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شبكة المعلومات الجامعية

بسم اللّه الرحمن الرحيم

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التوثيق الالكتروني والميكروفيلم

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شبكة المعلومات الجامعية

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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بالرسالة صفحات
لم ترد بالأصل

Effect of melatonin and nifedipine on brain neurotransmitters and cellular redox state of global ischaemic rats

A Thesis Presented
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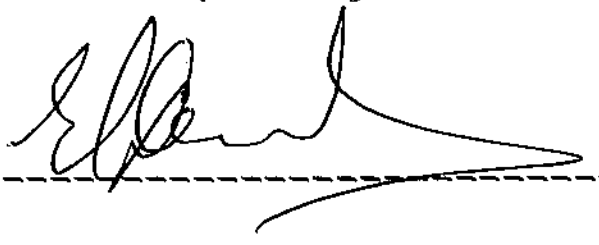
(2) 

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To my mother, husband and children
Nour, Riem and Nadiem

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Abstact

The chief factors that play a role in ischaemic damage include calcium homeostasis, formation of free radicals, interruption of energy metabolism and disturbance in neurotransmission. A close correlation is evidenced to exist between ischaemia-induced surge of glutamate and the release of other neurotransmitters such as serotonin, NE and dopamine in brain ischaemic tissues. The elevated levels of such neurotransmitters are connected to the ischaemic dire events viz., brain oedema, Ca^{2+}influx, excessive depolarization, energy failure and free radical formation. These events could perturb both synthesis and re-uptake mechanisms of these neurotransmitters. GABA, which is an inhibitory neurotransmitter, is expected to have a role, by counteracting the excessively released neuronal excitability.

The disturbance in brain energy metabolism, as a result of discrepancy between oxygen demand and supply, cause a decline in high energy phosphate, a lowering in the glucose level and accumulation of lactate level. Alternative energy substrates such as lactate and β- hydroxybutyrate (β -HB) could successfully replace the role of glucose

Upon reperfusion, which follows the ischaemic hour, free radicals are excessively released causing the so called" reperfusion injury". Antioxidant enzymatic systems, superoxide dismutase (SOD) and glutathione reductase (GR) are expected to trap the released free radicals in blood and brain, reflecting, thereby, the oxidation-reduction state.

Therefore, the aim of this work was to study the effect of melatonin, a well known free radical scavenger, and nifedipine, a Ca^{2+}- channel blocker, on the previously mentioned neurotransmitters, energy substrates and antioxidant enzymes in both ischaemia and ischaemia/ reperfusion states. To fulfill this purpose, male adult Wistar rats were subjected to global ischaemia, by occlusion of the two carotid arteries for 1 hr, followed by their declamping for another hour. Drugs were injected after ischaemia in a group, and before or after reperfusion in another two groups. After killing the rats, their brains were removed, ice-cooled and dissected into four areas: cerebral cortex (C.C), thalamus and hypothalamus (Th/H.Th), midbrain (M.B) and medulla, pons and cerebellum (M.P.C).

Our study shows that ischaemia elevated all neurotransmitters under investigation, while declamping leveled off this increase close to normal levels. Melatonin (10mg/ Kg; i.p.) and nifedipine (1.5mg/ Kg; i.p.), when given after ischaemia averted nearly the ischaemic effect, while GABA levels were increased in ischaemia/ reperfusion (I/R) treated groups. Regarding 5-HT, melatonin injected in I/R groups increased their levels, while the effect of nifedipine was minimal.

Regarding the energy state, ischaemia elevated the brain content of β-hydroxybutyrate and the plasma levels of lactate, glucose and β-hydroxybutyrate. Recirculation succeeded to normalize the brain contents of glucose and β-hydroxybutyrate, as well as the plasma levels of lactate and β-hydroxybutyrate, while failed to correct the plasma levels of both lactate and glucose. Both drugs were able to normalize the ischaemia and I/R contents of the energy fuels.

Concerning the antioxidant enzymes (SOD & GR) and lactate dehydrogenase enzyme (LDH), ischaemia increased the activity of cytosolic LDH and erythrocytic GR, while decreased the activity of the cytosolic SOD and GR enzymes. Allowing blood to flow normalized the altered activities of the erythrocytic antioxidant enzymes as well as LDH, while elevated the cytosolic antioxidant activities. Both drugs were able to normalize the ischaemic effect on the erythrocytic SOD and GR activities added to the I/R effect on their cytosolic activities.

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