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Quinine Modulates Cholinergic, Monoaminergic and Purinergic Systems of Neurotransmission in Isolated Rat Brain

Ademiluyi Adedayo O.

Functional Foods, Nutraceuticals and Phytomedicine Unit, Department of Biochemistry, The Federal University of Technology, Akure, Nigeria

Corresponding Author: Ademiluyi, A.O.: aoademiluyi@futa.edu.ng

ABSTRACT: Quinine is a bitter compound from the bark of cinchona tree commonly found in tropical regions of the world and is a widely used antimalarial drug with neuromodulatory effect that is not fully understood nor defined. Hence this study sought to investigate the effect of quinine on cholinesterase (acetylcholinesterase and butyrylcholinesterase), monoamine oxidase, E-NTPDase and Na^+/K^+-ATPase in rat brain homogenates *in vitro*. The results revealed that quinine exerted inhibitory effects on acetylcholinesterase, butyrylcholinesterase, monoamine oxidase, and Na^+/K^+ ATPase activities in a concentration-dependent manner (0 – 13 µM) with IC_{50} values of 382.3 nM, 17.1 nM, 125.8 nM and 483.3 nM respectively. However, quinine stimulated E-NTPDase activity in a concentration dependent pattern with an IC_{50} value of 8.2 nM. The observed alteration in the activities of these critical enzymes involved in neurotransmission and/or neuromodulation could be partly responsible for some neurochemical side effect of quinine. However, further molecular studies in experimental animals are necessary to validate this observed alterations.

Keywords: Quinine; alkaloids; cinchona; neuromodulation; neurotransmission

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INTRODUCTION

Quinine is the most important alkaloid compounds extracted from the bark of *Cinchona* (quina-quina) species trees or shrubs native to the Andes Mountains of South America (Achan *et al.*, 2011). It is a stereoisomer of quinidine, belonging to the quinoline group of alkaloids. Quinine is characterized by bitter taste and as such, it is used as flavouring in drinks and beverages. The compound is used for the treatment of severe malaria and nocturnal leg cramps amongst several applications however, its toxicity has limited it widespread use (Hogan, 2015). It is associated with neurological symptoms broadly categorized as cinchonism which suggest direct interaction with the nervous system (Bateman and Dyson, 1986). Neurotoxicity of quinine and quinine derivatives as well as several antimalaria drugs have been reported. Artemisinins and its derivatives caused neurotoxicity in mammalian brain (Brewer *et al.*, 1994; Nontprasert *et al.*, 2000) while degeneration of brainstem nuclei in rats is associated with mefloquine-induced neurotoxicity (Dow *et al.*, 2006).

Neuronal function is a complex system mediated by several networks of neurotransmission and neuromodulatory system in response to internal and external stimuli. These systems involve cascades of enzyme catalysed reactions giving rise to several excitatory or inhibitory molecules (neurotransmitter and neuromodulators) with peculiar neuronal function and to facilitate communications between neurons. However, studies have shown that neurotransmission and neuromodulatory systems are special targets for drugs and neurotoxic compounds which could bring about alteration in neuronal function. Cholinergic, monoaminergic and purinergic

enzymes are critical enzymes which mediate neurotransmission and neuromodulatory signaling in mammalian brain. Cholinergic enzymes are involved in nerve impulse transmission in the CNS and they include acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). AChE catalyzes the hydrolysis of the neurotransmitter, acetylcholine while BChE hydrolyzes both butyrylcholine and acetylcholine; these neurotransmitters plays important role in memory and cognition. Therefore, AChE and BChE inhibitors are used to increase the brain acetylcholine levels. However, the action of this inhibitors could lead to heightened availability of acetylcholine at the nerve synaptic vesicles and neuromuscular junctions, consequently resulting in increased synaptic vesicles activities and over-stimulation of acetylcholine receptors which could lead to nerve and muscle damage (Racchi *et al.* 2004; Mukherjee *et al.* 2007).

Monoamine oxidase (MAO) is a monoaminergic enzyme involved in the oxidative deamination of monoamines such as serotonin, histamine and catecholamines (dopamine, epinerphrine and norepinephrine) to their corresponding aldehyde and free amines. These monoamines are important for brain development and functions (Takano, 2018). Also, the products obtained from the oxidative deamination is the major source of hydrogen peroxide (H_2O_2) in the brain. H_2O_2 can be chemically converted by Fe^{2+} ions (Fenton reaction) into the highly reactive hydroxyl radical which can cause neuronal damage (Ramsay and Gravestock, 2003). Therefore, MAO inhibitors will prevent the oxidative deamination of monoamines. However, increased monoamine levels could become toxic as its inhibition could result in the accumulation of monoamines which has been reported to stimulate phosphate depletion, intracellular Ca^{2+}- overload and cell death (Thomas 2000).

The purinergic enzymes mediated by ATP are responsible for the synthesis, release, action and extracellular inactivation of purines; particularly adenosine. Ecto-5'- nucleotidase catalyzes the extracellular hydrolysis of adenosine triphosphate (ATP) and adenosine-5-monophosphate (AMP) to adenosine and consequently activates the inorganic phosphate (Pi) and adenosine receptors (Zimmerman et al. 1993; Node *et al.* 1997). Na^+/K^+-ATPase is an enzyme responsible for the maintenance of ionic (low intracellular Na^+ and high intracellular K^+) concentration gradient necessary for neuronal excitability (Zimmerman *et al.* 1993).

Alkaloids are naturally occurring chemical compounds that contain basic nitrogen atoms. They are primarily found in plants, but they can also be produced by a large variety of organisms, including bacteria, fungi and animals (Buckingham, 1994). Alkaloids are amines which include: quinine, berberine, morphine, heperzine, caffeine, galanthamine, nicotine etc. They have complex chemical structures with multiple ring systems and diverse important physiological effects on humans and animals. The neuromodulatory effects of alkaloids on the central nervous system; either as a neuroprotective or neurotoxic agent has been reported (Berkov *et al.* 2008). The abilities of alkaloids to influence important and critical enzymatic systems necessary for normal neuronal function are used as basis for studying neuromodulatory effects (Da Silva *et al.* 2006) of these class of compounds.

However, there is limited scientific information on the effects of quinine on some enzymes involved in cholinergic, monoaminergic and purinergic systems of neurotransmission despite reported physiological and neurological changes following quinine exposure. Hence, this study sought to investigate the effects of quinine on some critical enzymes of these neurotransmission systems.

MATERIALS AND METHODS

Chemicals and reagents

Quinine sulphate, acetylthiocholine iodide, butyrylthiocholine iodide, semicarbazide, benzylamine, adenosine triphosphate (ATP), ouabain, ammonium molybdate, thiobarbituric acid, (TBA), dinitrophenylhydrazine (DNPH),

adenosine monophosphate (AMP), sodium hydroxide, benzene, and 5,5'-dithio-bis(2-nitrobenzoic acid) (DTNB) were obtained from Sigma-Aldrich, Inc., (St Louis, MO, USA). All other chemicals and reagents used were of analytical grade and glass-distilled water was used.

Animals

Albino rats (*Wistar strain*) weighing 220 - 260 g, purchased from the Central Animal House of University of Ibadan were used for this study. They were housed in wire mesh cages and fed with commercial rat chow and water.

Sample preparation for biochemical assays

0.1 M solution of quinine sulphate was prepared and appropriate dilutions of this solution were used for subsequent studies as appropriate.

Biochemical analysis

Determination of Acetylcholinesterase (AChE) and Butyrylcholinesterase Activity

Inhibition of AChE was assessed by a modified colorimetric method of Perry et al. (2000). The AChE activity was determined in a reaction mixture containing 200 µL of a solution of AChE (0.415 U/mL in 0.1 M phosphate buffer, pH 8.0), 100 µL of 5, 5'-dithiobis (2-nitrobenzoic) acid solution (3.3 mM in 0.1 M phosphate-buffer solution, pH 7.0) containing $NaHCO_3$ (6 mM), quinine solutions (0-13 µM), and 50 µL phosphate buffer, pH 8.0. After incubation for 20 min at 25 ºC, 100 µL of 0.05 mM acetylthiocholine iodide solution was added as the substrate, and AChE activity was determined as changes in absorbance reading at 412 nm for 3 min at 25 °C using a spectrophotometer. 100 µL of butyrylthiocholine iodide was used as a substrate to assay butyrylcholinesterase activity, while all other reagents and conditions were the same. The AChE and BChE inhibitory activities were expressed as percentage inhibition.

Determination of Monoamine oxidase (MAO) Activity

The effect of quinine on MAO activity was carried out according to Green and Haughton, (1961) with slight modification. Briefly, the reaction mixture contained 25 mM phosphate buffer (pH 7), 12.5 mM semicarbazide, 10 mM benzylamine (pH adjusted to 7), brain homogenate and appropriate dilutions of quinine in a total reaction volume of 2 mL. After 30 min, 1 mL of acetic acid was added and boiled for 3 min in boiling water bath followed by centrifugation. The resultant supernatant (1 mL) was mixed with equal volume of 0.05% of 2, 4-DNPH and 2.5 mL of benzene was added after 10 min incubation at room temperature. After separating the benzene layer, it was mixed with equal volume of 0.1 N NaOH. The alkaline layer was decanted and heated at 80 °C for 10 min. The orange-yellow colour developed was measured at 450 nm.

Determination of Ecto-5'-nucleotidase Activity

Ecto-5'-nucleotidase activity was determined in whole brain homogenate incubated with quinine as described (Heymann et al. 1984). The assay mixture consisted of 10 mM MgSO4 and 100 mM Tris–HCl buffer, pH 7.5, in a final volume of 200 µL. Twenty microliters of enzyme preparation (8–12 µg of protein) were added to the reaction mixture and pre-incubated at 37 °C for 10 min. The reaction was initiated by the addition of AMP to a final concentration of 2.0 mM and proceeded for 20 minutes. In all cases, reaction was stopped by the addition of 200 µL of 10% trichloroacetic acid (TCA) to obtain a final concentration of 5%. Following, the tubes were chilled on ice for 10 min. The released inorganic phosphate (Pi) was assayed by the method of Fiske and Subbarow (1925) using ascorbic acid as colorimetric reagent and KH_2PO_4 as standard. Enzyme activity was expressed as expressed in nmol of Pi/mg of protein/min.

Determination of Na^+/K^+ -ATPase Activity

The Na^+/K^+ ATPase activity was measured in whole brain homogenate incubated with quinine as described (Wyse *et al.* 2000). The assay mixture consisted of 50 µL of Na^+/K^+ -ATPase substrate buffer (pH 7.4) (containing 30 mM Tris–HCl, 0.1 mM EDTA, 50 mM NaCl, 5 mM KCl, and 6 mM $MgCl_2$), 50 µL of

quinine (0 – 13 µM), 50 µL of supernatant (50 µg of protein) in the presence or absence of 50 µL of ouabain (1 mM), in a final volume of 200 µL. The reaction was initiated by the addition of 50 µL adenosine triphosphate (ATP) to a final concentration of 3 mM. After incubating for 30 min at 37 °C, the reaction was terminated by the addition of 70 µL of 50% (w/v) trichloroacetic acid. The amount of inorganic phosphate (Pi) released was quantified as described by Fiske and Subbarow (1925) using a reaction mixture that contained 100 µL of ammonium molybdate (50 mM), 40 µL of reaction mixture from first grid and 10 µL of ascorbic acid (8%). Different concentrations (0, 4, 8, 10, 20, 40 nMol) of NaH_2PO_4 (1 mM) was used to make a calibration curve of inorganic phosphate. Specific Na^+/K^+-ATPase activity was calculated by subtracting the ouabain-insensitive activity from the overall activity (in the absence of ouabain). The enzyme activity was expressed in nmol of Pi/mg of protein/min.

Percentage enzyme inhibition

Except stated otherwise for all enzyme inhibition assay, the percentage (%) enzyme inhibition was taken as implied in the equation;

Percentage (%) enzyme inhibition

$= 100 \times (1 - ABS_{Test} / ABS_{Reference})$

where, ABS_{Test} is the absorbance of test in the presence of quinine and $ABS_{Reference}$ is the absorbance reading in the absence of the quinine.

Statistical analysis

The results of three replicates were pooled and expressed as mean ± standard deviation (SD). The means were analyzed using one-way analysis of variance (ANOVA) and Duncan test was used for the post hoc treatment. Significance was accepted at $P \leq 0.05$. IC_{50} was calculated using nonlinear regression analysis. GraphPad Prism software for windows was used for all the analysis.

RESULTS AND DISCUSSION

Quinine is a quinoline alkaloid compound, belonging to the family Rubiacaea, extracted from the bark of *Cinchona* species trees and it has been used from time immemorial in the treatment of malaria. Quinine is being called "a general protoplasmic poison" because it affects a large variety of biological systems. The basis for the therapeutic use of quinine in man for malaria and muscle cramps is due to its curare-like action on skeletal muscle and its toxic effects on plasmodium (Gilman *et al.,* 1980). Quinine has been reported to produce major toxic effects on the nervous system, which results in neuronal injury and consequently leading to optic and auditory nerve damage with cinchonism symptoms.

Quinine-induced cholinesterase inhibition in the rat brain as observed in this study (Figures 1a and 1b; Table 1) could be a function of the neurotoxic effect of quinine. Acetylcholinesterase (AChE) plays critical role in mammalian cholinergic synapses where it regulates neurotransmission via the hydrolysis of acetylcholine (major neurotransmitter in cholinergic neurons) to choline and acetic acid. Inhibition of AChE results in accumulation of acetylcholine at the synapses, causing post-synaptic membrane to remain in a state of permanent stimulation, which results in ataxia (general lack of co-ordination in the neuromuscular system, and possibly death (Aygun *et al.,* 2002). The concentration-dependent inhibition of AChE and BChE activities by quinine in the rat brain is of immense importance in the modulation of intricate enzymes involved in neurodegeneration.

The inhibition of AChE activity could lead to heightened accumulation of toxic levels of acetylcholine at the nerve synaptic vesicles and neuromuscular junctions, consequently resulting in increased synaptic vesicles activities and over-stimulation of acetylcholine pathways and desensitization of acetylcholine receptors which could lead to oxidative stress as well as nerve and muscle damage (Sidell and Borak 1992; Mukherjee *et al.* 2007). Hence, cholinesterase inhibition could be responsible for some symptoms of cinchonism as observed in quinine toxicity. The inhibitory effect of quinine on cholinesterase activities is consistent with previous studies showing inhibitory effect

of quinine and its enantiomers on mammalian acetylcholinesterase (Katewa and Katyare, 2005; Ngiam and Go, 1987). Furthermore, the AChE and BChE inhibitory activities of quinine correlates with earlier reports on inhibition of cholinesterases by alkaloids and alkaloid rich plant extracts (Racchi et al. 2004; Benamar et al. 2010).

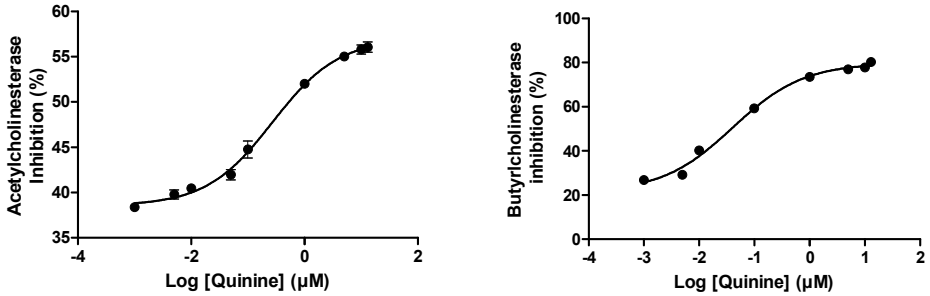

Figure 1: The Effect of quinine on (a) acetylcholinesterase and (b) butyrylcholinesterase activities in isolated rat brain homogenate

Table 1: The IC_{50} values for the effect of quinine on cholinesterase, monoamine oxidase and E-NTDase activities in isolated rat brain *in vitro*

Enzyme	Quinine IC_{50} (nM)
Acetylcholinesterase	382.3 ± 9.7
Butyrylcholinesterase	17.1 ± 2.1
Monoamine oxidase	125.8 ± 5.6
E-NTPDase	8.2 ± 0.8
Na^+/K^+-ATPase	483.3 ± 10.2

Values represent mean ± standard deviation

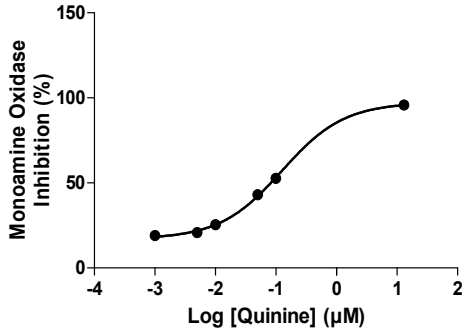

Figure 2: The effect of quinine on monoamineoxidase activity in isolated rat brain homogenate

The observed quinine-induced inhibition of monoamine oxidase activity in the brain homogenate (Figure 2 and Table 1) may portend certain neurotoxic effect. Monoamine oxidase is involved in the mechanism of dopaminergic transmission and its regulatory role is critical to neuronal function. This enzyme system is important in the regulation of biogenic amines such as dopamine, serotonin, histamine and catecholamine; thus keeping them within physiologic levels (Bortolato, 2008). However, inhibitory effect of quinine on the enzyme may compromise the clearance of these amines from the synaptic cleft after neurotransmission leading to their bioaccumulation and subsequent generation of neurotoxic aldehydes and enhanced neuronal oxidative stress; each of which influence and accelerate the course of neurodegeneration (Riederer and Müller, 2017).

Complications associated with over-accumulation of biogenic amines such as histamine include headache, nausea, vomiting and edema which are similar symptoms of cinchonism observed in quinine toxicity (Gillman 2016). Beside its involvement in neurotransmission, monoamine oxidase also metabolises tyramine (a blood pressure modulator) thus, the inhibition of these enzyme could also result in accumulation of tyramine with its attendant adverse effects on blood pressure and serotonin syndrome. Monoamine oxidase dysfunction is associated with many psychiatric and neurological disorders such as, migraines (Bussone et al. 2016), depression (Meyer et al. 2006), schizophrenia (Schildkraut

et al. 1976) and attention deficit disorder (Domschke *et al.* 2005).

Over-expression of ecto-5 nucleotidase (E-NTDase) is associated with some neurodegenerative diseases resulting from neuroinflammation and neuroimmune reactions (Burnstock, 2008). Ecto-5'nucleotidase is a magnesium-dependent glycoprotein with important role in purinergic transmission and nucleotide-mediated signaling through the regulation of adenosine monophosphate hydrolysis to inorganic phosphate and adenosine; and subsequently activation of the inorganic phosphate (Pi) adenosine receptors (Zimmerman *et al.* 1993). The observed stimulatory effect of quinine on E-NTPDase activity in the rat brain homogenate (Figure 3 and Table 1) could have also contributed to its neurotoxic tendencies due to possible accumulation of adenosine in the synaptic cleft and over-stimulation of the adenosine receptor in neurons. Increased level of adenosine in the cleft is associated with the disruption in the release of neurotransmitters such as acetylcholine, dopamine, glutamate and catecholamines which are vital to neurotransmission, signal transduction as well as neuronal survival (da Silva et al. 2006). Adenosine plays an important role in neuromodulation and homeostasis regulation of the central nervous system (Cunha et al. 2000; Dunwiddie and Masino, 2001). Furthermore, E-NTPDase have been shown to play an indirect role in the modulation of nucleotide and nucleoside mediated processes (Marti *et al.* 1997).

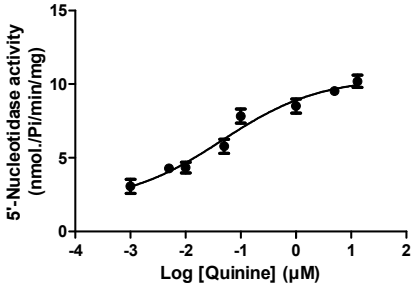

Figure 3: The effect of quinine on 5'-Nucleotidase (E-NTPDase) activity in isolated rat brain homogenate

Furthermore, the observed inhibitory effect of quinine on Na^+/K^+-ATPase activity in the rat brain homogenate (Figure 4 and Table 1) is also an indication of its neurotoxic effect. Na^+/K^+-ATPase is a transmembrane protein of nervous tissues which plays a critical role in the normal functioning of the central nervous system and alteration in the activity of this enzyme has been implicated in selective neuron damage and several neurodegenerative diseases (Cousin *et al.,* 1995; Ziegelhoffer *et al.,* 2000). This enzyme plays a critical role in the regulation of cell membrane potential, Ca^{2+} concentration and neuronal excitability by pumping Na^+ and K^+ against the electrochemical gradient across the cell membrane (Wyse et al., 2004). Indication exits that decreased Na^+/K^+-ATPase activity impairs learning and memory as well as induces neuronal hyper-excitability which is associated with some neurodegenerative diseases.

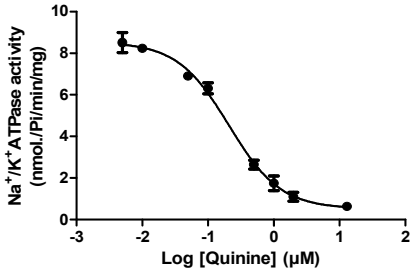

Figure 4: The effect of quinine on Na^+/K^+-ATPase activity in isolated rat brain homogenate

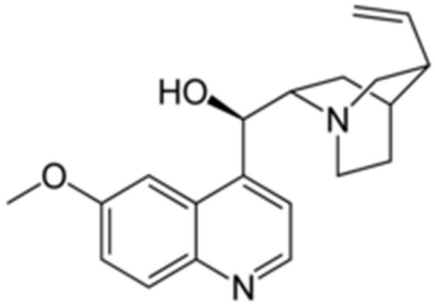

Figure 5: Structure of Quinine

Decrease in the enzyme activity alters axonal membrane sodium gradient, which drives neurotransmitters release across the cell membrane; and leading to alteration in the ionic gradient balance and impairment in the reuptake of certain neurotransmitters (Wyse *et al.,* 2004). Andrea and Roland (1994) reported interaction of Na^+/K^+ ATPase with drugs such as quinidine results in anorexia, nausea, vomiting, diarrhea, headache, delirium, cardiac rhythm disturbances, manic and depressive syndrome which are some of the symptoms associated with cinchonism; a known quinine toxicity. Report has also shown that a mild reduction in Na^+/K^+ ATPase activity could lead to mania by increasing membrane excitability and neurotransmitter release (El-Mallakh *et al.* 1993).

CONCLUSION

These inhibitory activities of cholinergic and monoaminergic enzymes coupled with stimulatory and inhibitory activities of E-NTDase agreed with previous reports in which quinine has been shown to be toxic (Goldenberg and Wexler, 1988; Taylor and White 2004). In addition, the symptoms of cinchonism which occurs as a result of quinine toxicity are some of the complications associated with excessive inhibition of acetylcholinesterases, monoamine oxidase and Na^+/K^+-ATPase. Therefore, the modulation of these important enzymes may be partly responsible for the observed neurotoxicity during treatment with quinine.

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