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REVIEW ARTICLE

Estrogen and Serotonin: Complexity of Interactions and Implications for Epileptic Seizures and Epileptogenesis

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Abstract: A burgeoning literature documents the confluence of ovarian steroids and central serotonergic systems in the injunction of epileptic seizures and epileptogenesis. Estrogen administration in animals reduces neuronal death from seizures by up-regulation of the prosurvival molecule *i.e.* Bcl-2, anti-oxidant potential and protection of NPY interneurons. Serotonin modulates epileptiform activity in either direction *i.e* administration of 5-HT agonists or reuptake inhibitors leads to the activation of 5-HT3 and 5-HT1A receptors tending to impede focal and generalized seizures, while depletion of brain 5-HT along with the destruction of serotonergic terminals leads to expanded neuronal excitability hence abatement of seizure threshold in experimental animal models. Serotonergic neurotransmission is influenced by the organizational activity of steroid hormones in the growing brain and the actuation effects of steroids which come in adulthood. It is further established that ovarian steroids bring induction of dendritic spine proliferation on serotonin neurons thus thawing a profound effect on serotonergic transmission. This review features 5-HT1A and 5-HT3 receptors as potential targets for ameliorating seizure-induced neurodegeneration and recurrent hypersynchronous neuronal activity. Indeed 5-HT3 receptors mediate cross-talk between estrogenic and serotonergic pathways, and could be well exploited for combinatorial drug therapy against epileptogenesis.

Keywords: Epileptic seizures, epileptogenesis, neuroprotection, estrogen, serotonin, neuronal plasticity.

1. INTRODUCTION

The term epilepsy is procured from the Greek word *epilam-banein*, connoting to attack or seize [1]. Epilepsy is a chronic neurological disorder pronounced with abrupt recurring events of sensory disturbance, loss of consciousness, or convulsions correlated with abnormal electrical activity in the brain [2]. Epilepsy is mainly classified as Partial Seizures (Simple Partial Seizures, Complex Partial Seizures & Secondarily Generalized Seizures) and Generalized seizures (Absence Seizures, Myoclonic Seizures, Atonic Seizures, Tonic Seizures, Tonic-Clonic Seizures) [3]. Partial seizures are restricted to distinct zones of the cerebral cortex; only a definite part of the body is typically involved, at least at the beginning. On the contrary, generalized seizures are eminent in disverse areas of the brain. A person is diagnosed with epilepsy if two or more seizures are evoked, which could not be defined by a medical condition, fever or drug withdrawal [1]. The causes of epilepsy remain diverse including but not limited to neurodegenerative diseases, cerebrovascular diseases, traumatic head injury, intracerebral tumors *etc* [4].

The high firing of neurons during epileptic seizures is brought about by the inability of neurons to conserve equilibrium between excitation and inhibition virtually because of inflated glutaminergic transmission (which is excitatory in nature) and suppressed GABAergic transmission (which is inhibitory in nature). Epilepsy is a social and economic burden, usually, patients suffering from epilepsy also suffer from social stigma. Singh and Trevick, (2016) reported that

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70 million people worldwide suffer from epilepsy while developing nations contribute 90% of such cases [5]. A recent study summarizing epidemiological studies of epilepsy in the Arab world concluded prevalence rates of 7.5/1000 as median lifetime epilepsy and 4.4/1000 as active epilepsy, except for pediatric studies. While median incidence reported was 56.0/100,000 [6].

The treatment of seizures was unleashed with the launch of bromides. In 1910, phenobarbital (PHB) was introduced which ruled the market for several years. Phenytoin (PHT), Carbamazepine (CBZ), Ethosuximide (ETX), and Sodium Valproate (SVP) were later additions in the market. These drugs continued to be the backbone of epilepsy treatment till the 1990s, when second-generation antiepileptic drugs *e.g* Oxcarbazepine, Lamotrigine, Gabapentin, Topiramate, and Levetiracetam, with comparatively good efficacy, better tolerability, little side effects and rare necessity for therapeutic drug monitoring were invented [7]. However, still the treatment of epilepsy remains grueling, as 30% to 40% of patients remain unresponsive to the effect of current AEDs or their combination therapies [8]. Undoubtedly, none of these drugs have been able to target epileptogenesis *i.e* process through which neurons transform into epileptic. During epileptogenesis the underlying neurodegeneration (AEDs have meager neuroprotective potential) degenerates drug targets, or alters the properties of the binding site, leading to the onset of drug refractory epilepsies. In this review, we have tried to end this misery by focusing on the role of reproductive hormone (estrogen) and neurotransmitter (serotonin) and their interaction to possibly unleash a new target for antiepileptic therapy, and a possible strategy to interfere with the process of epileptogenesis.

2. ESTROGEN

Estrogen is a gonadal steroid hormone with a small molecular weight which is associated with the female reproductive system and easily reaches out to the neuronal tissue by crossing the blood-brain barrier due to its highly lipophilic nature [9, 10]. Accordingly, on reaching neuronal tissues, it starts to unveil effects on neuronal areas associated with seizures and seizure-related damage including cholinergic and GABAergic neurons of the basal forebrain region [11, 12], supramamillary area [13] monoaminergic nuclei of the midbrain [13], and the hippocampus [14, 15]. These effects are mediated by different estrogenic receptors [16, 17]. The ligand-activated transcription factors form the classic intracellular estrogen receptors (ER) *i.e.* ERα and ERβ [18, 19]. The mRNA distribution of intracellular ERα and ERβ is notably divergent; ERα is imperious in pituitary, kidney, epididymis and adrenal glands while ERβ in prostate, lung, bladder and brain. The overlapping high expression of both estrogen receptor subtypes is reported in female reproductive organs like ovary and uterus as well as in male reproductive organs like testis [13, 20]. In the hippocampus, ERα is found in the pyramidal cell layers of CA1, CA2, and CA3 while ERβ in the CA1, CA2 and DG [21, 22]. ERβ is further subdivided into two isoforms *i.e*. ERβ1 & ERβ2 [17]. ERβ1 is having a greater affinity towards estrogens than ERβ2 because the ligand-binding domain of ERβ2 holds an insertion of 18 amino acid [23]. Subcellularly, ER was identified in synaptic spines, nuclei, cytoplasm, and presynapses [24]. Estrogen also tends to act by nongenomic mechanisms which involve the interaction of putative non-nuclear estrogen receptors with second messenger systems resulting in rapid actions on neuronal excitability by the activation of many cellular pathways like the cyclic AMP and mitogen activated protein kinase (MAPK) [25-28].

2.1. Estrogen as Proconvulsant

It is a central tenet that seizures result owing to the disparity between excitatory transmission mediated by glutamate and inhibitory transmission mediated by GABA. Estradiol increases excitatory (glutamatergic) transmission and that facilitation of transmission extends to seizures [29-30]. Lange & Julien, (1978) observed an increase in cortical electroencephalogram (EEG) signal in case of a seizure after they applied bolus of estradiol to the cortex of anesthetized cats [29]. Estradiol facilitates long-term potentiation (LTP) [30, 31] and induces dendritic spine growth resulting with a net excitatory effect [32]. Electrophysiological and ultrastructural studies signal that administration of estradiol to rat for 24 h exhibited null impact on excitatory synapses while a significant reduction in transmission of the inhibitory synaptic GABAergic signal was observed in hippocampus conceivably because the release of GABA was reduced [33]. Estrogen affects IPSCs without affecting excitatory postsynaptic currents, reducing the amplitude and frequency of IPSCs evoked synaptically and amplitude but not the frequency of miniature IPSCs [34], paired-pulse depression of evoked IPSCs and docking of vesicles at inhibitory synapses [35]. In the brain, estrogen also targets growth factors, more exclusively the neurotrophin *i.e* Brain Derived Neurotropic Factor (BDNF) which is encoded by BDNF gene. The ovariectomy of adult female rats emanated in shrunken BDNF levels while such effects were reversed on subsequent treatment with estrogen. BDNF is elevated during seizures in the hippocampus, an area that is thought to be important in seizure generation [36]. For example, recombinant BDNF when applied to hippocampal slices potentiates glutamatergic transmission [37-39] and is required for LTP in the hippocampus [40-43]. Estradiol is reported to exert its effects on NMDA and dendritic spine morphology, similar effects have been observed with BDNF although they vary in relation to effect on spines [44]. BDNF binds to the ectodomain of a tyrosine kinase (TrkB) receptor emanating in dimerization of receptor, receptor tyrosine kinase activity activation and consequential creation of docking sites for adaptor proteins (shc) or enzymes (PLCγ1) in the cytoplasmic domains in the event of tyrosinase phosphorylation, henceforth coupling to intracellular signaling cascades. BDNF inhibits signal mediated by GABA and produces structural plasticities in the hippocampal dentate granule cells by activating TrkB analogous to an epileptic brain [45-51]. Thus BDNF is potentially proconvulsant and BDNF at least in part, mediates estrogenic actions.

2.2. Estrogen and Neuroprotection

The subtypes of estradiol *i.e* α-estradiol and β-estradiol exhibit opposite effect on neurons *i.e.* former may impair DNA, in fact, be damaging while later exhibits neuroprotec-

tive potential. Indeed effect of β-estradiol on neurons can be well established during menopause *i.e*. state of slackening levels of β-estradiol leading to a heightened cascade of neurodegenerative disorders, while consequent administration of β-estradiol around menopause delays the onset of such disorders [52]. However use of estrogens is still limited by a dint of their feminizing effects for which recently non-feminizing estrogens have been investigated as postmenopausal neuroprotectants [53]. These non-feminizing estrogens are described to exert such effects because of the inadequate binding affinity towards estrogen receptors (ERs). Estrogen apart from direct effects on neurons also protects the neurons by changing the physiology and morphology of astrocytes [54]. Neuronal injury exerts upregulation of neuronal ERs [55] and aromatase enzyme in astrocytes which bring aromatization of testosterone to synthesize β-estradiol in astrocytes [56]. These results implicate towards an endogenous protective mechanism offered by β-estradiol. GPR-30 (also GPER1) is pertussis toxin-sensitive G-protein operated membrane receptor for estrogen [57] having significant abundance in the hypothalamus [58, 59], CA1 area of the hippocampus [60] and basal forebrain [61, 62]. The neuroprotective effects of estradiol can also be mediated *via* activation of this receptor [60], though the pathway requires transactivation of IGF-1 receptors [63, 64]. Further, GPR-30 mediates a cross-talk between the genomic and non-genomic mode of estradiol action, since the action of estradiol tends to be mediated by both non-genomic and genomic pathways.

2.3. Estrogen Neuroprotection in Seizure-induced Hippocampal Damage

Hippocampal sclerosis is the most typical pathology amalgamated with limbic system seizures [65-68]. Seizure-induced neuronal debt leads to restructuring of hippocampal axonal networks [69]. The degeneration of pyramidal cells and interneurons leads to retiring of the hippocampus [70]. The state is mimicked by administration of chemoconvulsants: pilocarpine- or kainic acid in animals [71, 72]. These chemoconvulsants lead to profound cell death of CA1, CA3 and NPY/somatostatin containing neuronal cells in hilar regions of the hippocampus, in a similar pattern resembling hippocampal sclerosis [73]. Estrogen administration in animals upregulates the prosurvival molecule *i.e*. Bcl-2, exhibits anti-oxidant potential and protects NPY interneurons thereby reducing the neuronal mortality from seizures [69, 74-78]. Neuropeptide-Y (NPY) behaves as a natural barrier against the progression of seizures in hippocampus from the perforant path to dentate gyrus granular cell [79]. Estrogen induces NPY formation through BDNF-TrkB signaling hence estrogen *via* BDNF increases NPY levels in the brain [80-85]. Estrogen in inhibitory presynaptic boutons promotes the higher release of NPY during seizures. The effect of estradiol on the release of NPY can further be correlated because of predominating ERα (an estrogen receptor subtype) over large dense-core vesicles in the hippocampal region [81]. Thus putative neuroprotective efficacy of β-estradiol in the dentate gyrus cells of the hippocampus are well characterized *via* involvement of NPY [80]. OVX female rats are highly susceptible against SE-induced hippocampal neuronal damage, however β-estradiol administration protects the same. The protection appears to be dose dependent with lower dose of β-estradiol protecting hilus of the dentate gyrus, CA1 and CA3 areas of the hippocampus [69, 86-88] while very high doses of β-estradiol administered (40 μg/animal) seem to play opposite behavior in the KA model [89]. Now the question arises whether genomic or non-genomic mechanisms of estrogen are involved in this and it was ingrained that longer pretreatment with β-estradiol is relatively more efficacious with respect to an acute parental dose of β-estradiol perhaps due to its activity at genetic level [80, 89]. Tamoxifen (an ER antagonist) blocks neuroprotection exerted by β-estradiol supports the fact that both types of intracellular ER are responsible for the genomic effects found in the hippocampal region [14, 21, 69].

2.4. Catamenial Epilepsy

Women with epilepsy display distinct issues than men with epilepsy. A menstrual cycle-associated variation of convulsions has been recounted to affect 10-70% of women with focal and generalized epilepsy; Catamenial epilepsy [90]. Catamenial epilepsy is inferable to (1) the neuroactive acreage of steroid hormones and (2) the cyclic fluctuation in their serum levels [91]. The three paradigms of Catamenial aggravation of epilepsy incongruity to serum estradiol (E2) and progesterone (P) ratio are; C1 = perimenstrual; C2 = preovulatory; C3 = luteal phase. This ratio is maximal during the days prior to ovulation and menstruation but is lowest during the early- and mid-luteal phase. Herzog *et al*., (1997) also defined Catamenial epilepsy as higher than average seizure frequency amid perimenstrual and periovulatory periods in normal ovulatory cycles and during the luteal phase in anovulatory cycles. Estradiol amplifies glutamatergic and restrains γ-aminobutyric acid (GABA) transmission. It augments neuronal metabolism and discharge rates, facilitates kindling, experimental as well as clinical seizures [92]. Whilst progesterone depresses neuronal metabolism, epileptiform discharges, suppresses kindling as well as experimental and clinical seizures [92], the lopsidedness of which leads to Catamenial epilepsy. Estrogen (i.v; infusion) in women with epilepsy was bound with rapid interictal epileptiform activity, and that seizures were aggravated when estrogens were given premenstrually [93]. Hormone Replacement Therapy (HRT) inculpates taking hormone supplements to mitigate hot flushes and night sweats of the menopause. Estrogen is prescribed in hysterectomised women, while in others a natural/synthetic progesterone hormone is added to protect overgrowing womb lining. Harden 2008, reported an increase in seizure frequency in women with epilepsy at perimenopause (39 subjects were included in the study; 25 reported an increase), 15% of subjects were on synthetic HRT and 72% were having catamenial epilepsy pattern. The results corroborated that HRT insignificantly and catamenial seizures significantly escalated seizures at perimenopause. The reason being increase in the ratio of estrogen-to-progesterone [94]. However, after menopause (one year without menses), HRT was associated with a significant increase, while catamenial seizure pattern was concorded with a significant abatement in seizures [94]. In rodent postmenopausal model, estrogen pretreatment was effective in restricting "spread," neuronal loss, and mortality in ovariectomized rats, while seizure severity grossly remained the same against KA-induced seizures [95]. Estrogen pretreatment in

ovariectomized rats reduced the number of seizures against NMDA-induced seizures, further estrogen replacement returned seizure number to that of the intact state [96]. Neuroprotective effect of estrogen in ovariectomized rats was reported for lithium–PILO model of SE [97]. Scharfman *et al*., 2009 confirmed the protection of hypothalamic centers controlling reproductive function by Raloxifene in PILO treated rats. Further results suggest that Raloxifene might be a suitable alternative for hormone replacement in postmenopausal women with epilepsy, in which estrogens are often avoided because they are considered as proconvulsant [98]. Thus hormone replacement therapy with estrogens has the potential to increase seizure frequency and thus cannot be recommended for women with epilepsy.

3. SEROTONIN

Serotonin (5-hydroxytryptamine; 5-HT), a ubiquitous substance, first identified in enterochromaffin cells by Vialli and Erspamer in 1937 and named as "enteramine" was later confirmed to be same substance identified in 1952 possessing clotted blood vasoconstrictor effects [99]. Serotonergic system is intricately involved in regulation of neurologic and psychiatric functions, the disturbances of which leads to physiological and functional anomalies including psychosis, chronic impulsivity, obsessive-compulsive disorder, bulimia, epilepsy *etc*. [100-104]. The categorization of 5-HT receptor subtypes has been done on the basis of their affinity towards ligands into seven receptor families encompassing fourteen 5-HT mammalian receptors [105, 106]. Except for serotonin 5-HT$_3$ receptor (Cys-loop superfamily of ligand-gated ion channels) serotonin generally transduces through G-protein coupled receptors to modulate neuronal excitement [107-110]. Hippocampus consists of both pre- and postsynaptic serotonin receptors which play a role in serotonergic neurotransmission. Tryptophan hydroxylase (TPH1 and TPH2); the precursor for producing serotonin and monoamine oxidase A (MAO-A); responsible for 5-HT degradation have been reported in the hippocampus [101, 111]. The serotonin transporter seems to be condition-regulated in the hippocampus and crucially affects serotonergic neurotransmission [112].

3.1. Serotonin, Serotonin Receptors and Epilepsy

In mice with genetically raised 5-HT levels, the threshold to KA-induced seizures was elevated [113]. Further serotonergic neurons in the raphe nuclei had been reported to be significantly compromised during PILO induced SE [114]. Trindade-Filho *et al*., (2008) stereotaxically injected 5,7-dihydroxytryptamine (5,7-DHT; a neurotoxin used to reduce the concentration of serotonin in the brain) into the median raphe nucleus of rat brain and later upon PILO administration postulated increased inclination towards SE (acute phase) and spontaneous seizures (chronic phase) [115]. It is widely known that enhancement of 5-HT release by standard anti-seizure drugs (*e.g*., Valproic acid, Carbamazepine, Phenytoin, Lamotrigine and Zonisamide) contributes to antiseizure effects [116-118], while in brain depletion in the level of 5-HT by agents such as *p*-chlorophenylalanine enhances seizure induction [119, 120]. Taken together, these results conjecture that normal serotonin levels could have an inhibitory action on seizure activity.

Chemoconvulsions induced by administration of Bicuculline, Picrotoxin, or PILO were inhibited by 5-HT$_{1A}$ receptor agonist; 8-hydroxy-2-(di-*n*-propylamino)-tetralin (8-OH-DPAT) [121-123]. Buspirone (5-HT$_{1A}$ receptor agonist) protected against PILO-induced seizures, the possible mechanism inculcated was 5-HT$_{1A}$ receptor stimulation and inhibition of oxidative stress [124]. In severe seizure GEPRs (GEPR-s) the combination of fluoxetine with 5-HT$_{1A}$ somatodendritic autoreceptor antagonists (-)-pindolol and LY 206130 (1-[1-H-indol-4-yloxy]-3-[cyclohexylamino]-2-propanol maleate) appended anticonvulsant action [119]. The threshold for KA-induced seizures was lowered in 5-HT$_{1A}$ receptors knockouts [125-126]. Further 5-HT$_{1A}$ receptor binding was reduced in the limbic areas on the ipsilateral side in patients with TLE, and that 5-HT1A-binding asymmetry was greater for patients as compared with healthy controls [127].

Pentylenetetrazole (PTZ) and electrically-evoked convulsions were inhibited by 5-HT2 agonist; *m*-chlorophenylpiperazine (mCPP) [128, 129]. Krishna Kumar *et al*., (2009), reputed that PILO induced epilepsy leads to down-regulation of the 5-HT content, 5-HT2C gene expression and 5-HT2C receptor binding with an increased affinity in rat cerebellum which was reversed upon treatment with Carbamazepine and *B. monnieri* [128]. Audiogenic seizures were triggered in mice due to genetic deletion of 5-HT$_{2C}$ receptors [130-132]. Freitas *et al*., (2005), reported that PILO-induced SE was not able to instigate variation in 5-HT2 receptor density in the hippocampus, but inflated the *K*d values, indicating that the affinity of 5-HT for 5-HT2 receptor reduces in this tissue [133]. Contrary O'Dell *et al*., (2000) reported that 5-HT2 receptor has convulsant activity, advocating the idea that during the SE a decline in the binding could shield limbic areas [134]. However, the role of 5-HT2 receptors in epileptogenesis needs to be further investigated.

Pentylenetetrazole (PTZ) evoked clonic seizures threshold in mice was reduced by Granisetron (5-HT3 receptor antagonist) alone and in combination with L-arginine. Contrary SR57227 (5-HT3 receptor agonist) exhibited anticonvulsant effect which was enhanced with L-NAME indicating that NO system modulates the action of 5-HT3 receptors during brain excitability [135]. Singh *et al*., (2009), described a case study involving administration of Ondansetron (5HT3 antagonist) to patients complaining of severe nausea and vomiting in association with a migraine, gastritis and diabetic ketoacidosis emanating in a generalized tonic– clonic seizure even though patients were unlinked parenterally to seizures [136]. Palonosetron (5-HT$_3$ receptor antagonist) induced repeated generalized tonic-clonic seizures in a patient complaining of nausea in postanesthetic recovery unit [137]. Payandemehr *et al*., (2012) reputed that 5-HT3 receptors conciliate anticonvulsant effects of low dose Citalopram (SSRI) alone and in combination with mCPBG (5-HT3 receptor agonist) against PTZ induced convulsions in mice, while corresponding higher doses of citalopram produced-proconvulsive effects. Further Tropisetron (5-HT$_3$ receptor antagonist) prevented the anticonvulsive properties of low

dose Citalopram [138]. Bahremand *et al*., (2011) also revealed the anticonvulsant effect of low dose citalopram, which was augmented with morphine and 1-(m-chlorophenyl)-biguanide (mCPBG, a 5-HT3 receptor agonist) against clonic seizures induced by PTZ in male NMRI mice. The anticonvulsant effect was prevented with Tropisetron (5-HT3 receptor antagonist). High doses of citalopram were pro convulsant while morphine, mCPBG and tropisetron failed to alter such effect [139]. Intrahippocampal perfusions of Citalopram failed to prevent seizures at 0.5 μM, while the anticonvulsant effect was evident at 1 μM, mediated through 5-HT1A receptors [140]. Thus the anticonvulsant effect of Citalopram is dose-dependent, mediated in part by 5-HT3 & 5-HT1A receptors, which indicate 5-HT1A & 5-HT3 ought to be the most relevant in the process of epileptogenesis and maintenance of epilepsy (Tables **1**-**6**, **9**).

3.2. Serotonergic Drugs and Epilepsy

The reduction in brain 5-HT along with the destruction of serotonergic terminals leads to increased neuronal excitability/reduction of seizure threshold in experimental animal models [141]. The administration of 5-HT receptor agonists or reuptake inhibitors tends to inhibit limbic and generalized seizures [142-144]. Wada *et al*., (1992) recited that 5-HTP (the serotonin precursor) has a potent antiepileptic action as regards to hippocampal and lateral geniculate nucleus-kindled seizures, implying that the serotonergic system is entangled in the abolishment of epileptic activity in these brain areas [145]. In addition, patients with myoclonus had low cerebrospinal levels of 5-Hydroxyindoleacetic acid (5-HIAA; the main metabolite of serotonin) indicating that some forms of myoclonus might be pertinent to a dearth of brain serotonin [146]. Related studies have corroborated that 5-HTP was effective in reducing the severity of myoclonic seizures in several patients [147, 148]. Naffah-Mazzacoratti *et al*., (1996) observed an escalation in the 5-HT and 5-HIAA content of spiking tissue collected from patients with complex partial seizures indifferent to current anticonvulsants. These authors hypothesized that these changes could be a compensatory effect, trying to block the tissue hyperexcitability [149].

In line with this, several serotonergic drugs had been evaluated in epilepsies; fluoxetine (SSRI) in rats was claimed to suppress maximal electroshock- induced seizures [143], PTZ-induced convulsions in mice [150], audiogenic seizures in genetically epilepsy-prone DBA/2J or GEPRs rats [151] and focally elicited limbic motor seizures in rats [143]. Faingold *et al*., 2011 recited that fluoxetine (SSRI) reduces the incidence of respiratory arrest (RA) without terminating seizure susceptibility (*i.e*. seizure induced respiratory arrest (S-IRA) was deterred at doses not reducing tonic seizures), indicating highest degree of selective suppression of S-IRA [152, 153]. The mechanism involves increasing 5-HT availability, leading to enhanced respiratory function in reaction to elevated blood CO_2 levels that occur during convulsions [154, 155]. In PILO model of temporal lobe epilepsy (TLE) fluoxetine was able to reduce spontaneous seizures [156]. In addition, fluoxetine when combined with anticonvulsants like Phenytoin, Carbamazepine and Ameltolide had been reported to produce a dose-dependable reduction in their ED50 values, to protect against MES-induced tonic-extensor seizures in mice [157]. Fluoxetine significantly enhanced the anticonvulsive action of sodium valproate but not that of ethosuximide against PTZ-induced clonic convulsions in mice [158]. Further, unblind, open level add-on trial in 17 patients having a complex partial seizure with and without secondary generalization reputed anticonvulsant properties of Fluoxetine (complete disappearance of daily seizure in 6 patients and 30% reduction in seizure activity in 11 patients) [159]. Contrary, fluoxetine (10.0 mg/kg) enhanced the pro-convulsive effect of PTZ (50.0 mg/kg) but inhibited PTZ-stimulated c-Fos expression in some regions of the hippocampus without altering PTZ brain concentration denoting that this phenomenon was not allied to the pharmacokinetic interaction [160]. Further preliminary result from an observational study reported an increase in ictal activity in a patient with epilepsy following SSRI co-medication [161]. Hence critical monitoring of dose during fluoxetine therapy is essential for sustained anti-epileptic effects.

Fluoxamine (SSRI) completely suppressed seizure-begot respiratory arrest (S-IRA) and Tonic Hind Limb Extension (THLE) while other audiogenic seizure (AGSz) behaviors (wild running and/or clonus) remained unaffected [152]. Paroxetine (another SSRI) exhibited the same response at higher doses but with an adjourned (24 h) onset and considerable toxicity (including mydriasis, jerking and shivering) [152]. Venlafaxine (selective norepinephrine serotonin reuptake inhibitor; SNRI) significantly reduced the incidence of S-IRA and THLE while other audiogenic seizure (AGSz) behaviors (wild running and/or clonus) remained unaffected. However, interestingly Venlafaxine displayed a U-shaped dose-effect relationship, which may be fraternal to the dual effects of this drug on both 5-HT and NA levels [162] Cyproheptadine (nonselective serotonin antagonist) significantly increased the incidence of seizure-incited respiratory arrest (S-IRA) and tonic seizures in DBA/1 mice [152]. The 5-HT7 receptors are urged to play a role in mediating these effects of SSRIs, and these receptors are also involved in the central control of respiration (Tables **7**, **8**).

3.3. Serotonin and Neuroprotection

The eventual motive of neuroprotective strategies is to restrain the severity of initial damage and to improve neurological outcome and, hence the quality of life. It is surprising that given the realm of conditions subjugated under the term epilepsy, each with diverse, acquired or genetic origins and distinct behavioral manifestations, electrographic signatures, pharmacological profiles and histopathologies, no single animal model of epilepsy fully represents this disease [163]. Hence a substantially limited number of rodent models have emerged as the primary choices for most investigations involving neuroprotection. Repinotan (5-HT_{1A} receptor agonist) is reported to afford neuroprotection against permanent middle cerebral artery occlusion (pMCA-O), transient middle cerebral artery occlusion (tMCA-O) and traumatic brain injury (acute subdural hematoma, aSDH) models. The proposed mechanism involves activation of 5-HT_{1A} GPCR-coupled inwardly rectifying K+ channels manifesting as hyperpolarization, which in turn emanates in the reduction of

Table 1. Effect of serotonin & serotonergic drugs on pentylenetetrazol induced convulsions.

Drug and Category	Dose	Pharmacological Effect	Refs.
Citalopram (SSRI)	0.5 & 1 mg/kg	Increased the seizure threshold (Anticonvulsant effect)	[138]
Citalopram (SSRI)	25 & 50 mg/kg	Reduced the seizure threshold (Proconvulsive effects)	[138]
meta-Chlorophenylbiguanidine (5-HT3 receptor agonist)	10 mg/kg	Increased the seizure threshold (Anticonvulsant effect)	[138]
Citalopram (SSRI) + meta-Chlorophenylbiguanidine (5-HT3 receptor agonist)	0.1 & 10 mg/kg + 1 & 5 mg/kg	meta-Chlorophenylbiguanidine augmented antiseizure effect of Citalopram in a dose dependent manner.	[138]
Tropisetron (5-HT3 receptor antagonist)	5 & 10 mg/kg	Reduced the seizure threshold (Proconvulsant effect).	[138]
Citalopram (SSRI) + Tropisetron (5-HT3 receptor antagonist)	1 & 10 mg/kg + 1 & 2 mg/kg	Tropisetron prevented the anticonvulsive properties of Citalopram	[138]
WAY-100635 (5HT1A antagonist)	0.6 mg/kg	Reduced the seizure threshold (Proconvulsant effect)	[138]
Citalopram (SSRI) + WAY 100635 (5HT1A antagonist)	1 mg/kg + 0.3 & 0.6 mg/kg	WAY 100635 failed to influence the anticonvulsant effect of Citalopram	[138]
SR57227 (5-HT3 channel/receptor agonist)	5 mg/kg	No effect	[135]
SR57227 (5-HT3 receptor agonist)	10 mg/kg	Increased the seizure threshold (Anticonvulsant effect)	[135]
Granisetron (5-HT3 receptor antagonist)	3 mg/kg	No effect	[135]
Granisetron (5-HT3 receptor antagonist)	10 mg/kg	Reduced the seizure threshold (Proconvulsant effect)	[135]
L-Arginine	50 & 75 mg/kg	No effect	[135]
L-Arginine	100 mg/kg	Reduced the seizure threshold (Proconvulsive effect)	[135]
L-NAME	10, 20 & 60 mg/kg	No effect	[135]
L-NAME	100 mg/kg	Increased the seizure threshold (Anticonvulsive effect)	[135]
SR57227 (5-HT3 agonist) + L-NAME	10 + 60 mg/kg	Increased the seizure threshold (Anticonvulsive effect)	[135]
Granisetron + L-arginine	3 + 75 mg/kg	Reduced the seizure threshold (Proconvulsive action)	[135]
Fluoxetine (SSRI)	20 mg/kg	Increased both the rate and duration of survival, demonstrating protective effect against seizures.	[128]
Norfluoxetine (metabolite of fluoxetine)	20mg/kg	Increased both the rate and duration of survival, demonstrating protective effect against seizures.	[128]
1-(m-chlorophenyl)-piperazine (mCPP) (5-HT2C/2B receptor-preferring agonist)	2.5-7 mg/kg	Protection against myoclonic and/or tonic seizures. (Anticonvulsive effect)	[129]
1-[5-(2-thienylmethoxy)-1H-3-indoyl]propan-2-amine hydrochloride (BW-723C86) (5-HT2B receptor agonist)	3-30 mg/kg	No effect on the threshold for generalized seizures	[129]
Citalopram (SSRI)	0.5 & 1 mg/kg	Increased the threshold for clonic convulsions (Anticonvulsive effect)	[139]
Citalopram (SSRI)	50 mg/kg	Proconvulsant effect	[139]
Morphine	1 mg/kg	Anticonvulsant effect	[139]

(Table 1) contd….

Drug and Category	Dose	Pharmacological Effect	Refs.
Morphine	≥30 mg/kg	Proconvulsant effect	[139]
Citalopram (SSRI) + Morphine	0.1 & 0.5 mg/kg + 0.1 & 0.5 mg/kg	Morphine had additive effects on the anticonvulsive properties of citalopram	[139]
mCPBG (a 5-HT3 receptor agonist)	1& 5 mg/kg	No effect	[139]
mCPBG (a 5-HT3 receptor agonist) + Citalopram (SSRI) + Morphine	(1& 5 mg/kg) + (1 & 0.5 mg/kg) + 0.1 mg/kg	mCPBG augmented additive anticonvulsant effect of Morphine in combination with Citalopram	[139]
Tropisetron (a 5-HT3 receptor antagonist)	0.25 & 2 mg/kg	No effect	[139]
Tropisetron (a 5-HT3 receptor antagonist) + Citalopram (SSRI) + Morphine	0.25 & 2 mg/kg + 1 & 0.5 mg/kg + (0.5 mg/kg)	Tropisetron prevented additive anticonvulsant effect of Morphine in combination with Citalopram	[139]
Citalopram (SSRI) + Morphine	50 mg/kg + 0.1 & 0.5 mg/kg	Morphine could not alter proconvulsive properties of high dose Citalopram.	[139]
mCPBG (a 5-HT3 receptor agonist) + Citalopram (SSRI) + Morphine +	5 mg/kg + 50 mg/kg + 0.1 & 0.5 mg/kg	Morphine & mCPBG could not alter proconvulsive properties of high dose Citalopram	[139]
Tropisetron (a 5-HT3 receptor antagonist) + Citalopram (SSRI) + Morphine	2 mg/kg + 50 mg/kg + 0.1 & 0.5 mg/kg	Morphine and Tropisetron could not alter proconvulsive properties of high dose Citalopram	[139]
Fluoxetine (SSRI)	10.0 mg/kg	Reduced the seizure threshold (Proconvulsive effect)	[160]
Fluoxetine (SSRI)	15 mg/kg	Increased the threshold for clonic convulsions (Anticonvulsive effect)	[158]

Table 2. Effect of serotonin & serotonergic drugs on pilocarpine induced convulsions.

Drug and Category	Dose	Pharmacological Effect	Refs.
Buspirone (5HT1A agonist)	5 mg/kg	Protected against seizures (Anticonvulsive effect)	[124]
5,7-DHT (5,7-dihydroxytryptamine)	0.2 µl stereotaxically Injected	Aggravated status epilepticus (SE) and spontaneously occurring seizures. (Proconvulsant effect)	[115]
Fluoxetine (SSRI)	20 mg/kg	Reduced the frequency of spontaneous motor seizures. (Anticonvulsive effect)	[156]
Citalopram (serotonin re-uptake blocker)	0.5 µM (intrahippocampal perfusions)	Failed to prevent seizures	[140]
Citalopram (serotonin re-uptake blocker)	1 µM (intrahippocampal perfusions)	Anticonvulsant action, mediated through 5-HT1A receptors.	[140]

neuronal firing and inhibition of glutamate release. Repinotan also affects neuronal death by annihilating protein Bcl-2, serotonergic glial growth factor S-100β and Nerve Growth Factor. It also suppresses the activity of caspase-3 through MAPK and PKCα; this effect may also accord to its neuroprotective efficacy [164]. These effects were blocked by WAY 100635 (5-HT_{1A} receptor antagonist), thereby confirming the neuroprotective properties of 5-HT_{1A} receptors [164]. Marco *et al*., (2011) reported that a high-affinity and potent 5-HT_{1A}R agonist (2-{6-[(3,4-dihydro-2H-chromen-2-ylmethyl)amino]hexyl}-tetrahydro-1Hpyrrolo[1,2c]imidazole-1,3(2H)-dione) exhibits neuroprotective effect, which was validated using neurotoxicity assays in primary cell cultures from rat hippocampus and in the MCAO model of focal cerebral ischemia in rats [165]. Li *et al*., (2010) recited neuroprotective effect of fluoxetine against 3,4-methylenedioxymethamphetamine (MDMA) induced reduction in serotonin transporter (SERT; a reliable marker for accessing the integrity of serotonergic neurons) in rat brain as examined with N,N-dimethyl-2-(2-amino-4-[18F]-fluorophenylthio) benzylamine (4-[18F]-ADAM; a SERT radioligand) and micro positron emission tomography (micro-PET) analysis. The mechanism probably involved inhibition of the SERT interaction with MDMA and its neurotoxic metabolites [166]. Sanchez *et al*., (2001) reputed that 2 and 4 days pre or concurrent administration of fluoxetine with MDMA provides complete protection against MDMA induced loss of 5-HT and 5-hydroxyindoleacetic acid (5-

Table 3. Effect of serotonin & serotonergic drugs on genetic epilepsy prone rats (effect on audiogenic seizures).

Drug and Category	Dose	Pharmacological Effect	Refs.
Fluoxetine (SSRI)	15 mg/kg	Decreased audiogenic seizures in 33% of GEPR-9s	[117]
5-Hydroxytryptophan (immediate synthetic precursor of serotonin)	12.5 mg/kg	No effect	[117]
Fluoxetine (SSRI) + 5-Hydroxytryptophan (immediate synthetic precursor of serotonin)	15 + 12.5 mg/kg	Decreased audiogenic seizures in 83% of GEPR-9s	[117]
Fluoxetine (SSRI)	15 mg/kg	No effect on audiogenic seizures in GEPR-9s	[119]
Pindolol (5-HT receptor antagonist)	10 mg/kg	No effect of audiogenic seizures in GEPR-9s	[119]
Fluoxetine (SSRI) + Pindolol (5-HT receptor antagonist)	15 + 10 mg/kg	Substantial reduction in seizure severity (*i.e* audiogenic seizure severity scores in GEPR-9s) (5-HT1A receptor antagonist Pindolol enhances the ability of fluoxetine to increase extracellular 5-HT in brain)	[119]
(±) LY 206130 (5-HT1A receptor antagonist)	5 mg/kg	Ineffective in suppressing audiogenic seizures in GEPR-9s	[119]
Fluoxetine + (±) LY 206130	15 + 5 mg/kg	Conspicuous reduction in seizure severity (*i.e* audiogenic seizure severity scores in GEPR-9s)	[119]
Paracholorophenyl alanine + Fluoxetine + (-) LY 206130	100 + 15 + 5 mg/kg	Ineffective in preventing seizures (This treatment was found to be highly effective in depleting brain 5-HT)	[119]
Fluoxetine (SSRI) + 5-hydroxytryptophan (immediate synthetic precursor of serotonin)	15 mg/kg + 12.5, 25 & 50 mg/kg	The severity of audiogenic seizures was decreased dose-dependently (The antiseizure effect was potentiated)	[144]

Table 4. Effect of serotonin & serotonergic drugs on bicuculline induced seizures.

Drug and Category	Dose	Pharmacological Effect	Refs.
Serotonin	20 μM	Inhibited epileptiform bursts induced by single presynaptic stimuli in the presence of Bicuculline	[121]
Serotonin + MDL 72222 (5-HT 3 receptor subtype antagonist)	20 μM + 30 μM	Serotonin produced a similar inhibition of the Bicuculline -evoked bursts (membrane hyperpolarization)	[121]
Serotonin + Ketanserin (5-HT 2 antagonist)	20 μM + 3 μM	Serotonin produced inhibition of the Bicuculline evoked bursts	[121]
8-OH-DPAT (5-HT1A agonist)	20 μM	Mimicked serotonin in completely blocking the burst of action potentials evoked in the presence of Bicuculline	[121]
Fluoxetine	5, 10 & 20 mg/kg	Dose-dependent protection from clonic motor seizures (50% protection occurring after the 5-mg/kg dose)	[143]

HIAA) in cortex, hippocampus and striatum of rats, while Fluvoxamine (SSRI) provides neuroprotection only upon concurrent administration, however both drugs failed to alter MDMA-induced acute hyperthermia [167]. Choi *et al*., (2015) reported dose-dependent neuroprotective potential of Duloxetine (serotonin/norepinephrine reuptake inhibitor) against KA-induced neuronal death in the hippocampal CA3 region (mediated *via* reducing TNF-α and IL-1β levels) without any noticeable effect on seizure behavior [168]. 5-HT1A receptor agonist, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) prevented neuronal loss in CA1 subfield and reduction in CA1 BDNF immunoreactivity against global ischemia in the gerbil hippocampus [169]. Bay R 1531 (5-HT1A-receptor agonist) and ipsapirone (5-HT1A-receptor partial agonist) exhibited 100% & 53% neuroprotection in the CA1 area of the hippocampus from ischemic damage in the model of transient global ischemia in the Mongolian gerbil [170] (Table **10**).

4. INTERACTION BETWEEN ESTROGEN AND SEROTONIN

In the adult nervous system, excitatory type of neurotransmission is represented by basic structural elements of

Table 5. Effect of serotonin & serotonergic drugs on picrotoxin induced seizures.

Drug and Category	Dose	Pharmacological Effect	Refs.
8-OH-DPAT ((±)-8-hydroxy-2-(di-*n*-propylamino) tetralin)	1 & 3 mg/kg	Increased the doses of picrotoxin producing running/bouncing clonus, tonic hindlimb extension and death in stressed and unstressed mice, respectively (Anticonvulsant effect)	[123]
WAY-100635 (a selective agonist and antagonist of 5-HT_{1A} receptors), + 8-OH-DPAT ((±)-8-hydroxy-2-(di-*n*-propylamino) tetralin)	0.3 mg/kg + 3 mg/kg	Pre-treatment with WAY (0.3 mg/kg) prevented the anticonvulsant effect of 8-OH-DPAT (3 mg/kg)	[123]
DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane)	2.5 mg/kg	Failed to affect seizure threshold for picrotoxin	[123]
ketanserin (a 5-$HT_{2A/2C}$ receptor agonist and antagonist)	1 mg/kg	Failed to affect seizure threshold for picrotoxin	[123]

Table 6. Effect of serotonin & serotonergic drugs on electroshock induced convulsions.

Drug and Category	Dose	Pharmacological Effect	Refs.
5-HT2C/2B receptor-preferring agonist 1-(m-chlorophenyl)-piperazine (mCPP)	2.5-7 mg/kg	Weakly elevated seizure threshold in the mouse (but not the rat) electroshock test	[129]
5-HT2B receptor agonist 1-[5-(2-thienylmethoxy)-1H-3-indoyl]propan-2-amine hydrochloride (BW-723C86)	3-30 mg/kg	No effect on the threshold for generalized seizures	[129]

Table 7. Effect of serotonin & serotonergic drugs on DBA/1 mouse model of sudden unexpected death in epilepsy (SUDEP).

Drug and Category	Dose	Pharmacological Effect	Refs.
Fluvoxamine (SSRI)	60, 70 & 80 mg/kg	Completely suppressed seizure-induced respiratory arrest (S-IRA) and Tonic Hind Limb Extension (THLE)	[152]
Fluvoxamine (SSRI)	55 mg/kg	Completely suppressed seizure-induced respiratory arrest (S-IRA) but not THLE	[152]
Paroxetine (SSRI)	50-100 mg/kg	Ineffective in reducing S-IRA	[152]
Paroxetine (SSRI)	120 mg/kg	Reduced S-IRA but with a delayed (24 h) onset	[152]
Venlafaxine (serotonin–norepinephrine reuptake inhibitor)	50 & 75 mg/kg	Reduced S-IRA incidence	[152]
Venlafaxine (serotonin–norepinephrine reuptake inhibitor)	25 & 100 mg/kg	Not effective in reducing S-IRA incidence	[152]
AS-19 (selective 5-HT7 agonist)	5–60 mg/kg	Totally ineffective in reducing S-IRA	[152]
AS-19 (selective 5-HT7 agonist)	60 mg/kg	Proconvulsant and Toxic effect	[152]
Cyproheptadine (nonselective 5-HT antagonist)	2 mg/kg	Greater incidence of S-IRA	[152]
Fluoxetine (SSRI)	15 & 25 mg/kg	No significant effect	[153]
Fluoxetine (SSRI)	45 & 70 mg/kg	Reduced the incidence of respiratory arrest following audiogenic seizures	[153]

Table 8. Effect of serotonin & serotonergic drugs on hippocampal kindled seizures.

Drug and Category	Dose	Pharmacological Effect	Refs.
5-hydroxytryptophan (5-HTP)	20 mg/kg	No effect on hippocampal kindled seizures and lateral geniculate seizures	[145]
5-hydroxytryptophan (5-HTP)	40 mg/kg	Inhibited both hippocampal kindled seizures and lateral geniculate seizures	[145]

Table 9. Effect of serotonin & serotonergic drugs on clinical seizures cases.

Drug and Category	Dose	Pharmacological Effect	Refs.
Ondansetron	4 mg	GTCS was observed in two females and one male.	[136]
Polonosetron	0.075 mg	GTCS was developed in female patient.	[137]
L-5-hydroxytryptophan (L-5-HTP) + Carbidopa	1600 + 400 mg/day	Effective in decreasing the severity of myoclonus secondary to cerebral hypoxia in some but not all patients.	[148]
Doxepin (TCA)	5-400 mg/day	Reduction in seizure frequency in epileptic patients	[200]

Table 10. Effect of serotonin & serotonergic drugs on experimentally induced neurodegeneration.

Drug and Category	Dose	Pharmacological Effect	Refs.
Fluoxetine (SSRI)	5 mg/kg	Prevented MDMA-induced loss of serotonin transporters in rat brain (Neuroprotective effect)	[166]
Fluoxetine (SSRI)	10 mg/kg	Fluoxetine administered concurrently with MDMA or given 2 and 4 days earlier provided complete protection, and significant protection when given 7 days earlier against MDMA induced neurotoxicity	[167]
Fluoxamine (SSRI)	15 mg/kg	Fluvoxamine only produced neuroprotection against MDMA induced neurotoxicity when administered concurrently	[167]
Duloxetine (serotonin/norepinephrine reup-take inhibitor)	10, 20 & 40 mg/kg	Duloxetine exhibited dose dependent neuroprotection against Kainic acid (KA)-induced neuronal death in the hippocampal CA3 region	[168]
(8-OH-DPAT) 8-hydroxy-2-(di-n-propylamino)tetralin	1 mg/kg	(8-OH-DPAT) prevented the neuronal loss in CA1 subfield induced by transient global ischemia	[169]
Ipsapirone (5-HT1A-receptor partial agonist)	3 mg/kg	Ipsapirone protected 53% of pyramidal neurons in the CA1 area of the hippocampus from ischemic damage in Mongolian gerbil model of transient global ischemia	[170]
Bay R 1531 (5-HT1A-receptor agonist)	3 mg/kg	Bay R 1531 showed a powerful neuroprotective effect with 100% preservation of neurons in the CA1 area of the hippocampus (Model Used: Ischemic damage model of transient global ischemia in the Mongolian gerbil)	[170]
Repinotan (5-HT1A receptor agonist)	1 - 10 μg/kg	Neuroprotection against Permanent middle cerebral artery occlusion (pMCA-O)	[164]
Repinotan (5-HT1A receptor agonist)	1, 10 & 100 μg/kg/h	Neuroprotection against Transient middle cerebral artery occlusion (tMCA-O)	[164]
Repinotan (5-HT1A receptor agonist)	10 - 100 μg/kg	Neuroprotection against Traumatic brain injury (acute subdural hematoma, aSDH)	[164]
WAY 100635 (5-HT1A receptor antagonist)		Abolished neuroprotection of Repinotan	[164]

neuroplasticity *i.e.* dendritic spines [171-173]. In the hippocampus and cortex, estrogen had been reported to expand dendritic spines [174-177]. In order to find out the exact relationship between spine proliferation and role of ERβ, serotonin neurons of macaques were deeply investigated and further it was reported that they possess the exclusive expression of ERβ [178-181]. Ovarian steroids favor the proliferation of dendritic spine on serotonin neurons thus profoundly affect the transmission of a neuronal signal in serotonergic functions [182]. The proliferation of dendritic spines on serotonergic neurons is supported by estrogen but in menopausal age women ovaries fail to produce estrogen, as a result, gene expression mediated by estrogen for serotonergic support is also reduced, leading to atrophy and shrinkage of dendritic spines on serotonin neurons [182]. Organizational activity exhibited by steroid hormones in the development stage of the brain and activational effects of these hormones which come in adulthood stage, directly affect serotonergic neurotransmission in the brain. The sexual differentiation of serotonergic system *i.e.* differences in the densities of 5-HT innervations to many brain regions is disparate among males and females that is virtually brought about by estrogen. During adulthood, reproductive cycle shows fluctuations in the level of estrogen and progesterone

Table 11. Effect of estrogen & estrogenic drugs on PTZ induced convulsions.

Drug and Category	Dose	Pharmacological Effect	Refs.
Genistein (Phytoestrogen)	10 mg/kg	Increased the seizure threshold (Anticonvulsant effect)	[199]
Genistein (Phytoestrogen) + Fulvestrant	10 + 1 mg/kg	Fulvestrant reversed the effect of Genistein	[199]
Genistein (Phytoestrogen) + Tropisetron (5HT3 antagonist)	10 + 10 mg/kg	Tropisetron eliminated the anticonvulsant effect of Genistein	[199]
Genistein (Phytoestrogen) + m-chlorophenylbiguanide (5-HT3 receptor agonist)	1 + 5 mg/kg	Increased the seizure threshold (Anticonvulsant effect)	[199]

thereby affecting 5-HT neurotransmission [183]. Serum estradiol levels in women of reproductive age have been shown to correlate positively with blood levels of serotonin [184]. Serotonin has been observed to be diminished in postmenopausal women and that it is replenished by ERT to premenopausal levels [184]. The increase in the concentration of 5-HT is bought by estrogen via; increasing the production of hydroxylase (TPH) and inhibiting the gene expression for serotonin reuptake transporter (SERT) [185-189]. Estrogen and tryptophan (the precursor of serotonin) both bind to plasma albumin, the estrogen competing with the same site makes more of tryptophan available to the CNS [190]. The allocation and density of 5-HT receptor subtype and SERT in the brain are also invoked by estrogen [191]. Ovariectomy abates tryptophan hydroxylase (TPH) level as well as mRNA in the raphe of macaques and in the hypothalamus of guinea pig but is replenished by administration of estrogen [192].

Estrogens prompt upsurge in the 5-HT2A receptor density in areas of the brain such as anterior frontal, cingulate and primary olfactory cortex and in the nucleus accumbens, involved with mood, mental state, cognition, emotion and behavior, which describe the differences in the incidences of schizophrenia, in males and females mediated by estrogen *via* 5-HT2A receptors [193]. Benmansour *et al*., (2014) utilized *In vivo* chronoamperometry to examine the hippocampal CA3 region of ovariectomized (OVX) rats for 5-HT clearance upon local application of estradiol or selective agonists for ERα (PPT) or ERβ agonist (DPN) and the possible signaling mechanisms involved therein were also investigated. Further the receptors involved in slowing of 5-HT clearance upon fluoxamine administration were elucidated. The results revealed that stimulation of ERβ by estradiol or DPN (ERβ agonist) induces slowing of 5-HT clearance which is mediated by inhibition of MAPK/ERK1/2 but not of PI3K/Akt signaling pathways. TrkB, and IGF-1 receptors were also involved in exhibition of such effect. However stimulation of ERα with estradiol- or PPT (ERα agonist) inhibited fluvoxamine-mediated slowing of 5-HT clearance, which was halted after inhibition of MAPK/ERK1/2 or PI3K/Akt signaling pathways. Further, IGF-1 receptor, metabotropic glutamate receptor 1, but not with TrkB, was implicated in the said effect. This study clarifies that estrogen exhibits diverse effects on SERT function mediated by ER subtypes transducing through different signaling pathways [194]. Serotonin expresses many of metabotropic effects through BDNF and because of significant influence of estrogens on BDNF, role of estrogens not only in development but also in functioning of serotonergic receptors is well comprehended. Estrogen in the presence of progesterone downregulates E2α receptors (ERα) and upregulates E2β receptors (ERβ) [195]. Activation of E2α receptors (ERα) increases $5HT_{1A}$ receptors by nuclear factor kappa B (NFkB), while E2β receptors (ERβ) activation increases $5HT_{2A}$ receptors [196, 197].

Sumner *et al*., (1999) reported that estrogen proliferates expression of 5-HT(2A)R mRNA and SERT mRNA in the DRN and the densities of 5-HT(2A)R and SERT binding sites in the forebrain by cytoplasmic estradiol receptors, confirmed with administration of tamoxifene, a selective estrogen receptor modulator (agonist/antagonist), which reversed estrogenic effects. Tamoxifene acts as a pure estrogen antagonist in relation to serotonergic mechanisms in brain, and had no effect per se on serotonergic gene expression or the density of binding sites [198]. Genistein (phytoestrogen) was reported to exhibit anti-convulsant property against pentylenetetrazole-induced seizures in ovariectomized mice, while the effect was abolished by administration of fulvestrant (an estrogen receptor antagonist) and tropisetron (5-HT3 receptor antagonist). On the contrary co-administration of low non effective dose of Genistein with m-chlorophenylbiguanide (5-HT3 receptor agonist) potentiated anti-seizure effect, which suggests involvement of estrogenic/serotonergic systems in the anticonvulsant properties of Genistein [199]. Thus estrogens also act through non-specific type of receptors, as of neurotransmitter ion channels, precisely affecting neurotransmission in the nervous system (Table **11**).

CONCLUSION

Human epilepsies beset a comprehensive array of clinical, behavioral and electrical ostentations. Correspondingly, studies of this neurological disorder have brought forward wide range of antiepileptic drugs, yet about 20-30% of patients continue to experience seizures. Nonetheless anticipated clinical benefits of estrogens as promising candidates for prevention of seizure induced neuronal damage (*via* enhancement of NPY levels, antioxidant potential and upregulation of prosurvival molecule; Bcl-2) and serotonergic agonists/reuptake inhibitors as propitious agents regulating abnormality in ionic conductance (*e.g*. SSRIs , 5HT3 agonists and 5-HT1A agonists protect against seizures), could further be exploited as combinatorial salubrious strategy, planted by the certitude that estrogens promote release of BDNF which promotes development and functioning of serotonergic neurons, escalate production of hydroxylase (TPH; the rate lim-

iting enzyme for serotonin production) and also inhibits gene expression for serotonin reuptake transporter (SERT). The concept is further strengthened by pharmacological studies emphasizing anticonvulsant properties of Genistein (phytoestrogen; SERM). The said characteristics of Genistein are transposed with Fulvestrant (estrogen receptor antagonist) and Tropisetron (5HT3 antagonist). Hence 5-HT3 receptors interlink estrogenic and serotonergic pathways and could well be exploited for combinatorial drug therapy against epileptogenesis.

HIGHLIGHTS

Estradiol increases excitatory (glutamatergic) transmission, facilitates long-term potentiation (LTP) and induces dendritic spine growth resulting in a net excitatory effect.

Estrogen not only modulates neuronal function through ERα and ERβ receptors but also tends to act *via* nongenomic mechanisms.

SSRIs (Citalopram, Fluoxetine), 5HT3 agonists (meta-Chlorophenylbiguanide) and 5-HT1A agonists (Buspirone) escalate seizure threshold.

SSRIs (Fluoxetine, Fluoxamine) and SNRIs (Venlafaxine) suppress seizure induced respiratory arrest and THLE, accordingly, these drugs might castoff SUDEP. The 5-HT7 receptors are stated to play a role in conferring these effects of SSRIs as these receptors are also inculpated in the pivotal control of respiration.

5HT3 antagonists (Tropisetron) and 5-HT1A antagonists (WAY 100635) plunge anticonvulsant threshold.

5HT1A antagonist (WAY 100635) failed to influence anticonvulsive properties of SSRIs (citalopram), while 5HT3 antagonists (Tropisetron) descent the same *i.e* anticonvulsive properties of SSRIs are conciliated through 5-HT3 receptors.

5HT2C/2B agonist weakly elevated seizure threshold, while 5-HT2B agonist had no such effect, indicating less relevancy of 5HT2C/2B and 5-HT2B receptors in seizure states.

5-HT1A receptor mediates neuroprotective properties of Repinotan *via* incitement of G protein-coupled inwardly rectifying K+ channels culminating in hyperpolarization and suppression of glutamate release.

Genistein (phytoestrogen; SERM) inflates seizure threshold which is reversed with Fulvestrant (estrogen receptor antagonist) and Tropisetron (5 HT3 antagonist).

5-HT3 receptors interlink estrogenic and serotonergic pathways, and could be exploited for combinatorial drug therapy against epileptogenesis.

5-HT1A and 5-HT3 receptors are ought to be the most potential targets for seizure-induced neurodegeneration and recurrent hypersynchronous neuronal activity, while 5-HT7 receptors that for seizure-induced respiratory arrest.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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