ABSTRACT

Topiramate (TPM) is a novel therapeutic agent effective in the treatment of migraine and induces weight loss. The objective of the present study was to assess the action of TPM treatments on dietary induced obese mice. Herein, thirty two male albino mice were fed with different high fat diets (HFD) groups, comprises of animal fat, soybean oil, animal fat + soybean oil and a control group (fed on normal rodent diet) for six months. At the end of six months, the subjects were given the drug treatment at different doses (10, 30 and 100 mg/kg) daily for one month. The mice underwent cardiac puncture after TPM treatment and organs (brain, heart and pancreas) were removed and weighed. Tissues of all organs (brain, heart and pancreas) were analyzed for histological and quantitative methods. Body weights of all mice were registered daily before and after the TPM treatment. In addition, blood glucose levels, glucose tolerance tests and insulin levels of all mice were measured twice in a month throughout the experiment. The feeding with HFD induced a significant ($P < 0.001$) increase in body weights of mice as well as blood glucose and insulin levels in comparison to control group. These measurements were suppressed by TPM treatment at 100 mg/kg significantly ($P < 0.001$) in all HFD groups.

The histopathological changes in the brain sections revealed significant increase in number and size of neurons in the hypothalamic region of obese mice as compared to controls ($P < 0.001$). After TPM treatment (100 mg/kg), the number of neurons were significantly higher ($P < 0.001$) in group IV (animal fat + soybean oil), whereas there was also significant increase ($P < 0.05$) in size of neurons in group III (soybean oil) and IV (animal fat + soybean oil). The cortex of mice brain in control group showed normal structure and distribution of neuronal cells but there were slight increase in number of glial cells, degenerated neurons and vacuolization observed in all HFDs groups. After TPM treatments, fibrillary debris, necrosis, infiltration, more vacuolization and glial cells were prominent in the cortex of mice. The mean cortical thicknesses of mice brain in HFDS groups (III and IV) were significantly increased as compared to control group ($P < 0.001$). After TPM treatments, the cortical thickness were reduced significantly at 30 mg/kg in all HFDs and control groups ($P < 0.001$). In addition, the thickness of molecular layer, granular layer and white matter of cerebellum exhibited significant reduction in all HFDS fed mice in comparison to controls ($P < 0.001$), whereas the granular layer and white matter of cerebellum in all HFDS group showed significant increase at 30 and 100 mg/kg TPM treatments in comparison

to 10 mg/kg ($P < 0.001$). The molecular layers were increased significantly at 100 mg/kg TPM treatment in all HFDs groups as compared to 10 and 30 mg/kg ($P < 0.001$). Furthermore, purkinje cells revealed swollen and irregular with pyknotic nuclei in all HFDs groups as compared to controls. After TPM treatments, the loss of linear arrangement of elongated purkinje cells with prominent pyknotic nuclei were observed in all HFDs and control groups.

In addition, the disorganization of acinar cells, infiltration, congestion, fat droplets and irregular shape of islets in pancreas sections of mice were observed in HFD groups. There were no morphological changes in islets but congestion, fat droplets and disorganized acinar cells were examined in different TPM treatments in all HFD groups. The heart sections of obese mice showed disarrangement of myofibrils, interstitial edema and acidophilic sarcoplasm in all HFD groups whereas congestion, inflammation, disorganization of central and flat nuclei were prominent at different TPM treatments in HFD groups. Therefore, it is concluded that TPM treatments tend to increase the neuronal cell density, reduces the body weights and improves insulin levels in dietary induced obese mice as an anti-obesity drug.