RESEARCH ARTICLE

Effect of Hydroxychloroquine Drugs on Amino Acids in the Kidneys of White Mice (*Mus musculas*)

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ABSTRACT

Hydroxychloroquine (HQC) and chloroquine drugs belong to a class of drugs known as 4-aminoquinoline, its structure weak bases due to the presence of the essential side chain, and this chain contributes to the accumulation of drugs in the intracellular parts.

A 21 mice were taken and divided into three groups, the first group (A) was the control group that administered oral distilled water for 30 days, and the second group (B) treated group that was dose with 15 mg/kg/day of drug for 30 days, and the third group (C) was the treated group by injected drug with a concentration of 30 mg/kg/day for 30 days also.

The result of amino acids studied in the kidney of adult white mice (Mus musculus) showed the presence of (18) amino acid represented: asparagine (Asn), alanine (Ala), arginine (Arg), citrulline (Cit), glutamine (Glu), glycine (Gly), histidine (His), isoleucine (Ile), leucine (Leu), lysine (Iys), methionine (Met), proline (Pro), phenylalanine (Phe), serine (Ser), threonine (Thr), taurine (Tau), tyrosine (Tyr) and valine (Val). Statistical analysis showed high significant differences in the concentration of amino acids between the two groups of experiments treated with the drug (HQC) with a concentration (15 and 30) mg/kg/day and control group, as well as significant differences between the three groups.

Keywords: Hydroxychloroquine, Amino acid, Kidney, Mouse.

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INTRODUCTION

Hydroxychloroquine, which is sold under the brand name Plaquenil, has been adopted as a preventive treatment for certain types of malaria,[1] treatment of rheumatoid arthritis and lupus erythematosus, improved autoimmune conditions,[2] rashes, recurrent basal cell carcinoma, skin tumor, antiphospholipid antibody syndrome, retinopathy disease, as described in 1959 as chloroquine for retinopathy.[3]

The positive effect of chloroquine and hydroxychloroquine on patients with rheumatic diseases was subsequently observed over time.[4,5] HCQ and chloroquine QC, have been approved by the Food and Drug Administration (FDA) as a treatment for virus testing, with laboratory studies in cell cultures showing that HCQ (more effective than chloroquine against corona virus associated with acute respiratory syndrome Type 2.[6] It has been used for coronavirus (COVID-19) as an experimental treatment.[7] Many studies have shown that the drug has health effects on various organs and body organs, including the urinary system.

The kidneys are considered organs of the output in the body that are rapidly affected by drugs, as some of them reduce kidney efficiency and weakening and over time the drugs may cause kidney failure, and the process of subtracting the drug through glomerular filtration and then absorbing it in the tubular part.[8] The kidneys contribute to homeostasis the human body's chemical composition, which is done through three complex processes: filtration, absorption and elimination.[9] Amino acids are molecules that combine to form proteins and form the basis for the construction of peptides and proteins. They are formed from the amino group NH_2 with the carboxyl group COOH. There are 20 amino acids found in nature, all containing asymmetric carbon atoms except glycine, and amino acid is found in tissues in the form of letters D. Amino acid is produced by hydrolysis of proteins, some of which are found in the body's tissues freely, the kidneys play a role in the synthesis and exchange of many amino acids between organs, where the kidney absorbs amino acid (Gln) and converts it into ammonia, while maintaining the balance of pH and nitrogen secretions.[10]

Amino acid is divided into two types: essential amino acids (EAA) and includes: isoleucine (Ile), leucine (Leu), lysine (Lys), methionine (Met), phenylalaine (Phe), threonine (Thr),

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tryptophan (Try), valine (Val) and histidine (His) which the organism is obtained by food, and non-essential amino acids (NAA) includes: alanine (Ala), arginine (Arg), aspartate (Asp), cysteine (Cys), glutamine (Glu), glycine (Gly), proline (Pro), serine (Ser) and tyrosine (Tyr) which are synthesis by the organism through simple reaction pathways.

MATERIALS AND METHODS

Animal Breeding: This study was conducted on male adult and healthy white mouse, *Mus musculus*, all mice were approximately (2–3) months old, and weighed approximately (28.40–40.65 g), obtained from the Iraqi Center for Cancer Research and Medical Genetics, near Al-Yarmouk Hospital, mice have been taken care of for the length of the study in terms of hygiene, ventilation, lighting and temperature, and giving the feed for mice and water continuously.[11]

Treatment: Hydroxychloroquine was used in the current study and obtained from Bristol company.

Experimental Design: Twenty-one adult white mice were used and divided into three groups: group (A): the control group that administrated oral distilled water for 30 days. group (B): Treated group with the drug concentration 15 mg/kg/day for 30 days, group (C): The treated group with the drug concentrated 30 mg/kg/day for 30 days.

Analysis of Amino Acid: Amino acid was separated and diagnosed for the kidney in the white mouse depending on Standard samples, using a high-performance liquid chromatography device (HPLC), injecting the device with known concentrations (20 µL) per standard amino acid.

The method was conducted based on[12] as follows:

- 0.2 g was homogenized of mouse kidney tissue with 20 mL of deionized water, then add 1.50 g of sulfosaliyclic acid was using sulfosaliyclic acid hand homogenizer.
- Samples were discarded for an hour by centrifuge.
- HCL with a concentration of (0.1N) (pH 2.0) was added to the floating substance.
- Samples were discarded with centrifuges at a speed of 3,000 rpm.
- Mix (10) microliters of the high solution with 10 mL of phenyl isothiocyanate PITC reagent, after a minute, add 50 mL of sodium acetate (0.1) (pH 7.0).
- Amino acid was measured using an HPLC.
- Depending on the concentration of amino acid use the following equation:
- Amino acid concentration=

RESULTS

The results of amino acids studied in the kidneys of adult white mice *Mus musculus* showed the presence of 18 amino acid forms (1), (Table 1) which are: asparagine (Asn), alanine (Ala), arginine (Arg), arginine (Arg), citrulline (Cit), glutamine (Glu), glycine (Gly), histidine (His), isoleucine (Ile), leucine (Leu), lysine (Iys), methionine (Met), proline (Pro), phenylalanine (Phe), serine (Ser), threonine (Thr), taurine (Tau), tyrosine (Tyr) and valine (Val). The significant differences were high probability level ($p \leq 0.001$) of (Tau) at concentration (15 mg/kg/day) at (436.97 ± 18.97) compared to control group (508.02 ± 63.40), while the rest amino acids there were no significant differences at the probability level ($p > 0.05$), and in the concentration of 30 mg/kg/day there was a high significant difference under the probability level ($p \leq 0.001$) in (Ser) acid with an average (107.71 ± 20.36) compared with control group (20.88 ± 1.88), (Arg) found a high significant difference with an average of (246.04 ± 151.96) compared to the control group of (39.16 ± 9.9. 84), and the presence of significant differences at the probability level ($p \leq 0.05$) of (Asn) acid averaged (60.83 ± 20.90) compared to the control group (16.09 ± 2.72), the average amino acid (Gly) was (95.94 ± 19.10) compared to the group control (50.43 ± 6.15), (His) acid amino acid averaged (88.73 ± 11.79) compared to the group control (40.87 ± 5.31), (Cit) (94.28 ± 7.45) compared to the control group (39.86 ± 7.89) and (Val) acid (72.57 ± 8.66) compared to the control group of (25.00 ± 3.59), and the absence of significant differences at the probability level ($p > 0.05$) between the concentration of 30 mg/kg/day compared to the control group and the whole amino acid. Concentrations (15 and 30 mg/kg/day) also observed non-significant differences for all amino acids, except (His) observed a significant difference at the probability level ($p \leq 0.05$) in a concentration group 15 mg/kg/day (45.12 ± 6.97) compared to a concentration group of 30 mg/kg/day (88.73 ± 11.79), and (Cit) in a concentration group of 15 mg/kg/day (53.21 ± 6.83) compared to a concentration group of 30 mg/kg/day (94.28 ± 7.45), and (Val) found a significant difference in the concentration group of 15 mg/kg/day (32.00 ± 4.38) compared to a concentration group of 30 mg/kg/day if it reached (72.57 ± 8.66). A high significant difference was found under the probability level ($p \leq 0.001$) between the 30 concentrations, 15 mg/kg/day for each (Ser) amino acid in the concentration group of 15 mg/kg/day (38.98 ± 5.14) compared to the concentration of 30 mg/kg/day where it was (38.98 ± 5.14) compared to the concentration of 30 mg/kg/day (107.71 ±

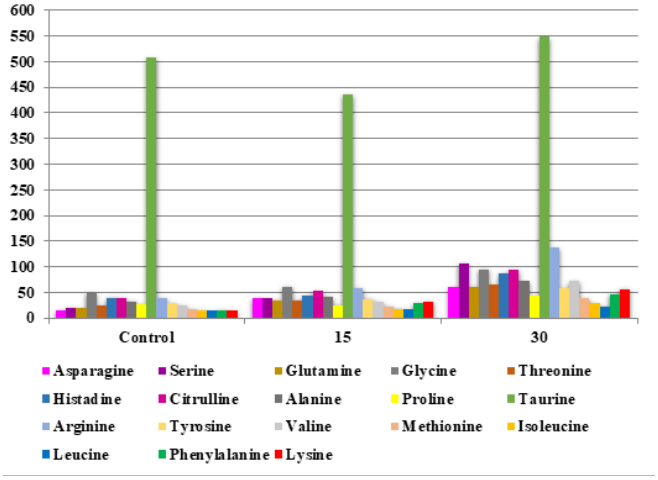

Figure 1: The relationship between the rate of amino acid concentrations in adult white mouse Mus musculus kidney of the control group and the two esperimental groups treated with hydroxychloroquine HQC at a concentration of (15 and 30) mg/kg/day.

Table 1: The rate of concentration of amino acids in white mouse M. musculus kidney of the control group and the two experimental groups treated with hydroxychloroquine HQC at a concentration of (15 and 30) mg/kg/day

Amino acid	Control group	15 concentration	30 concentration
Asparagine (Asn)	16.09 ± 2.72	39.61 ± 6.96	60.83 ± 20.90
Serine (Ser)	20.88 ± 1.88	38.98 ± 5.14	107.71 ± 20.36
Glutamine (Gln)	19.63 ± 1.75	36.05 ± 4.59	61.73 ± 11.24
Glycine (Gly)	50.43 ± 6.15	61.70 ± 5.46	95.94 ± 19.10
Threonine (Thr)	25.66 ± 3.09	35.89 ± 5.77	66.01 ± 11.63
Histadine (His)	40.87 ± 5.31	45.12 ± 6.97	88.73 ± 11.79
Citrulline (Cit)	39.86 ± 7.89	53.21 ± 6.83	94.28 ± 7.45
Alanine (Ala)	33.50 ± 4.01	43.19 ± 6.28	72.37 ± 12.64
Proline (Pro)	26.94 ± 7.31	26.31 ± 3.30	43.54 ± 9.75
Taurine (Tau)	508.02 ± 63.40	436.97 ± 18.97	548.60 ± 34.84
Arginine (Arg)	39.16 ± 9.84	59.44 ± 4.96	246.04 ± 151.96
Tyrosine (Tyr)	29.90 ± 8.74	38.43 ± 3.45	137.88 ± 38.61
Valine (Val)	25.00 ± 3.59	32.00 ± 4.38	72.57 ± 8.66
Methionine (Met)	17.47 ± 4.97	24.05 ± 2.09	38.86 ± 7.39
Isoleucine (Ile)	16.12 ± 2.12	18.80 ± 2.36	29.23 ± 7.53
Leucine (Leu)	14.89 ± 1.60	17.32 ± 2.23	23.59 ± 4.80
Phenylalanine (Phe)	16.33 ± 3.75	29.80 ± 2.90	47.66 ± 5.31
Lysine (Lys)	15.42 ± 4.21	32.59 ± 5.34	57.52 ± 7.00

20.36), (pro) amino acid in a concentration group of 15 mg/kg (26.31 ± 3.30) compared to a concentration group of 30 mg/kg/day (43.54 ± 9.75) and (Tau) acid in the concentration group of 15 mg/kg/day (436.97 ± 18.97) compared to a concentration group of 30 mg/kg/day (548.60 ± 34.84), and amino acid (Arg) in a concentration group of 15 mg/kg/day (59.99 ± 4.96) compared to a concentration group of 30 mg/kg/day (246.04 ± 151.96), and the result showed that the differences between the concentrations (30,15) mg/kg/day compared to a high significant control group under the probability level ($p \leq 0.001$) among all amino acid.

DISCUSSION

Amino acids are the main component of peptides and proteins in the body and play a key role in various body activities and functions,[13] amino acids are functionally active substances and form naturally and work to repair tissues and cells, and the kidneys play a role in the synthesis and exchange of many amino acids among organs.[14]

The current result showed that the total number of amino acids in the kidneys of adult white mice, *M. musculus* treated with HQC concentration (15 mg/kg/day) and (30 mg/kg) for 30 days, it was (18) amino acid, and there were 18 amino acids in the *Gallus gallus domesticus* chicken liver study,[15] while the number in Iraqi frog brain tissue (17) amino acid,[16] and in the study of embryogenesis and histogenesis of the brain and spinal cord of the *Coturnix coturnix* was (16) amino acid.[17]

Fisher RS[18] stated that non-essential amino acids containing two groups of dicarboxylic amino acid such as (Gln) plays an active role in metabolic processes, as well as can be easily synthesis in all tissues of the body and converted into ammonia while maintaining pH balance in the kidney and nitrogen secretions. Zuhairi GGS[16] pointed out when studying amino acid in the brain tissue and spinal cord of the Iraqi frog, the highest concentration of (Gln) in the mesencephalon was (134.612), and the lowest rate in the rhombencephalon brain was (37.565), and in the current result found a highly significant in amino acid (Gln) when treated with HQC concentration (30 mg/kg/day), with a concentration rate of (61.73 ± 11.24) compared to the control group with a concentration of (19.63 ± 1.75)[19] noted that (Gly) plays a role in protecting tissues when oxygen or ischemia is lacking.[16] when studying amino acid in the brain tissue and spinal cord of the Iraqi frog, the highest concentration of (Gly) amino acid was in the rhombencephalon brain (51.526) and the lowest concentration in the mesencephalon was (24.854), and found a significant increase in (Gly) amino acid when treated with HQC concentration (30 mg/kg/day), with a concentration rate of (95.94 ± 19.10) compared to control group with a concentration of (50.43 ± 6.15).

(His) amino acid is essential and cannot be synthesized in food[20] noted that (His) is essential for the release of proteins, also plays an important role in the active location of enzymes, and can act as a neurotransmitter[17] when studying amino acidity in the brains of the embryos of the quail bird, the highest concentration of His was (0.098) for embryos aged 10 to 16, and in the current result found a significant increase of amino acid (His) when treated with (HQC) concentration (30 mg/kg/day), with a concentration rate of (88.73 ± 11.79) compared to the control group with a concentration of (40.87 ± 5.31).

The Arg is essential and can be synthesized in sufficient quantities in the body to maintain growth and balance, which is an essential component of proteins.[21] noted in their study on amino acid in chicken that (Arg), (Tyr) and (Phe) increased their concentration in the adult bird's brain to 0.064, 0.103, 0.123, respectively.

Zuhairi GGS[16] pointed out, when studying amino acid in the brain tissue and spinal cord of the Iraqi frog, the highest concentration of amino acid (Arg) appeared in the mesencephalon at 115,423 and the lowest concentration in the rhombencephalon was 62, and Phe showed its highest concentration in the rhombencephalon at (27.145) with the lowest concentration in the mesencephalon (14.951) , and no (Tyr) acid was observed. As for the result of the current study, there was a significant increase in Arg, Tyr and Phe, when treated with (HQC) concentration (30 mg/kg/day), and their concentration rate (246.04 ± 151.96, 137.88 ± 38.61, 47.66 ± 5.31), respectively, when compared to the control group of (246.04 ± 151.96, 137.88 ± 38.61, 47.66 ± 5.31) respectively.

Ganong WF[9] noted that Tyr amino acid and Lys amino acid are essential amino acids that the body cannot synthesize and are obtained through food,

Zuhairi GGS[16] also noted when studying amino acid in the brain tissue and spinal cord in the Iraqi frog, the highest concentration of amino acid (Tyr) appeared in the rhombencephalon brain at (36.855), and the lowest concentration in the telencephalon was (25.504). As for the result of the current study, there was a high significance in (Tyr) amino acid when treated with HQC concentration (30 mg/kg/day) was (137.88 ± 38.61) compared to a control group was (29.90 ± 8.74). Branched-chain amino acids BCAA include (Val), (Ile) and (Leu), found in muscle proteins and stimulate muscle growth.

Kumar MA et al.[22] pointed that plasma levels of branched-chain amino acid (BCAA), especially (Val) and (Leu), are well associated with nutritional status for patients with chronic kidney disease. A significant decrease ($p > 0.05$) was observed in levels of (Val) and (Leu) in plasma for patients with chronic renal insufficiency (CKD) compared to control. At the same time, the study result showed a significant increase in concentration (30 mg/kg/day) of Val, (Ile) and (Leu) at 72.5 7 ± 8.66, 29.23 ± 7.53, 23.59 ± 4.80 respectively, compared to control group 25.00 ± 3.59, 16.12 ± 2.12, 14.89 ± 1.60 respectively.

The amino acid (Ala), which is a non-essential amino acid, and the administration of mice with phenelzine (PLZ) leads to increased levels of the main inhibitory neurotransmitter in the central nervous system of the rat brain and increase only amino acid (Ala), and the reason for the increase in the (Ala) in the brain is due to the inhibitory effect that depends on the length of the dose time and dose concentration,[23] the result of the current study found a significant increase in amino acid (Ala), when treated with HQC concentration (30 mg/kg/day), amounted to (72.37 ± 12.64) compared to the control group of (33.50 ± 4.01).

The Tau amino acid is a semi-essential amino acid, and the highest concentration of Tau in the current study was in a concentration group (30 mg/kg/day) at (548.60 ± 34.84)) and lower concentration in a group of concentration (15 mg/kg/day) was (436.97 ± 18.97) compared to the control group was (508.02 ± 63.40).

The Pro amino acid is a non-essential amino acid that the body can synthesis, and is found in collagen that makes up skin tissues, fiber, ligaments and bones, it maintains skin moisture, and is important in healing after injury, in addition to its role in cell differentiation and organ formation.[24]

Al-Hamawandy DH[15] pointed out in their study of *G. gallus domesticus* chicken liver, the lowest concentration of (Pro) amino acid (Pro) was (99.80 ± 7.54) at the age of 19 days of incubation, while the result of the current study showed a significant increase in amino acid (Pro) when treated with HQC at concentration of 30 mg/kg/day was (43.54 ± 9.75) compared to the control group (26.94 ± 7.31).

(Asn) is an important regulator of amino acid balance in cancer cells, metabolism and reproduction[25].

Al-Hamawandy DH[15] noted in their study of *G. gallus domesticus* chicken liver, the highest concentration of asparagus amino acid (Asn) was (175.94 ± 24.089) in a young chicken aged 14 days after hatching and its lowest concentration was (24.19 ± 1.30) in a fetus aged 14 days of incubation. The result of the current study showed a significant increase of (Asn) when treated with HQC at a concentration of 30 mg/kg/day of (60.83 ± 20.90) compared to the lowest concentration in the control group (16.09 ± 2.72).

(Ser) also has an important role in the metabolic processes of amino acid and has a stimulant and stimulant role, repairing damaged tissues while maintaining pH balance in the body.[26,27]

Al-Hamawandy DH[15] noted in their study of *G. gallus domesticus* chicken liver that the highest concentration of (Ser) amino acid was (2.14 ± 160.88) in adults. The result of the current study showed a significant increase in (Asn) when treated with HQC in concentration of 30 mg/kg/day, at (107.71 ± 20.36) compared to the lowest concentration in the control group (20.88 ± 1.88).

Heys[28] noted that (Cit) is a non-essential amino acid, synthesized in the gut and produces nitrogen in the metabolism of glutamine in the small intestine, not absorbed by the liver, any (Cit) synthesized by the intestines up to the systemic circulation and then absorb the kidneys most of the (Cit) made by the gut, the result of the current study showed a significant increase in amino acid (Cit) when treated with a drug (HQC) in concentration (30 mg/kg/day) was 94.28 ± 7.45 compared to its lowest concentration in the control group (39.86 ± 7.89).

An increase in all amino acids of mice treated with HQC concentration (30 mg/kg/day) was observed, with the lowest concentration of acid in the control group except Tau, the lowest concentration in the concentration group (15 mg/kg/day) compared to the concentration (30 mg/kg/day). The diversity of amino acid concentrations in the HQC and concentrations (1.530 mg/kg/day) may have occurred because of its effective importance in biological organizing and functional events in kidney cells and protecting them from the harmful effect of the drug. It is important to note that we didn't find a previous study dealing with the amino acids in mice kidney to compare the results with ours.

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