cells, and immune cells. It is also considered heavily involved in traumatic brain injury (TBI) and spinal cord injury (SCI).

The study was conducted on eighty people divided into three groups, thirty non addicted men as a control group(G1), taking into account and excluding, cigarette smoking, age, social and cultural conditions, and chronic diseases, also thirty people addicted to methamphetamine(G2), and twenty people addicted to methamphetamine and other narcotic substances (mix)(G3), whose ages ranged between (15-45) years and the period of methamphetamine abuse ranged between (1-7) years.

The results of study showed that CX3CL1 values were higher among addicted persons compared to non-addicts (G1), this difference in values shows us the effect of meth on the total values of CX3CL1.

Keywords: *CX3CL1. Fractalkine .CX3CR1. Chemokines. Methamphetamine. blood–brain barrier (BBB).*

Introduction

Methamphetamine(Meth) is an amphetamine derivative that is abused increasingly world-wide [(1)]. And it is a widely abused psychostimulant contributes to altered neuronal function, addiction, and cellular damage[(2, 3)].

Meth affects glial cell activity, and glial cell activity that lead to modulate the neurotoxic and addictive effects of methamphetamine. Microglia are the major antigen-presenting cells in brain and when activated, they secrete an array of signaling molecules (e.g., proinflammatory cytokines and chemokines) that can cause neuronal damage.

Astrocytes are the most numerous and diverse glial cells in the CNS, with a variety of functions including, but not limited to maintenance of brain homeostasis, storage and distribution of energy substrates, synaptogenesis, and brain defense.

Like microglia ,astrocytes can also secret a number of signaling molecules that play a putative role in methamphetamine-induced neurotoxicity, such as pro- and anti-inflammatory cytokines including interleukins (ILs), interferons (IFNs), and tumor necrosis factors (TNFs), as well as chemokines [(4)].

Activation of microglia and astrocytes are normal compensatory reactions to brain injury, but excess neuro inflammation can lead to further brain damage. Indeed, repeated or neurotoxic (i.e., high dose) Meth

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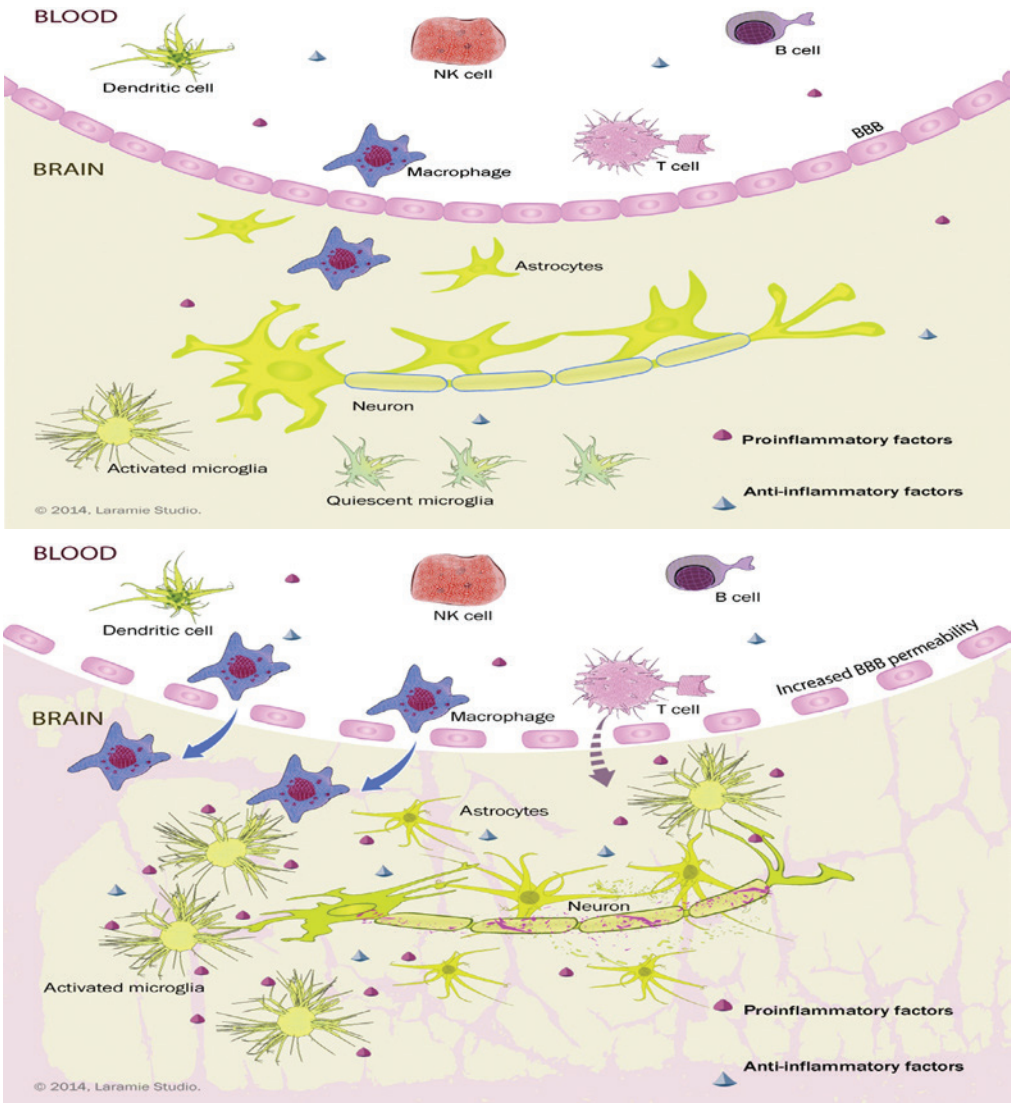
exposure induces alterations in glial cell functions that contribute to a complex cascade of events, leading to neuro inflammation, neuronal damage, and behavioral impairments (Fig. 1)[5] .

Pre-clinical in vivo studies and cultured human brain microvascular endothelial cell in vitro experiments show that methamphetamine contributes to inflammation-induced BBB dysfunction in a dose- and time-dependent manner[6] .

Methamphetamine exposure, in combination with stress, can synergistically exacerbate BBB damage via inflammatory mechanisms that persist for at least 7 days following methamphetamine[7]. Collectively, these methamphetamine-induced effects on BBB contribute to immune dysfunction, such as increased leukocyte/monocyte transmigration across the endothelium and into the CNS [8, 9] as shown in (Fig. 1).



(Figure 1): simplified schematic of brain and periphery the blood–brain barrier (BBB).[5]

Fractalkine is a large cytokine protein of 373 amino acids, that has a chemokine domain located on top of a mucin-like stalk [10, 11], it contains multiple domains and is the only known member of the CX_3C chemokine family. It is also commonly known under the names fractalkine (in humans) and neurotactin (in mice).[10]

The main source of chemokines is white blood cells (WBC), but CX3CL1 is mainly produced in endothelial cells and neurons.[12] It is not surprising that CX3CL1 expression is elevated in highly vascularized and well-innervated organs and also in locations with an increased concentration of immune system cells, such as the CNS,

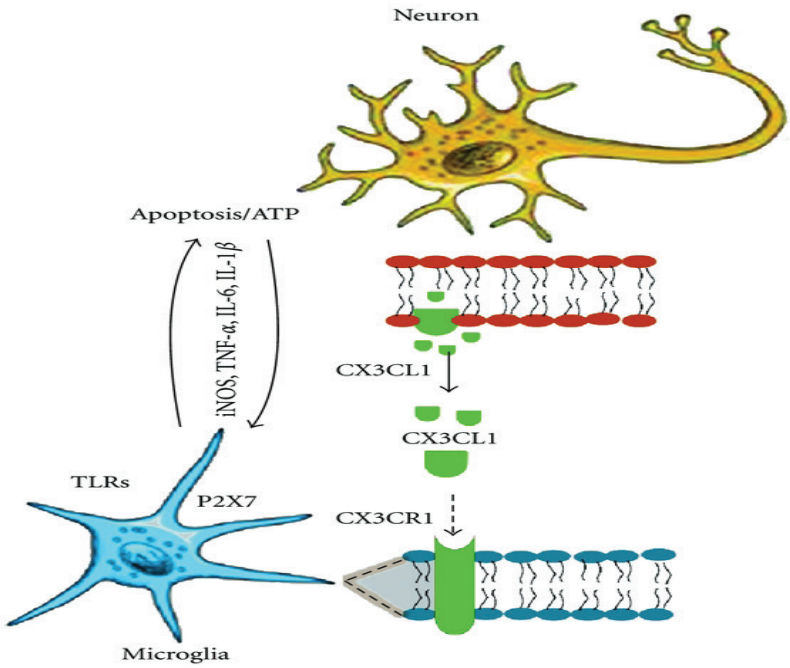
lungs, cardiac muscle, liver, intestines, and placenta .[13, 14]

Soluble CX3CL1 potently chemo-attracts T cells and monocytes, while the cell-bound chemokine promotes strong adhesion of leukocytes to activated endothelial cells, where it is primarily expressed.[10] CX3CL1 elicits its adhesive and migratory functions by interacting with the chemokine receptor CX3CR1.[15]

Fractalkine is found commonly throughout the brain, particularly in neural cells, and its receptor is known to be present on microglial cells. It has also been found to be essential for microglial cell migration.[16]

CX3CL1 is also up-regulated in the hippocampus during a brief temporal window following spatial learning, the purpose of which may be to regulate glutamate-mediated neurotransmission tone. This indicates a possible role for the chemokine in the protective plasticity process of synaptic scaling.[17]

The disruption of homeostatic paracrine and autocrine interactions of the CX3CL1/CX3CR1 axis in the context of neuron-microglia communication may be seen as one of fundamental elements in the pathogenesis of CNS related diseases [18]. One inducer through which neurons and microglia can communicate to regulate inflammation is fractalkine (CX3CL1) (Fig 2).[19]



(Figure 2): The scheme shows intraneuronal protein accumulation. [19]

Material and Method

The study was conducted on eighty people divided into three groups, thirty non addicted men as a control group(G1), taking into account and excluding, cigarette smoking, age, social and cultural conditions, and chronic diseases, also thirty people addicted to methamphetamine(G2), and twenty people addicted to methamphetamine and other narcotic substances (mix) (G3), whose ages ranged between (15-45) years and the period of methamphetamine abuse ranged between (1-7) years.

This study was conducted at the University of Babylon / College of Science / Chemistry Department, and also in Baghdad Governorate, Ibn Rushd Teaching Hospital for Psychiatry.

The addicted persons were chosen for study after being clinically examined and diagnosed by

the laboratories of Ibn Rushd Teaching Hospital for Psychiatry. The results of the screening of people taking methamphetamine during the past (24-48) hours were positive.

Determination of Fractalkine: Human Fractalkine (CX3CL1) (Chemokine C-X3-C-Motif Ligand 1) measured according to method that described in ELISA Kit.

Results and Discussion

The current study included fifty addicted males their ages were 26.7±7.4 years who had a history they of meth abuse for 1-7 years as test group, While the control group was thirty persons non addicted males their ages 27.9±6.9 years as shown in Table (1).

Table (1). Age(Years) for addicts group and non addicts (controls)

Groups	N	Ages Mean± SD	SE
Age for addicts	50	26.7 + 7.4	1.04
Age for non addicts	30	27.9 + 6.9	1.27

Also, the addict group was divided into: two groups, thirty people were addicted to methamphetamine and considered as G2, and twenty people were addicted to methamphetamine with other drugs G3.

Table (2) Fractalkine levels, the ressults in table (2) show the levels of Fractalkine for addict groups compared with non-addict group.

Groups	N	Mean + SD	SE	CI 95%		Compared group		P value
				Lower	Upper			
G1	30	0.414 + 0.13	0.02	0.36	0.46	1	2	0.65
							3	0.09
G2	30	0.500 + 0.22	0.04	0.41	0.58	2	1	0.65
							3	0.97
G3	20	0.502 + 0.17	0.03	0.42	0.58	3	1	0.09
							2	0.97

Also, the group of meth addicted (G2), and the group of mix addicted (G3), were divided dependent on addict age to A1 (15-21) years, A2 (22-27) years, A3 (up 27) table (3) and (4), as well as they divided depend on abuse duration for D1 (1-2) years, D2 (3-4) years, D3 (5-6) years, the results are show in Table (5) and (6).

The results in Table (3) that show of Fractalkine level were higher in METH addicts group (A3) as compared to addicts group (A1) and (A2) (P >0.05).

Table (3) CX3CL1 level, for addict (Meth) sub groups within variable ages.

Addicts age (Meth)	N	Mean + SD	SE	CI 95%		Compared group		P value
				Lower	Upper			
A1	7	0.40 + 0.12	0.04	0.28	0.51	1	2	0.29
							3	0.18
A2	10	0.51 + 0.19	0.06	0.37	0.65	2	1	0.29
							3	0.77
A3	13	0.54 + 0.26	0.07	0.38	0.70	3	1	0.18
							2	0.77

The results in Table (4) that show of Fractalkine level were higher in METH addicts group (A2) as compared to addicts group (A1) and (A3) (P >0.05).

Table (4) CX3CL1 level, for addict (Mix) sub groups within variable ages.

Addicts age (Mix)	N	Mean + SD	SE	CI 95%		Compared group		P value
				Lower	Upper			
A1	7	0.47 + 0.14	0.05	0.34	0.59	1	2	0.57
							3	0.64
A2	7	0.52 + 0.20	0.07	0.34	0.70	2	1	0.57
							3	0.93
A3	6	0.51 + 0.19	0.08	0.31	0.71	3	1	0.64
							2	0.93

Table (5) CX3CL1 level, Subgroups Dependent on Abuse Duration(Years) for Addicts Group (Meth)

Duration of addicts (Meth)	N	Mean + SD	SE	CI 95%		Compared group		P value
				Lower	Upper			
D1	20	0.50 + 0.24	0.05	0.38	0.61	1	2	0.96
							3	0.97
D2	6	0.49 + 0.20	0.08	0.28	0.70	2	1	0.96
							3	0.95
D3	4	0.50 + 0.08	0.04	0.38	0.64	3	1	0.97
							2	0.95

Table (6) CX3CL1 level, Subgroups Dependent on Abuse Duration(Years) for Addicts Group (Mix)

Duration of addicts (Mix)	N	Mean + SD	SE	CI 95%		Compared group		P value
				Lower	Upper			
D1	10	0.51 + 0.15	0.05	0.40	0.63	1	2	0.85
							3	0.69
D2	5	0.49 + 0.24	0.10	0.19	0.79	2	1	0.85
							3	0.86
D3	5	0.47 + 0.14	0.06	0.29	0.65	3	1	0.69
							2	0.86

Table (2) show that CX3CL1 levels were higher among addicted compared to non-addicts (control group), and this results explained the effect of meth on the CX3CL1 levels.

METH abuse is also shown to exert neurotoxic effects by increasing the secretion of pro-inflammatory cytokines IL-6 and TNF-alpha in the brain [20, 21]. METH abuse appears to impair blood-brain barrier (BBB) vascular function [22, 23].

These myriad effects of METH on cardio-neurovascular function and on astrogliosis-related neurotoxicity clearly emphasize the importance of the blood and brain interface. The blood-brain barrier, principally composed of the brain endothelium tight junction proteins, is a dynamic interface. BBB function is maintained at the expense of huge bio-energy consumption [24-26].

Fluctuations in CX3CL1 levels are also observed in many neurodegenerative diseases. Increased levels of serum CX3CL1 are reported in patients with multiple sclerosis[27, 28], traumatic brain injury [29], and human immunodeficiency virus (HIV) with CNS complications [30].

The CX3CL1/CX3CR1 axis acts in many physiological phenomena including those occurring in the central nervous system (CNS), by regulating the interactions between neurons, microglia, and immune cells. CNS injuries represent a serious public health problem, despite improvements in therapeutic management. To date, no effective treatment has been determined, so they constitute a leading cause of death and severe disability. Recent evidence implicated the role of the CX3CL1/CX3CR1 axis in neuro inflammatory processes occurring after CNS injuries [31].

there are numerous newly discovered phenomena as regards the influence of the CX3CL1/CX3CR1 axis on CNS physiology and pathology, such as the effect on the synaptic plasticity, maturation, activity and a marked effect on the functioning of hippocampal formation [32].

Conclusion

The study showed an increase in the levels of Fractalkine among meth addicts. This increase may lead to infection with various diseases such as traumatic brain injury (TBI) and spinal cord injury (SCI).

Also, the study shows us that the Fractalkine levels increase with age, which increases the risk of developing various diseases directly related to the Fractalkine.

Ethical Clearance: The college's ethical committee has no objection to conducting the research and the numbers and date of acceptance are (no: 3275 ,13/9/2019)

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