Elevated of Calcium and Sodium Levels as a Result of Methamphetamine Addiction, Causes and Consequence

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Abstract. Methamphetamine (METH) is an addictive drug causes toxicity and degeneration in the brain. Several evidence have demonstrated that METH toxicity results oxidative stress that regulate an intracellular signaling cascade that leads to cell death. In this paper we studied the effect of METH on calcium levels because of its great importance on human health. Calcium, is a messenger of extracellular signals in a great variety of cells; it regulates several neuronal functions, such as neurotransmitter synthesis and release, neuronal excitability, phosphorylation. Calcium is also involved in long-term processes, like memory. As well, we highlighted sodium levels to find out the main course in nerve function and to keep body fluids in balance.

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.

Calcium levels were highly significant in addicts group (P < 0.05), as compared to non addicts group. as well, when dividing by age, Calcium level were higher in METH and MIX addicts group (A2) as compared to addicts group (A1) and (A3) (P >0.05). Also, Calcium level were higher in METH and MIX addicts group (D3) as compared to addicts group (D1) and (D2) (P >0.05). We have noticed Increased duration of abuse Increases calcium levels. In addition to, Sodium levels were highly significant in addicts group (P < 0.05), as compared to non addicts group. During the study, it was found that age had an effect on sodium levels, Sodium level were higher in METH addicts group (A1) as compared to addicts group (A2) and (A3) (P> 0.05). While, Sodium level were higher in MIX addicts group (A2) as compared to addicts group (A1) and (A3) (P> 0.05). As well, Sodium level were higher in METH and MIX addicts group (D2) as compared to addicts group (D1) and (D3) (P> 0.05). Indeed, the difference in the duration of the abuse affects the sodium levels.

Keywords Methamphetamine. Calcium. sodium. central nervous system (CNS). Neurons
Introduction
Methamphetamine, also known as “ice” or “crystal,” is an highly addictive potent and commonly abused stimulant pharmacologic (psychostimulant) drug with strong neurotoxic effects on the central nervous system (CNS). [1]
In the central nervous system (CNS), METH exerts a psychostimulant effect; however, long-term or toxic use of METH can cause many negative effects, such as violent behavior and psychotic features including paranoia, auditory hallucinations and delusions [2].
METH also significantly increased the cytosolic calcium levels. [3] Rising Ca$^{2+}$ concentration in the cytoplasm causes Ca$^{2+}$ influx into mitochondria and nuclei. In mitochondria Ca$^{2+}$ accelerates and disrupts normal metabolism leading to cell death. [4]
Calcium, the most abundant mineral in the body, the calcium ions play a vital role in the physiological and biochemical processes of organisms and cells: in signal transduction pathways where they act as a second messenger; in neurotransmitter release from neurons; in contraction of all muscle cell types; as cofactors in many enzymes, though less than 1% of total body calcium is needed to support these critical metabolic functions. Serum calcium is very tightly regulated and does not fluctuate with changes in dietary intakes; the body uses bone tissue as a reservoir for, and source of calcium, to maintain constant concentrations of calcium in blood, muscle, and intercellular fluids. The remaining 99% of the body’s calcium supply is stored in the bones and teeth where it supports their structure and function [5]. calcium is also involved in various neuronal functions, such as neurotransmitter synthesis and release [6] and the control of neuronal membrane excitability. It regulates neuronal plasticity and metabolic activity, such as phosphorylation and proteolytic activity, and it contributes to the anticonvulsant effect of some drugs [7]. Recent studies underlined the involvement of this ion in long-term processes, like memory [8], and changes in protein synthesis through the induction of specific genes [9]. Calcium is also involved in the transport of proteins and other molecules that are formed in neurons, from the cell body to its nerve endings. Ca$^{2+}$ exerts a complex regulatory role on the numerous cell functions, including cell death [10].
As well as, sodium is an essential mineral that regulates blood volume, blood pressure, osmotic equilibrium and PH. also, is one of the body's electrolytes, which are minerals that the body needs in relatively large amounts. Electrolytes carry an electric charge when dissolved in body fluids such as blood. Most of the body’s sodium is located in blood and in the fluid around cells. Sodium helps the body keep fluids in a normal balance. Sodium plays a key role in normal nerve and muscle function.
Sodium ions are the major cations of extracellular fluid, whereas, potassium ions are the major cations of the intracellular fluid [11]. In the nerve cells, this sodium-potassium flux generates the electrical potential that aids the conduction of nerve impulses. When potassium leaves the cell, it changes the membrane potential and allows the nerve impulse to progress. This physiologic function is of particular significance for excitable cells such as nerve cells, which depend on this pump for responding to stimuli and transmitting impulses [12].
Material and method:
1. Subjects
The study included fifty persons, thirty addicted to meth and twenty who were addicted to other drugs in addition to meth. Their ages ranged between 15-45 years and the duration of drugs using ranged from 1-7 years. We used a questionnaire answer to excluded people who had chronic diseases, cigarette smoking and the environment of the
addicts were included such as urban and rural areas. The study compared the results of these two groups with the control group, which consists of 30 enrolled persons, who matching with groups of addicts in age and environment, all people who had chronic disease were excluded
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.

2. Determination of **Calcium** and **Sodium**
In human serum we determine of Ca$^{2+}$ and Na$^{+}$ by Colorimetric method using AGAPPE Kit and Spinreact Kit according to manufacturer's instructions respectively.

3. **Statistical analysis**
Data analysis of in this study were expressed as mean ± SD, SE and 95% Confidence Interval of the parameters Difference. Data were statistically analyzed by one-way analysis of variance (ANOVA). using SPSS software v24. P values less than 0.05 were considered to be significance

**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).

| 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.
Calcium levels were highly significant in addicts group (G2, G3) (P < 0.05), as compared to non addicts group (G1) as shown in Table (2).

| groups  | N    | Mean ± SD   | SE  | Cl 95% | Compared group | P value |
|---------|------|-------------|-----|--------|----------------|---------|
|         |      |             |     |        | Lower | Upper | 1 | 2 | 3 | 0.0001 | 0.0001 | 0.55 | 0.0001 |
| G1      | 30   | 7.4 ± 2.3   | 0.42| 6.5    | 8.3   | 1     | 2 | 3 | 0.0001 |
| G2      | 30   | 12.8 ± 2.8  | 0.52| 11.7   | 13.9  | 2     | 1 | 3 | 0.0001 |
| G3      | 20   | 12.4 ± 2.2  | 0.49| 11.3   | 13.4  | 3     | 1 | 3 | 0.0001 |
Table (3) show that Sodium levels were highly significant in addicts group (G2, G3) (P < 0.05), as compared to non addicts group (G1).

Table (3) The Levels of Sodium (mmol/L) for Addict Groups (G2, G3) and non-Addict Group (G1)

| groups | N  | Mean ± SD | SE  | CI 95%      | Compared group | P value  |
|--------|----|-----------|-----|-------------|----------------|----------|
|        |    |           |     |             |                |          |
|        |    |           |     | Lower       | Upper          |          |
| G1     | 30 | 130.6 + 12.4 | 2.2 | 125.9       | 135.5          | 1        | 0.0001  |
|        |    |           |     | 2           | 3              | 0.0001  |
| G2     | 30 | 155.2 + 26.5 | 4.8 | 145.3       | 165.1          | 2        | 0.0001  |
|        |    |           |     | 1           | 2              | 0.78     |
| G3     | 20 | 153.6 + 21.1 | 4.7 | 143.6       | 163.5          | 3        | 0.0001  |
|        |    |           |     | 1           | 2              | 0.78     |

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 (4), (5), (6) and (7)

In Table (4), (5), when addict divided as age variable the Calcium level were higher in METH and MIX addicts group (A2) as compared to addicts group (A1) and (A3) (P >0.05).

Table (4) Calcium Levels (mg/dL), 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  | 11.7 + 4.2 | 1.61| 7.8         | 15.7           | 1        | 0.16    |
|                    |    |           |     | 2           | 3              | 0.52     |
| A2                 | 10 | 13.7 + 2.5 | 0.80| 11.9        | 15.6           | 2        | 0.16    |
|                    |    |           |     | 1           | 2              | 0.35     |
| A3                 | 13 | 12.6 + 2.2 | 0.61| 11.3        | 13.9           | 3        | 0.52    |
|                    |    |           |     | 1           | 2              | 0.35     |

Table (5) Calcium Levels (mg/dL), for addict (Mix) sub groups within variable ages.

| Addicts age | N  | Mean ± SD | SE  | CI 95%      | Compared group | P value  |
|-------------|----|-----------|-----|-------------|----------------|----------|
|             |    |           |     |             |                |          |
|             |    |           |     | Lower       | Upper          |          |
The results in Table (6), that show of Sodium level were higher in METH addicts group (A1) as compared to addicts group (A2) and (A3) (P >0.05). While, the results in Table (7), that show of Sodium level were higher in MIX addicts group (A2) as compared to addicts group (A1) and (A3) (P >0.05).

**Table (6) Sodium Levels (mmol/L), 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  | 175.0 + 35.4 | 13.3 | 142.0  | 207.9          | 1 2     | 0.16   |
|                   |    |            |     |        |                | 3       | 0.008  |
| A2                | 10 | 157.9 + 20.1 | 6.3  | 143.5  | 172.3          | 2 1     | 0.16   |
|                   |    |            |     |        |                | 3       | 0.14   |
| A3                | 13 | 142.6 + 18.8 | 5.2  | 131.2  | 154.0          | 3 1     | 0.008  |
|                   |    |            |     |        |                | 2       | 0.14   |

**Table (7) Sodium Levels (mmol/L), 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  | 147.0 + 20.0 | 7.5  | 128.4  | 165.5          | 1 2     | 0.32   |
|                  |    |            |     |        |                | 3       | 0.50   |
| A2               | 7  | 158.8 + 25.2 | 9.5  | 135.4  | 182.2          | 2 1     | 0.32   |
|                  |    |            |     |        |                | 3       | 0.76   |
| A3               | 6  | 155.1 + 18.8 | 7.6  | 135.3  | 174.9          | 3 1     | 0.50   |
|                  |    |            |     |        |                | 2       | 0.76   |
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 (8), (9), (10) and (11).

Also, Table (8) and (9) show the Calcium levels in METH and MIX addicts group (D3) as compared to addicts group (D1) and (D2) (P >0.05).

Table (8) Calcium Levels (mg/dL), 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 | 12.9 + 2.6    | 0.58| 11.6   | 14.1           | 1 0.17  |
|                           |    |               |     | 11.6   | 14.1           | 3 0.19  |
| D2                        | 6  | 11.1 + 3.9    | 1.59| 6.9    | 15.2           | 2 1 0.17|
|                           |    |               |     | 6.9    | 15.2           | 3 0.04  |
| D3                        | 4  | 14.9 + 0.5    | 0.25| 14.1   | 15.7           | 3 1 0.19|
|                           |    |               |     | 14.1   | 15.7           | 2 0.04  |

Also, the results in Table (10), (11) that show of Sodium level were higher in METH and MIX addicts group (D2) as compared to addicts group (D1) and (D3) (P >0.05).

Table (10) Sodium Levels (mmol/L), 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 | 147.1 + 21.7  | 4.8 | 136,9  | 157.3          | 1 2 0.01|
|                           |    |               |     | 136,9  | 157.3          | 3 0.23  |
Table (11) Sodium Levels (mmol/L), Subgroups Dependent on Abuse Duration (Years) for Addicts Group (Mix)

| Duration of addicts (Mix) | N  | Mean ± SD  | SE  | CI 95% Lower | CI 95% Upper | Compared group | P value |
|---------------------------|----|------------|-----|--------------|--------------|----------------|---------|
|                           |    |            |     |              |              |                |         |
| D1                        | 10 | 150.2 +    | 6.8 | 134.7        | 165.6        | 1, 2           | 0.40    |
|                           |    | 21.6       |     |              |              | 3              | 0.78    |
| D2                        | 5  | 160.4 +    | 9.6 | 133.5        | 187.2        | 2, 1           | 0.40    |
|                           |    | 21.6       |     |              |              | 3              | 0.63    |
| D3                        | 5  | 153.6 +    | 10.2| 182.1        | 182.1        | 3, 1           | 0.78    |
|                           |    | 22.9       |     |              |              | 2              | 0.63    |

Calcium ion Ca$^{2+}$ and maintenance of cellular Ca$^{2+}$ homeostasis, was essential for the proper function of the nervous system. Ca$^{2+}$ also critical for growth and development, necessary component for neurotransmission, and contributes to distinct patterns of differential gene expression in neurons. Calcium also appears to be required for most forms of activity-dependent synaptic plasticity, generally believed to be the cellular correlate for learning and memory.[13]

Changes in intracellular calcium levels act as signals for a variety of processes in neurons. Most notably, Ca$^{2+}$ is the major trigger of neurotransmitter release [14].

As the importance of Ca$^{2+}$ in a wide range of physiological functions in the nervous system is now well established, it is understandable that changes in the levels of intracellular Ca$^{2+}$ or alterations in Ca$^{2+}$ signaling could contribute to a variety of pathologies[15].

High Ca$^{2+}$ derived from drugs such as methamphetamine effects can activate Ca$^{2+}$-dependent protease which catalyzes the xanthine dehydrogenase conversion to xanthine oxidase and induce ATP degradation to hypoxanthine, a substrate of xanthine oxidase together with O$_2$ the other substrate of the reaction. xanthine oxidase is strongly activated and produces large amounts of uric acid to prevent further oxidative damage. However, due to its limited solubility, uric acid may precipitate and thus participate to neuronal suffering [16].

Tymianski M and Tator CH, 1996 demonstrated that Ca$^{2+}$ overload also activates endonucleases, a series of Ca$^{2+}$-dependent enzymes that degrade DNA and that may be involved in two morphologically distinct forms of neuronal degeneration: necrosis and apoptosis [17].

The change in calcium levels contributes to neurodegenerative diseases such as Huntington’s, Parkinson’s, and Alzheimer’s disease, as well as amyotrophic lateral sclerosis [18]. Disrupted signaling through Ca$^{2+}$ channels also contribute to epilepsy and migraine [19].
Sodium is essential for human health. It is important ions in the body and are associated with many physiologic and pathophysiologic processes. Sodium ions concentration are an excellent biomarker necessary for regulation of blood and body fluids, transmission of nerve impulses, heart activity, and certain metabolic functions. [20]

Hypernatremia involves dehydration, which can have many causes, including not drinking enough fluids, diarrhea, kidney dysfunction, and diuretics. If hypernatremia worsens, they may become confused or have muscle twitches and seizures. [21]

In this study, we found a high level of sodium for addicts compared to healthy people (control group), which may lead to health problems as we mentioned earlier. RM Reynolds, et al, 2006, found that a high concentration of sodium in the blood may cause symptoms such as a strong feeling of thirst, weakness, nausea, and loss of appetite. Typically, only occur when levels are above 160 mmol / L. [22]

**Conclusion**

The current study showed the effect of meth and other drugs on calcium and sodium levels. As these changes can contribute to many health problems. The rise in calcium levels contributes to many neurological problems, while the high concentration of sodium may cause many symptoms such as a strong feeling of thirst, weakness, nausea, and loss of appetite.

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