ABSTRACT

Women with epilepsy face a host of challenges due to use of antiepileptic drugs (AEDs) and reproductive endocrine disturbances are a major health problem in these patients. These disorders have been attributed both to epilepsy itself and to use of AEDs. Despite extensive clinical and experimental research, the underlying mechanism remains unclear. However a pathogenic role of epilepsy itself has been proposed by some researchers, whereas others suggest that the use of AEDs, in particular valproic acid (VPA), may mediate this association. VPA is an extremely potent and widely prescribed anticonvulsant agent and is generally agreed upon that VPA acts to potentiate gamma amino butyric acid (GABA) mediated postsynaptic inhibition within the central nervous system (CNS) via some, as of yet, unknown cellular mechanisms.

The gonadotropin releasing hormone (GnRH) system in the hypothalamus constitutes the final common pathway for the central regulation of pituitary gonadotrophin release. The median-eminence region undergoes functional remodelling in GnRH neurons involving participation of cell adhesion molecules, astrocytes and gonadal hormones to render the pulsatile secretions into the perivascular space. Taking into consideration both the inhibitory role of GABA as a neurochemical regulator of GnRH, as well as VPA’s proposed GABAergic mechanism of action, we hypothesized that VPA may mimic and/or elevate the activity of GABAergic system in hypothalamus and disrupt the GnRH pulse generator.

The present study was aimed to test whether VPA’s anticonvulsive effects via key molecules of GABAergic system may be having inhibitory effects on the hypothalamo-hypophyseal-gonadal (HPG) axis at the level of GnRH synthesis and/or release and thereby affect reproductive health of subjects taking VPA. Since VPA is also reported to cause cognitive and memory dysfunction so the neuronal plasticity and GABAergic function was also studied in hippocampus and piriform cortex regions which are associated with memory and cognitive function.
Our study demonstrated the VPA mediated changes both at protein and mRNA level in the key molecules which play an important role in the regulation of reproduction. Chronic administration of VPA had adverse effects on reproductive neuroendocrine system in non-epileptic female rats via its effect on GnRH pulse generator. These findings suggest a direct drug-induced effect through its GABAergic mode of action. Further VPA was also observed to affect the neuronal plasticity and GABAergic function in hippocampus and piriform cortex, brain regions known to be associated with learning and memory. Similar studies need to be carried out to analyse more such AEDs with GABAergic mechanism of action for their role in disruption of reproductive function and also to ascertain the safety levels to reduce their adverse effects on reproductive health and cognitive functioning.