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Full Length Research Paper

Neuronal activities of berberine in *Schistosoma mansoni*-infected mice

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The present study aimed to investigate the neuronal activities of berberine (BER) against *Schistosoma mansoni*-induced infection in mice. Animals were divided into four groups. Group I served as a vehicle control. Group III was gavaged with 100 µl of 12 mg/kg berberine chloride for 10 days. Group II and Group IV were infected with 100±10 *S. mansoni* cercariae, and on day 46 p.i. with *S. mansoni*. The animals of Group IV received 100 µl berberine chloride by gavage once daily for 10 days at a dose of 12 mg/kg body weight. All mice were sacrificed at day 55 post-infection. Schistosomiasis induced a highly significant reduction in contents of epinephrine (E), norepinephrine (NE), dopamine (DA), serotonin (5-HT), 5-hydroxyindole acetic acid (5-HIAA). On contrary, schistosomiasis resulted in a highly significant increment in the contents of calcium (Ca^{2+}), magnesium (Mg^{2+}), sodium (Na^{+}) and chloride (Cl^{-}) ions. Moreover, BER treatment induced a highly significant decrease in most investigated parameters. Collectively, BER could be considered as a neuro-modulator of *S. mansoni*-infected mice brain.

Key words: *Schistosoma mansoni*, Berberine, neurotransmitters, ions, mice.

INTRODUCTION

Schistosomiasis (bilharziasis) is a parasitic disease caused by blood flukes of the genus *Schistosoma.* It is the second most significant parasitic disease in the world after malaria (Fiore et al., 2002). More than 200 million people worldwide are infected, with 600 million people exposed to the risk of infection (Carod-Artal, 2008). *Schistosoma mansoni* is endemic in the Middle East (Egypt, Iraq), South America, the Caribbean, sub-Saharan Africa and southern areas of Africa. The infection is known to induce granulomas, not only in the liver and intestine, but also in the brain due to the presence of eggs, resulting in neuropathological and psychiatric disorders (Aloe and Fiore, 1998). Neuroschistosomiasis is referred to the schistosomal involvement of the central nervous system (Ferrari and Moreira, 2011). Fiore et al. (1998) reported that schistosome infection produced body weight reduction, increased analgesia, induced anxiety and decreased locomotion in mice.

For schistosomiasis, vaccine is nonexistent and drugs remain the mainstay of disease control. However, the current drug index is limited and/or inadequate and the problem is being further exacerbated by the emergence of drug resistance (Ismail et al., 2002; Silva et al., 2003). This raises a need for complementary and alternative drugs that are both effective and safe (Jatsa et al., 2009).

Attention has been focused on the protective effect of naturally occurring antioxidants, generally in biological systems (Asgarpanah and Ramezanloo, 2012; Nasri et al., 2012) and specifically against Shistosoma (Orledge et al., 2012). Berberine (BER) is a plant alkaloid with a long history of medicinal use in both Ayurvedic and Chinese medicine (Kulkarni and Dhir, 2008; Bhutada et al., 2010). Previous studies have shown that BER has a wide ranging pharmacological and biological activities including anthelmintic (Birdsall and Kelly, 1997), anti-

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inflammatory (Ivanovska and Philipov, 1996), anti-amnesic (Peng et al., 1997), anxiolytic (Peng et al., 2004), anti-depressant, analgesic and neuroprotective activities (Bhutada et al., 2010). All these effects of BER might be attributed to its capacity to modulate several neurotransmitters such as serotonin (Kong et al., 2001; Castillo et al., 2005). The present study aimed to investigate the neuronal activity of berberine (BER) against *S. mansoni*-induced infection in mice.

MATERIALS AND METHODS

Animals

Thirty two male Swiss albino mice were bred under specified pathogen-free conditions and fed a standard diet and water *ad libitum*. The experiments were performed only with male mice at an age of 9 to 11 weeks and were approved by state authorities and followed Egyptian rules for animal protection.

Infection of Mice

S. mansoni cercariae were from Schistosome Biological Supply Center at Theodor Bilharz Research Institute, Imbaba, Giza, Egypt. Mice were exposed to 100±10 *S. mansoni* cercariae per mouse by the tail immersion method, modified by Oliver and Stirewalt (1952).

Experimental design

Animals were allocated to four groups of eight mice each. Group I served as a vehicle control and received water (100 µl water/mouse) by oral administration for 10 days. Group III was gaveged with 100 µl of 12 mg/kg berberine chloride (Sigma, St. Louis, MO, USA) (Jahnke et al., 2006) for 10 days. Group II and Group IV were infected with 100±10 *S. mansoni* cercariae, and on day 46 p.i. with *S. mansoni.* The animals of Group IV received 100 µl berberine chloride by gavage once daily for 10 days at a dose of 12 mg/kg body weight. On day 55 p.i with *S. mansoni*, the animals of all groups were cervically dislocated. Brains were rapidly excised from skulls, blotted and chilled. The brain tissue was weighed, wrapped in plastic films and quickly stored at -70°C until used for estimation of the epinephrine (E), norepinephrine (NE), dopamine (DA), serotonin (5-HT), 5-hydroxyindole acetic acid (5-HIAA) according to the method of Ciarlone (1978). The levels of calcium (Ca^{2+}), magnesium (Mg^{2+}), sodium (Na^{+}) and chloiride ions (Cl-) were estimated according to Murphy (1987).

Statistical analysis

One way analysis of variance (ANOVA) according to Duncan's test (1955) was performed using the Statistical Package for the Social Science (SPSS) version 13. The Kolmorogov-Smirnov test was used to test for normal distribution of parameters. The histograms were drawn using Microsoft Excel. The percentage change was calculated as:

$$\% \text{ Change} = \frac{\textit{Mean of treated - Mean of control}}{\textit{Mean of control}} \times 100$$

RESULTS

Our data indicated that berberine treatment for 10 days has a pronounced effect of the level of the brain neurotransmitters. Infection of mice with *S. mansoni* induced a neuronal alterations in neurotransmitters as indicated with a significant decrease ($P \leq 0.05$) in the brain epinephrine, norepinephrine, dopamine, sertonine and 5-hydroxyindol acetic acid with a percentage change of approximately – 54% (Figure 1), -47% (Figure 2), -93% (Figure 3), -39% (Figure 4) and -65% (Figure 5), respectively.

BER was able to significantly ($P \leq 0.05$) lower the increased reduction in the level of dopamine (Figure 3), sertonine (Figure 4) and 5-hydroxyindol acetic acid (Figure 5) due to *S. mansoni* infection. However, the level of brain epinephrine (Figure 1) and norepinephrine (Figure 2) was not significantly changed after treatment of the infected mice with BER.

One aim of the present study was to identify infection associated changes of trace elements in the brain during the course of *S. mansoni* infection in mice. Table 1 showed the clear significant increase in the percentage of calcium in the brain of the infected mice compared to the vehicle control. BER treatment induced a highly significant decline in Ca^{2+} ion content versus the infected (-BER) group indicating the ameliorative role of BER on the increased level of Ca^{2+} ion content induced by *S. mansoni* infection. Also, compared to the vehicle control, the level of Mg^{+}, Na^{+}, and Cl^{-} was significantly increased due to infection of mice with *S. mansoni* (Table 1) with a percentage change of approximately 37, 12 and 275%, respectively. Again berberine could significantly ($P \leq 0.05$) improve the induced alterations in these minerals due to infection (Table 1).

DISCUSSION

Berberine induced a neuronal activity against schistosomiasis and could be considered as a neuro-modulator of *S. mansoni*-infected mice brain. Neuroschistosomiasis mansoni, referring to *S. mansoni* involvement of the central nervous system (CNS), may or may not result in clinical manifestations (Ferrari et al., 2008). Clinical studies have shown that humans affected with neuro-schistosomiasis suffer pain in the limbs and changes in peripheral sensory responses (Scrimgeour and Gajdusek, 1985).

Our results showed a reduction in E, NE, DA, 5-HT and 5-HIAA contents due to *S. mansoni* infection; on contrary, Ca^{2+}, Mg^{2+}, Na^{+} and Cl^{-} ions contents showed an increment in brain tissue. Several studies reported that schistosome infection induce epilepsy, seizures, cognitive impairments, deficits in learning abilities and behavioral changes (Katchanov and Nawa, 2010; Ferrari and

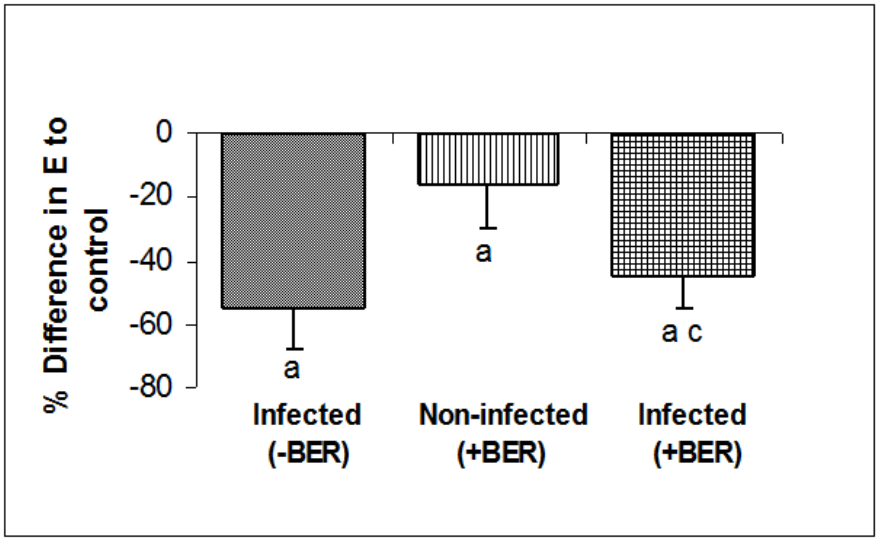

Figure 1. Berberine (BER) induced alterations in brain epinephrine (E) (µg/g tissue) of mice infected with *S. mansoni.* Values are means ± SE. a: Significant against non-infected (-BER) group at *P*≤0.05, b: Significant against infected (-BER) group at *P*≤0.05, c: Significant against non-infected (+BER) group at *P*≤0.05.

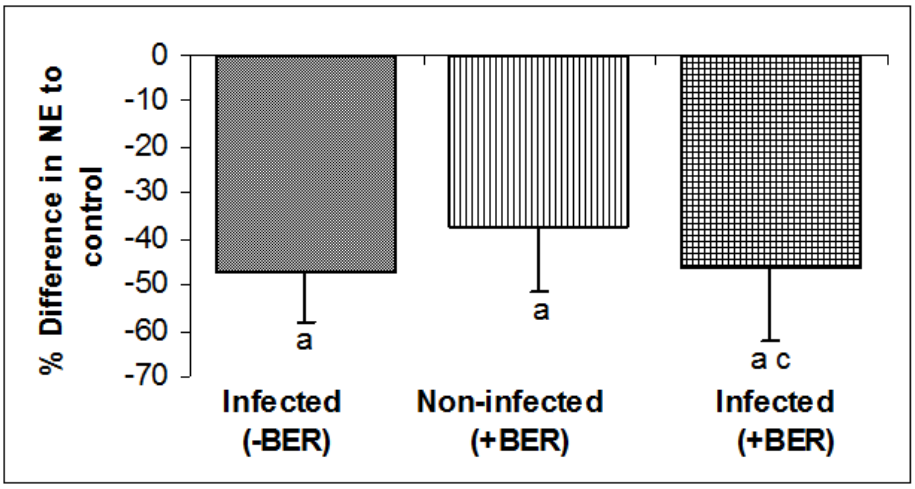

Figure 2. Percentage change in norepinephrine (NE) (µg/g tissue) in brain of mice infected with *S. mansoni* and treated with Berberine (BER). Values are means ± SE. a: Significant against non-infected (-BER) group at *P*≤0.05, b: Significant against infected (-BER) group at *P*≤0.05, c: Significant against non-infected (+BER) group at *P*≤0.05.

Moreira 2011). Some authors attributed the behavioral dysfunctions and the different types of seizures to deficiencies in the activities of the NE, DA and 5-HT systems (Applegate et al., 1986; Trindade-Filho et al., 2008).

The increment in Ca^{2+}, Mg^{2+} and Na^{+} ions concentration in brain tissue may be due to, in part, to an increase in the intracellular Na^{+} flow by binding to the Na^{+} ions channels and prolonging the opening time. Moreover, Mg^{2+} chelation is leading to prolong the opening time of the Ca^{2+} ion channel, thus increasing intracellular Ca^{2+} ions concentration (Davies and Maesen, 1989), this increase in intracellular Ca^{2+} ions concentration led to the rupture of the vesicles in the presynaptic terminals and increase the release of the neurotransmitters by exocytosis (Bullock et al., 1995) as a result the content of catecholamine is decreased in the present results. Moreover, the dysregulation in Cl^{-} homeostasis occurs in

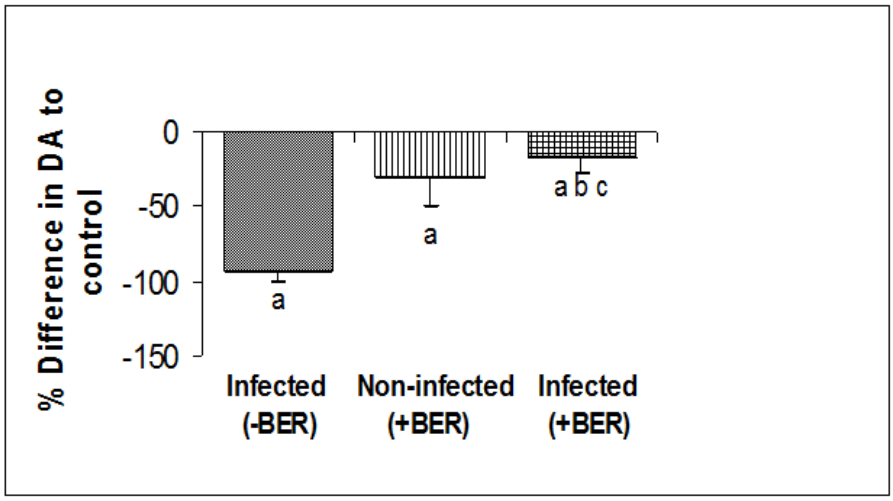

Figure 3. Changes in dopamine (DA) (µg/g tissue) percentage in brain of mice infected wit *S. mansoni* and treated with berberine (BER). Values are means ± SE. a: Significant against non-infected (-BER) group at *P*≤0.05, b: Significant against infected (-BER) group at *P*≤0.05, c: Significant against non-infected (+BER) group at *P*≤0.05.

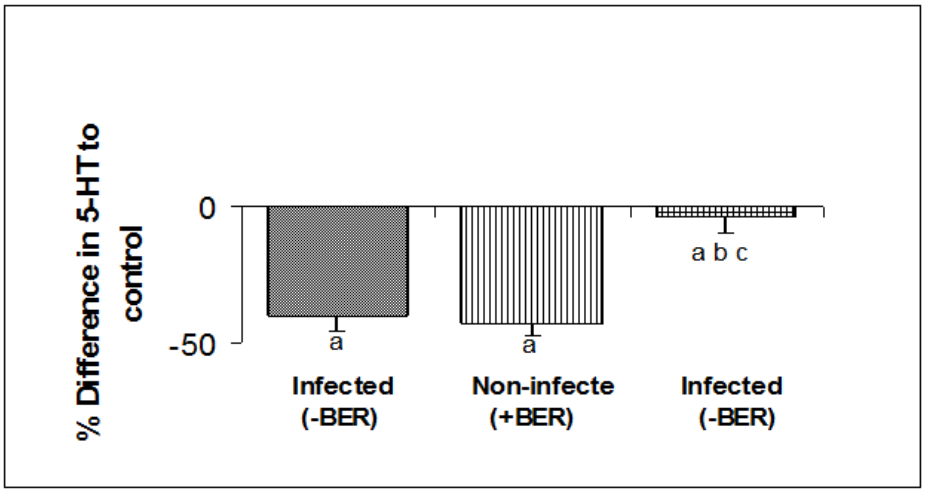

Figure 4. Changes in the serotonin (5-HT) (µg/g tissue) content in brain homogenate of mice infected with *S. mansoni* and treated with berberine (BER). Values are means ± SE. a: Significant against non-infected (-BER) group at *P*≤0.05, b: Significant against infected (-BER) group at *P*≤0.05, c: Significant against non-infected (+BER) group at *P*≤0.05.

many CNS pathologies including epilepsy and chronic pain (Asiedu et al., 2012). It was known that the enhancement of $GABA_A$ and $GABA_C$ receptors that are gated by Cl^- ion content, leading to increase the release of GABA and influx of Cl^- ion causing an increase in Cl^- ion content in brain tissue as a result Cl^- ion content was increased in brain tissue in this study. Thus, schistosome infection induces analgesia through the activation of Cl^- channel coupled GABA receptors.

Hu et al. (2012) reported that BER can cross the blood brain barrier, enter the cell and interact with DNA to act as a neuroprotectant. Several studies stated that BER produces anxiolytic (through modulation of 5-HTergic system), analgesic and antipsychotic (through modulation of DAergic system), antidepressant (through modulation of 5-HTergic, adrenergic and DAergic). Interestingly, modulators of these neurotransmitters are reported to implicate in anticonvulsant activity (Bhutada et al., 2010; Lee et al., 2010). BER gavage to schistosome infected mice group resulted in a highly significant reduction in E,

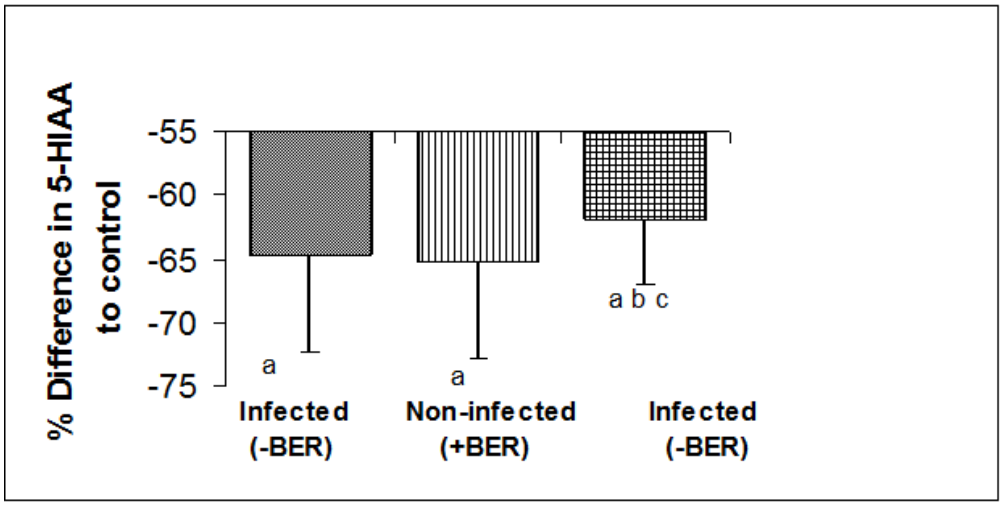

Figure 5. 5-hydroxyindole acetic acid (5-HIAA) (µg/g tissue) content in infected mice brain tissue with *S. mansoni* and treated with berberine (BER). Values are means ± SE. a: Significant against non-infected (-BER) group at $P \leq 0.05$, b: Significant against infected (-BER) group at $P \leq 0.05$, c: Significant against non-infected (+BER) group at $P \leq 0.05$.

Table 1. Changes in Ca^{2+}, Mg^{2+}, Na^{+} and Cl^{-} contents in brain of mice infected with *S. mansoni* and treated with Berberine (BER).

Group	Ca^{2+} (mg/g)	Mg^{2+} (mg/g)	Na^{+} (mg/g)	Cl^{-} (mg/g)
Non-infected (- BER)	33.63 ± 2.4	22.58 ± 1.0	141.7 ± 1.1	179.1 ± 13.3
Infected (- BER)	43.23 ± 1.7 [a]	30.81 ± 1.0 [a]	159.3 ± 2.5 [a]	671.4 ± 35.1[a]
Non-infected (+ BER)	25.73 ± 1.3 [a]	27.94 ± 1.7 [a]	161.4 ± 4.5 [a]	6146.8 ± 223.9 [a]
Infected (+ BER)	30.74 ± 1.1 [b]	24.57 ± 1.4 [b]	175.6 ± 2.0 [a b c]	8317.7 ± 103.8 [a b c]

Values are means ± SE. a: Significant against non-infected (-BER) group at $P \leq 0.05$, b: Significant against infected (-BER) group at $P \leq 0.05$, c: Significant against non-infected (+BER) group at $P \leq 0.05$.

NE, DA, 5-HT and 5-HIAA contents. On the other hand, BER administration induced a highly significant increment in Na^{+} and Cl^{-} ions contents. Moreover, a partial recovery was observed in Ca^{2+} and Mg^{2+} ions contents in brain tissue (Peng et al., 2004). Shin et al., (2000) showed that BER *in vitro* exerts an inhibitory effect on catecholamine biosynthesis, e.g. on DA synthesis in neuronal cells. Moreover, it has been suggested that BER is an antagonist of brain DA receptors (Huang and Jin, 1992). In addition, Peng et al. (2004) reported that BER at 100 mg/kg after acute treatment decreased the levels of monoamines and increased their turnover rates and possessed anxiolytic-like activity. The anxiolytic mechanism of BER might be related to the decrease in 5-HTergic system activity by activating somatodendritic 5-HT_{1A} autoreceptors and inhibiting postsynaptic 5-HT_{1A} and 5-HT_2 receptors. This may be explaining the reduction in 5-HT and 5-HIAA contents. Kulkarni and Dhir, (2008) concluded that BER influenced either DAergic system by monoamine oxidase-B inhibiting property or by blocking the reuptake of DA by inhibiting its transporter. Moreover, it has been reported that BER has potent inhibitory effects against Ca^{2+} influx via NMDA-receptor on hippocampal pyramidal cells (Yoo et al., 2006). Hence, BER was known as an antidepressant substance. Lau et al. (2001) and Nicholson et al. (2002) showed that in neuronal tissues, the tricyclic antidepressant drug has been shown to inhibit Ca^{2+}-activated K^{+} channels. These may be explaining the decline in Ca^{2+} ion contents in mice brain tissue in the present study. Moreover, Mg^{+2} depletion in mice produce an increase in anxiety and depression-like behavior (Singewald et al., 2004). BER was known as an anxiolytic and antidepressant, so this may explain the increment of Mg^{2+} ion content in mice brain tissue in this study. In addition, electrophysiological studies have demonstrated that BER prolonged the action potential duration and effective refractory period in Purkinje fibers (Dai, 2000). Na^{+} channels are present at distinct sites in neurons, where they sub-serve different functions and play distinct roles.

Some Na^+ channels, especially those at the initial axon segment, initiate action potentials and control firing thresholds. Postsynaptic somatodendritic Na^+ channels act in concert with a range of ligand-gated and voltage gated channels to generate neuronal discharges. In contrast presynaptic Na^+ channels contribute to the regulation of neurotransmitter release (Prica et al., 2008).

Collectively, BER increase the release of the neurotransmitters and consequently, decrease the contents of monoamines and could be considered as a neuro-modulator of *S. mansoni*-infected mice brain.

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