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Review article

Update on the pathophysiology of the epilepsies

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Abstract

The pathophysiology of convulsive and non-convulsive epilepsies is discussed in its primary generalised forms. Focal, clinical and experimental epilepsies, with emphasis placed on the temporal lobe epilepsies (TLE) and their pathophysiologies are also reviewed. Neurotransmitters and neuromodulators and between them, the second messenger systems are considered in the generation, maintenance or inhibition of the epileptic discharge. Action mechanisms of the more classic antiepileptic drugs are briefly summarized along with the therapeutic strategies that might achieve the final control of abnormal discharges, including genetic control as a promising alternative in the current state of research. We emphasized the study of all type of glutamate and GABA receptors and their relation with mRNA editing in the brain. Some of the genetic studies which have been so fruitful during the last ten years and which have brought new insights regarding the understanding of epileptic syndromes are summarized in this article.

Keywords: Dentate granule cells; GABA receptors; Glutamate receptors; Sodium channels; Calcium channel; G proteins; mRNA

1. Introduction

Epilepsy is a cluster of disorders rather than a single disease. It affects about one in 200 people and may last a person's whole life. The individual, who suffers from epilepsy is vulnerable to economic, social and legal difficulties and might experience deep psychological problems. The goals of epilepsy management are to prevent discharges and to avoid their propagation. The understanding of the pathophysiology of the epilepsies is still incomplete. This paper is a brief review of this subject.

2. Basic mechanisms related to generalised tonic–clonic seizures

Generalised seizures are studied by parenteral injection of convulsant drugs, e.g., metrazol in rats. In this animal model, small bilateral lesions of mammilothalamic tract or anterior thalamus, block the convulsive effect [1] suggesting that the generalised response is unrelated to a diffuse origin of the discharges. Generalised seizures are also evoked by the electrical stimulation of diverse cerebral and brainstem regions. Gale (1990) [2] has divided experimental models of generalised convulsive attacks into three groups, according to motor responses: (a) tonic attacks; (b) clonic attacks; and (c) explosive clonic movements of the four limbs. Tonic attacks (a) would be linked with mesencephalic and hindbrain reticular formation, and fail to disappear with supracollicular resection [3], the response proving to be self-sustained beyond the stimulation. Clonic attacks (b) are elicited by kindling with chronically implanted electrodes in various limbic cerebral areas (septum, amygdala, as well as in the entorhinal cortex, the piriform area and the hippocampus). They may be evoked or suppresed by microinjections in the depth of the prepiriform cortex (area tempestas). Explosive clonic movements (c) are the characteristic response of audiogenic seizures, induced by sound and attributed to inferior colliculus, whereas other models with the same

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response have no clear localization. These experiences underscore the concept of epileptic circuits, perhaps more accurately than that of epileptic neurones or neuronal aggregates.

In adult rats, which were treated with flurotil and muscimol (a $GABA_A$ agonist) injected bilaterally in substancia nigra (pars reticulata) attacks were suppressed. Bicuculline (a $GABA_A$ antagonist) facilitated seizures and baclofen (a $GABA_B$ agonist) had no effect [4]. The red nucleus may share inhibitory properties with the locus niger and the pontine reticular formation may inhibit spinal activity induced by convulsant drugs.

Various generalised tonic–clonic epilepsy models have been developed in animal strains with a genetic charge for this seizure type. The photosensitive baboon, presents a picture remarkably similar to the human ''grand mal'' type of seizures. Both clinically and electrically, attacks resemble those of human patients, but in contrast, monkeys hardly ever suffer spontaneous attacks. Studies with these models have attempted to find a genetic sequence and a structural enzyme or protein abnormality that may trigger tonic–clonic attacks. Since verapamil is able to depress generalised tonic–clonic activity in rats receiving systemic pentylenetetrazol, the suggestion has been advanced that calcium antagonists may be helpful in treating human epilepsy.

3. Basic mechanisms related to generalised absence seizures

The basic mechanism underlying generalised absence seizures seems to involve thalamocortical circuits alternating an inhibitory phase, mediated by $GABA_B$ and an excitatory phase, mediated by glutamate receptors.

Oscillatory phases result in bilateral spike and wave (SW) discharges that distinguish these attacks. Jasper and Droogleever-Fortuyn [5] showed that electrical stimulation of cat midline and intralaminar nuclei at 3 cycles/s can provoke bilateral synchronous SW as shown in cortical EEG.

In the cat receiving penicillin, the SW pattern seems to be initiated in the cerebral cortex, whereas in rat models, thalamus and cortex are necessary to trigger the SW discharge [6,7]. The thalamic reticular nucleus (TRN) commands oscillatory behaviours in thalamocortical circuits because of its low threshold for Ca^{2+}-dependent spikes mediated by the $GABA_B$ receptors, inhibitory postsynaptic potentials (IPSP), which then generate high rate action potentials [8]. Ethosuximide and trimetadione decrease these Ca^{2+} currents and antagonise clinical absence attacks. In contrast, an increase in GABAergic activity potentiates both, clinical and experimental absences.

In experimental epilepsy, during SW discharges recorded both in the cortex and in the thalamus, there is both GABAergic IPSP preservation and a lack of focal epileptogenic depolarising shifts. GABAergic discharges of TRN and its projections into thalamic specific nuclei would be involved in the initiation and control of absence attacks.

An increase in $GABA_A$ mediated inhibition, for example by benzodiazepines, may be useful for absence treatment by inhibiting TRN and its $GABA_B$ discharge. In turn, $GABA_B$ agonist baclofen exacerbates SW discharges in some experimental models, in a way not achieved using $GABA_A$ agonist muscimol [9]. In the rat with genetic epileptic absence of Strasbourg (GAERS), gamma-vinyl-GABA and glycine worsen the picture [10].

Long-term activation of NMDA receptors with agonist produces a tonic depolarisation of thalamic neurones, decreases low threshold calcium current ocurrence and blocks absence attacks [11]. NMDA antagonists blocks the excitatory postsinaptic potentials (EPSP) necessary to begin the cycle. Therefore, the full sequence would be as follows: (1) EPSP mediated by NMDA; (2) slow IPSP mediated by GABA A and B receptors; (3) low threshold calcium current; and (4) new depolarisation and the onset of a new cycle.

This cycle occurs at the TRN level and its projections. The clinical expression is an absence and the electroencephalographic correlate, the SW complex, reflects an alternate depolarisation and hyperpolarisation.

Hyperpolarisation may be an essencial element of the cycle, followed by an increased conductance of voltage-dependent Ca^{2+} currents (T channels) with subsequent occurrence of Na^+-dependent action potentials (AP) and repolarization through voltage-dependent K^+ currents. These findings show that there is a need for more research on drugs that block T channels Ca^{2+} currents for absence treatment, allowing selective cycle suppression. Another strategic point is slow IPSP blockade or sustained depolarization on thalamocortical relays to prevent T current activation [12]. Each SW complex appears to begin in the cerebral cortex, but oscillatory pattern requires the integrity of thalamocortical circuits, comprising specific and non-specific thalamic neurones showing that it is better to consider epilepsy as a network dysfunction rather than a single derangement of some nerve cells.

As for L calcium channels, their modulation may be opposite to that of T calcium channels in Wistar rats with spontaneous SW discharges [13]. L channels agonists (such as BAYK 8644) protect against SW discharges in Wistar rats, while antagonist such as nimopidine, facilitate them.

In photosensitive SW activity, Quesney and Reader have postulated a response of the hyperexcitable cerebral cortex to photically evoked thalamocortical discharges that decrease the dopamine cortical release or the net effect of this neurotransmitter which probably has an inhibitory effect on the occipital cortex [14].

There are no animal models that accurately replicate human absence seizures, however there are similar in-

vestigations of animal mechanisms, such as the Wistar or GAERS rats with spontaneous absences, or cats parentally injected with penicillin.

Myoclonic absences have been linked with 12 P trisomy and juvenile myoclonic epilepsy with 6 chromosome short arm. In the last years, 7 chromosomal loci for Mendelian forms of common idiopathic generalized epilepsies have been reported [15].

4. Mechanisms related to partial seizures: temporal lobe epilepsies

The histological pattern of temporal lobe epilepsy has been studied since 1880 by means of light microscopy studies and more recently by immunohistochemistry when the peroxidase–antiperoxidase method became available. Gliosis and neuronal loss are evident to a variable degree, as shown by massive degenerative changes in pyramidal neurones of hippocampus and in granular cells of fascia dentata. Subtler alterations include dendritic spine loss and dendritic bead and spindle deformation [16]. Tissue obtained from patients with a temporal focus provides the usual material for study. The significance of these microscopic changes is uncertain, since they may be due to repeated hypoxic-ischemic insults.

Experimental studies in focal epilepsy [17] have disclosed bioelectrical activation termed paroxysmal depolarisation shift (PDS), consisting of: (1) an abrupt 25–40 mV depolarisation for roughly 200 ms recorded with intracellular microelectrodes and underlying spike activity recorded with surface electrodes, e.g., in foci induced in cats by application of topical penicillin, followed by (2) action potential (AP) discharge at the peak of depolarisation (see Fig. 1) and (3) a long-lasting hyperpolarisation. Epileptic focus topography is such that neurones located in its centre exhibit PDS while peripheral ones only record hyperpolarisation [18] which tends to prevent discharge propagation. PDS is the huge EPSP expression probably resulting in synchronous activation of recurrent axonal collaterals [19]. Some of the associated AP may reflect ephaptic effects of the electrical field [20]. In turn, the ability of cortical cell to generate PDS may be linked with a marked decrease or blockade of IPSP [21].

As regards molecular events underlying PDS, depolarisation is the result of cell entry of Na^+ and Ca^{2+} currents. Na^+ enters with initial EPSP, whereas voltage-sensitive Ca^{2+} is activated by the same depolarisation (positive feedback), but also by activation of glutamate NMDA receptors (Fig. 2) that are also voltage-sensitive and capable of maximal effect at −30 mV, being blocked by Mg^{2+} presence. During repolarisation, K^+ and Cl^- conductance are raised so that K^+ ions flow through different channels, voltage-sensitive and calcium-dependent, and precede chloride ion entry, mediated by $GABA_A$ receptors, that produce post-hyperpolarisation [22]. Evidence that

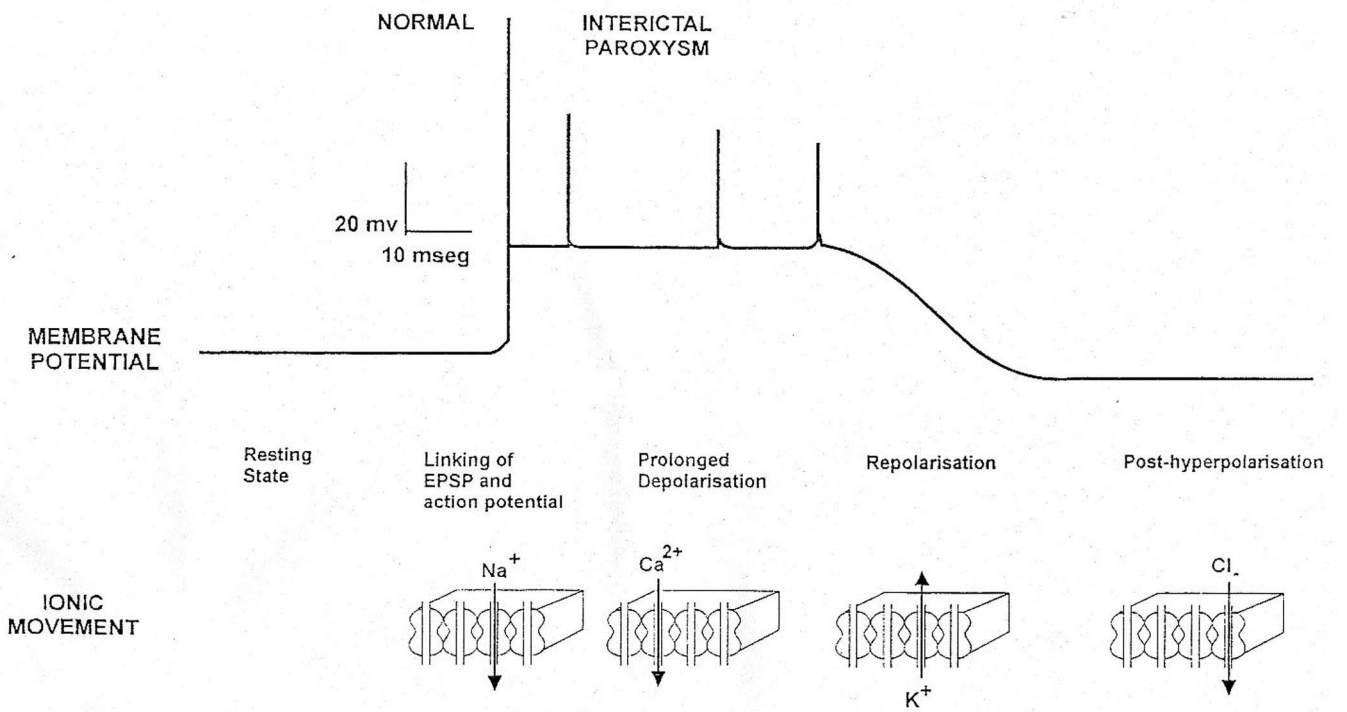

Fig. 1. Paroxysmal depolarisation shift (PDS). An initial excitatory postsynaptic potential (EPSP) and action potential (AP) are linked to Na^+ entry to the cell, which in turn promotes Ca^{2+} entry, thus prolonging depolarisation. Calcium-dependent K^+ conductance increases, repolarising the cell, an effect which persists (post-hyperpolarisation) due to Cl^- entry until metabolic pumps re-establish resting potential. Modified from Lothman EW and Collins RC. Seizures and epilepsy. In: Pearlman AL and Collins RC, editors. Neurobiology of disease. New York: Oxford, 1990: 276–98 [18].

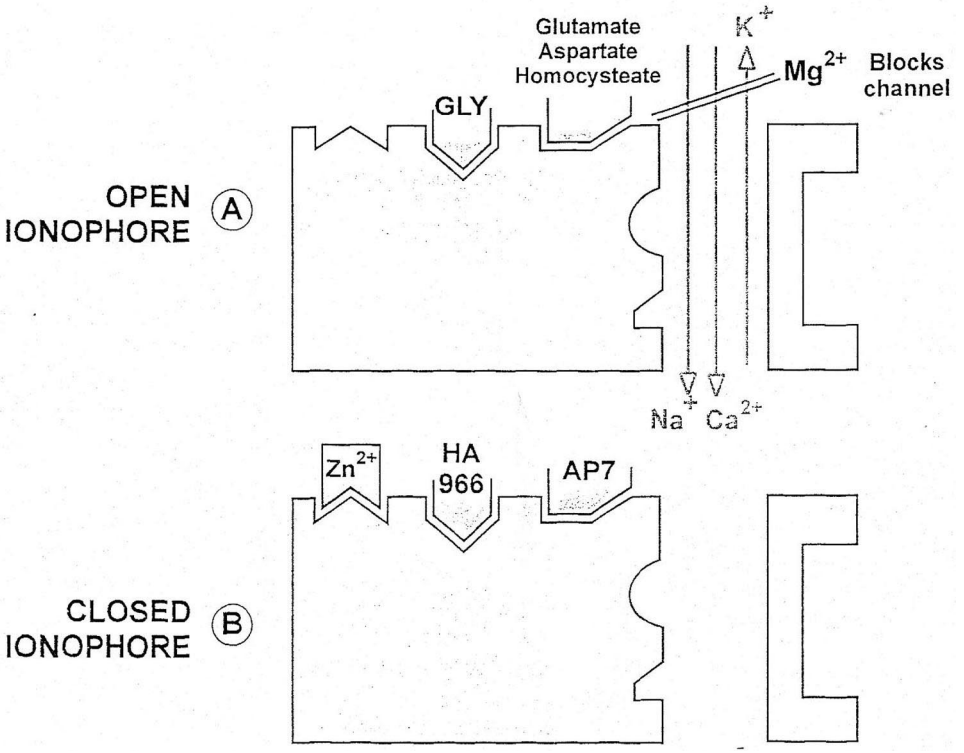

Fig. 2. NMDA receptor: functional states. A: Open ionophore allows Na^+ and Ca^{2+} entry in the presence of glycine and an NMDA receptor agonist; it is blocked by Mg^{2+}. B: Closed channel due to action of direct competitive antagonists as AP7, or by agents acting at the glycine site, as HA 966, or at the Zn^{2+} site. Modified from Faingold CL and Meldrum BS. Excitant amino acids in Epilepsy [163]. In: Avoli M, Gloor P, Kostopoulos G, Naquet R, editors. Generalized Epilepsy: Neurobiological Approaches. Birkhäuser: Boston, 1990: 102–117.

$GABA_B$ receptor activation in the hippocampus induces hyperpolarising currents, by K^+ efflux, responsible for slow IPSP during post-hyperpolarisation have also been presented [23].

It is generally assumed that temporal lobe attacks may arise in the hippocampus, where patients usually have neuronal loss in CA1 and CA3 and where there is also astrocyte proliferation. In hippocampus slices of adult animals, many proconvulsive treatments lead to recurrent discharges that begin in CA3 and spread to CA1, where ictal events are generated when the slice undergoes an increase in K_e^+ or a decrease in Ca_e^{2+} or Mg_e^{2+} [24]. Pyramidal CA3 cells may act as interictal spikes pacemakers, because of a very high Ca^{2+} conductance and a profuse disposition of recurrent axonal collaterals, predisposing to PDS. Conversely, CA1 region is able to maintain seizures by itself, without previous interictal spikes [18].

According to Heinemann and co-workers [25], when ictal activity encompasses dentate gyrus, it will increase in CA1, subiculum and entorhinal cortical deep layers, which can initiate the discharges via the perforant pathway, making epilepsy difficult to arrest (Fig. 3). In human temporal epilepsy, mossy fibre budding is seen in dentate gyrus from the granular to the molecular layer, providing the anatomophysiological basis for a recurrent excitation [26]. There is a good experimental correlation between such budding and hyperexcitability. Electron microscopy shows mossy fibre axonal endings making autosynapses with their own dendrites and with other ones, in both apical and distal sections [27], but also making synapses with inhibitory interneurones, building inhibitory circuits.

According to Lorente de No, mossy axon granular cells at the dentate gyrus project to pyramidal cell dendrites in CA3 [28]. The appearance of spikes in these neurones may depend on: (a) disturbances in their dendrite's physical properties, perhaps linked with the morphological changes mentioned above (spine loss, nodule appearance) and/or (b) increased synaptic input, which may be linked with abnormal proliferation of mossy axons. Another pathological component to be considered in human temporal epilepsy is hiliar neuronal loss in dentate gyrus, enhancing granular cell excitability [29]. Other aspects include: (1) synaptic neoformation processes, closer to the concept of neuronal plasticity than one involving cell degeneration, as mentioned with regard to dentate mossy fibres; (2) metabolic depression of interictal glucose, demonstrated by a combination of MRI and PET studies [30]; and (3) osmolality disturbances, that may change a silent area into a consistent epileptiform activity when extracellular osmolarity is decreased, shown in experimental conditions in CA1 and in dentate gyrus in the rat [31].

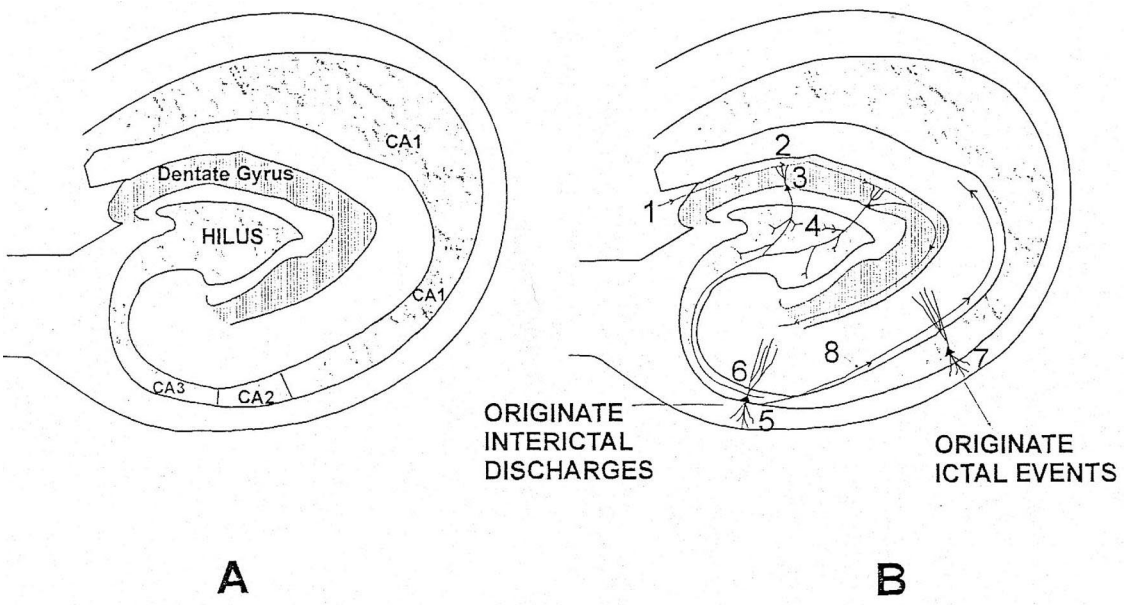

Fig. 3. Normal human hippocampus and its relation with epileptogenesis. Excitatory axons from the entorhinal cortex make up the perforant pathway (1) which ends in the outermost layer of the molecular dentate gyrus (2), exciting the distal portion of dendrites belonging to dentate granule cells (3), which in turn excite the hiliar neurones (4) through axonal collaterals, and pyramidal CA3 neurones (5) via mossy fibres (6). CA3 pyramidal neurones excite CA1 pyramidal neurones (7) via Schaffer's collateral bundle (8), subiculum and again entorhinal cortex. The functional state of disinhibition of the circuit led to epileptic discharges. Modified from Sloviter RS. The functional organization of the hippocampal dentate gyrus and its relevance to the pathogenesis of temporal lobe epilepsy. Ann Neurol 1994; 35: 640–654 [29].

Studying the transition from interictal to ictal activity, the latter can start without being preceded by interictal spikes. According to Dichter [32], voltage-dependent Ca^{2+} currents may contribute to PDS, to interictal–ictal transition and to discharge spread. A K^+ reuptake deficit by astrocytes may operate also as an epileptogenic mechanism. In this regard, various hypotheses have been advanced since K_e^+ accumulation increases hippocampus excitability [33].

A combination of increased NMDA receptor function and depressed GABAergic transmission due to reduced release, to receptor desensitivisation or to genetic abnormality, may well be responsible for the onset of an attack. In fact, NMDA receptors are increased in human temporal lobe epilepsy in the hippocampus [34], while GABAergic transmission appears to be less effective [35].

Decrease in inhibition in dentate granule cells from patientes with medial temporal lobe epilepsy have been recently reported [36]. Conversely Babb found GABA hyperinnervation in basket cells in human and rat hippocampal epilepsies between the attacks. It is not sufficient to avoid the attacks [37] as its function appears to be dormant (JC Lacaille, personal communication).

NMDA receptor binding may increase from 20 to 110% in CA1 area and in dentate gyrus of hippocampus in epileptic patients, in surgical specimen studies [38] The molecular lacunar stratum of CA1 also disclosed a 63% increase in quisqualate-type receptor binding, whereas benzodiazepine (BDZ) and $GABA_A$ binding was significantly decreased in CA1 and CA4, but not in the dentate gyrus.

Geddes and co-workers [34], documented that the increase in NMDA receptors is located at the parahippocampus, which also shows an increase in binding to kainate-type receptors. Wyler et al. [39] found that there is a decrease in the number of muscarine (cholinergic) receptors and an increase in NMDA receptors in temporal cortex removed from epileptic patients.

When aminoacid levels in tissues removed from patients with temporal epilepsy categorised as: (a) having interictal cortical spikes and (b) lacking cortical spikes — activity confined to amygdala/hippocampus — are compared, there is an increase of glutamate, aspartate and glycine, but not in GABA and the taurine in group (a), which causes a loss of equilibrium between excitatory and inhibitory aminoacids [40].

On studying frontal and temporal foci, Van Gelder and co-workers found a decrease in aspartate and GABA in all the examined areas, but only a decrease in glutamate and taurine and an increase in glycine in the more excitable regions, by comparing aminoacids concentrations in the focus and its surroundings [41]. Conversely, Kish et al. reported a 28% increase in aspartate concentration in surgical specimens from patients with temporal epilepsy [42]. Piredda and Gale [43] have shown aspartate's ability as a convulsant agent, when injected into a rat's prepiriform cortex. Chapman et al. reported a correlation between valproate anticonvulsant strength and its ability to

reduce cerebral aspartate levels [44]. An increase in glutamate and aspartate levels in CSF from epileptic patients has also been documented [45].

Neuronal habituation to subliminal repetitive stimulation (kindling) may produce biochemical changes and facilitate convulsive attacks in animals, when different areas in the limbic system are stimulated. This may provide a model applicable to some issues of human temporal epilepsy. With each stimulation, second messenger systems are activated within cells and proto-oncogens are formed, which in turn activate genes, whose products regulate synaptogenesis and cell survival [46]. In amygdaloid kindling, there is a reduction in acetylcholine (ACh) binding in dentate, hippocampus and amygdala [47], but an increase in BDZ receptor binding in hippocampus [48]. It has been suggested that cholinergic circuits may be directly or indirectly involved in amygdaloid kindling.

Experiments in freezing lesions show that the Na^+–K^+ pump in synapses of primary focus and mirror focus, exhibits changes in its activation that lead to a defect in its net operation [49]. Na^+–K^+ pump reduction increases neurone sensitivity to glutamate turning the neurones more excitable [50]. Although the Na^+ pump protein undergoes up regulation, as illustrated by studies in tissues surgically removed from patients with hippocampal sclerosis, its capacity is limited by low activity levels of cytochrome c oxidase enzyme, which is necessary to provide ATP for pump (Na^+, K^+–ATPase) to function. Decreases in cytochrome *c* oxidase and succine dehydrogenase were found in the periphery of epileptogenic scars in cats [51]. Comparing Na^+ pump densities in diverse hippocampal areas in human temporal epilepsy, CA1 has the least amount, predisposing its cells to the easiest neuronal death [50].

An inefficient Ca^{2+}–ATPasa has been incriminated in audiogenic seizures, a form of epilepsy in which the abnormality seems to be situated in granular cells of dentate fascia [52].

According to Delgado-Escueta and Horan [53] six steps lead from focal epileptogenesis to clinical epilepsy: (1) the generation of enhanced physiological responses; (2) PDS, which in turn lead to interictal spike appearance in EEG; (3) focus spread to perifocal neurones; (4) the utilisation or breakdown of control mechanisms with brain circuits that limit the propagation of seizure discharges via preferred routes of spread; (5) the appearance of secondary foci in regions synaptically linked to the primary focus; and (6) the emergence of clinical seizures.

Experimental models of partial epileptic seizures are obtained through foci generated by topical application of convulsants like penicillin, cobalt or aluminum hydroxide gel, or freeze-focus or by injecting intrahippocampally kainic acid or tetanus toxins. Recent studies have shown that even a single kindled seizure induces apoptotic neuronal death in the dentate gyrus and directly demonstrates that brief seizures provoke neuronal death [54,55].

5. Role of neurotransmitters and neuromodulators in relation with neuronal excitability

5.1. Aminoacids

(a) Glutamate–Aspartate: These excitatory aminoacids promote Na^+ and Ca^{2+} cell entry through NMDA receptors (Fig. 2) which incorporate 90% of Na^+ and 10% of Ca^{2+} [56]. Their influx is also voltage-dependent, thus increasing during depolarisation, generating a sustained depolarisation, and dependent on channel blockade by Mg^{2+} [57], whose depletion in extracellular space increases induced NMDA currents. Both, aspartate and glutamate are able to trigger epileptic seizures and provoke cell damage. According to Curtis and Johnston [58], aspartate and glutamate are the two quantitatively more important neurotransmitters in mammalian CNS.

NMDA receptor may have amplifier properties of excitatory synapses, indistinctly activated by aspartate, glutamate, homocysteate or quinolinic acid. There is evidence that NMDA receptors are more easily activated in the kindling model [59]. According to Krnjevic [60], the main trigger of long-lasting post-tetanic potentiation is the Ca^{2+} influx initiated by glutamate and mediated by NMDA receptors. As previously cited, there was an increased binding in the hippocampus [38] and parahippocampus [31] of ligands to NMDA receptors in the cortex removed from patients with temporal epilepsy, as well as an increase in NMDA receptor density [39].

The convulsant ability of aspartate and its possible relation (reverse) with anti-convulsant valproate effect was also cited [44].

While data related to glutamate in epileptic foci are contradictory, indicating indistinctly increased [61] or reduced [41,62] concentration, there is a discernible trend towards a ‘‘glutamate leakage’’ in experimental conditions, both in animals [63] and in humans [64]. Mutani and co-workers reported a decrease in CSF glutamate from epileptic patients with normal values of aspartate and other aminoacids [65].

The study of glutamate receptors has resulted in new classifications. AMPA has replaced quiscualate and currently there are: (1) ionotropic receptors; (a) Glu-R, subdivided into seven subunits, 1–4 sensitive to AMPA and 5–7 sensitive to kainate; (b) Ka (kainate) receptors 1 and 2; (c) NMDAr, 1 and 2 a-b-c-d; and (2) metabotropic receptors mGlu-R; coupled at least to seven different G proteins (1–7).

Merlin and Wong suggest that mGlu-R also participate in epileptic activity [66]. Benaise et al. show that increased AMPA activity in rat area tempestas changes occasional attacks into sustained epileptic activity [67]. According to Comair et al., raised NMDA receptor activation may contribute to hippocampal hyperexcitability in epileptic patients [68]. Hyperexpression of Glu6 (kainate) produces permanent changes in hippocampal excitability [69] which in turn may provoke epileptogenesis.

The role of glutamate as a convulsant and excytotoxic agent is well documented. It is also a precursor of the powerful inhibitor GABA and glutamate/GABA ratio which might exert more influence than any component per se in the generation of paroxysmal neuronal discharges.

Quinolinic acid is an endogenous ligand of the NMDA receptor which can be raised in the brain of some epileptic patients. Feldblum and co-workers describe a decrease in quinolinphosphoribosyltranspherase in the frontal and temporal cortex in epileptic human tissue, that could lead to quinolinic acid accumulation with the corresponding amplification of some excitatory synapses, thus predisposing to epileptogenesis [70].

(b) Glycine and taurine: Glycine is a short chain aminoacid which shows powerful inhibitory actions, long known in spinal cord, medulla and brain stem. Yet at the NMDA receptor level, glycine increases the affinity of this receptor for glutamate, thus proving excitatory for these synpases [71].

Conversely, Zn^{2+} modulates the receptor in the opposite direction [72]. Nonetheless, intracellular injection of Zn^{2+} is epileptogenic, possibly due to its inhibitory effect on Na^{+}, K^{+}–ATPase [73] and/or its stimulatory action on urinary excretion of taurine [74].

Taurine appears to be a weak inhibitor in the cerebral cortex, by decreasing the number of cobalt-induced epileptic seizures in mice and cats, as well as delaying the occurrence of seizures induced by ouabaine in rats, so that it could exert an anti-epileptic action [73]. Taurine may inhibit Ca^{2+} entry to synaptosomes, it increases spontaneous efflux of GABA and inhibit its release by stimulation [75]. Taurine reduction in human epileptic foci has been previously reported [41].

(c) GABA: GABA is the main inhibitory neurotransmitter in vertebrates as roughly 40% of all cerebral synapses are GABAergic. However, its powerful anticonvulsant action is site-dependent; thus, at the nigrocollicular projection, GABA action appears to be pro-convulsant [76]. Locus niger infusion of $GABA_A$ agonist muscimol is also pro-convulsant in rats treated with fluorotil [77].

A schematic representation of $GABA_A$ receptor (Fig. 4) includes four subunit families: alfa (1–6), beta (1–3), gamma (1–3) and delta. Selection of one of the subunits from the above 13 types allows for the possible existence of more than 10 000 pentameric subunit combination, although it has been suggested that less than ten major subtypes of $GABA_A$ receptors actually exist in the adult mammalian brain [78]. This receptor promotes the Cl^{-} influx thus provoking hyperpolarisation with a decrease in cellular excitation state, the inhibition being postsynaptic. BDZ and barbiturates increase the strength of $GABA_A$-mediated inhibitions [79]. BDZ increases the likelihood of opening the Cl^{-} ionophore [80], while barbiturates prolong opening time [81]. Picrotoxin and pentylenetetrazol may block the ionophore [82], while bicuculline is a $GABA_A$ competitive antagonist [83]. $GABA_B$ receptors mediate pre- and post-synaptic inhibitions, by efflux K^{+} currents or

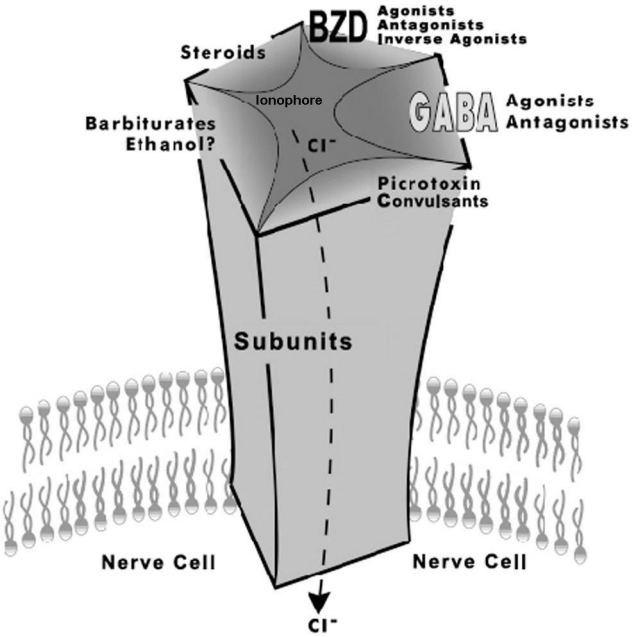

Fig. 4. A schematic representation of the $GABA_A$ receptor complex. Polymers made up by combinations of multiple subunit subtypes (alpha, beta, gamma and delta). The exact emplacement of each subunit is unknown. The schematic representation is hazardous. Binding site of benzodiazepines, Cl^{-} ionophore and GABA are also representated. Other domains allow binding of picrotoxin and barbiturates. The ligand-gated chloride channel proposed to be a pentamer composed by different subunits. Modified from Upton N and Blackburn T. Pharmacology of mammalian $GABA_A$ receptors. In: Enna SJ and Bowery NG, editors. The GABA Receptors, 2nd Edition. Totowa New Jersey: Humana Press Inc., 1997: 83–120 [164].

a decrease in Ca^{2+} influx. The role of these receptors in the production of slow post-hyperpolarisation IPSP is discussed in another section of this article. According to Ribak and co-workers [84], in monkeys subjected to aluminium gel, there is a significant reduction of GABAergic impulses in the affected cortices, with a decrease in the number of GABAergic nervous endings. Reduction in BDZ receptor density in epileptogenic foci of patients with partial epilepsy has been reported [85]. In tonic–clonic generalised seizures, enhanced binding to BDZ receptors in cerebellar nuclei and a decrease in thalamus has been described, due to the corresponding modifications in receptor density [86].

Although the data in the literature is contradictory, there is a consensus in stressing that GABAergic function may be depressed in focal epilepsies and in some models of generalised tonic–clonic epilepsy, whereas it is increased in generalised absences.

5.2. Biogenic amines

(a) Acetylcholine (ACh): ACh excites cortical neurones by the activation of a depolarising muscarinic receptor acting by blockade of sustained K^{+} currents operating during the resting potential. It also blocks Ca^{2+} dependent

slow K^+ currents ocurring during hyperpolarisation (after hyperpolarisation, AHP). AHP provides a useful tool to stop discharges in fast firing systems, as for example pyramidal neurones of the hippocampus.

Although little is known about cerebral nicotine receptors, topical cerebral application of nicotine exerts convulsant effects, as also does its systemic administration [87].

In spite of the conflicting data in the literature, there may be only an epileptogenic action for nicotine receptors, while muscarine receptors may play an excitatory or suppresor role, depending both on the circuit involved and on the neurotransmitter concentration [88]. An increase in ACh synthesising and degrading enzymes in the epileptic cortex of patients undergoing anterior temporal lobectomy has been reported [89], but discussion persists as regards the exact significance of such changes.

The presence of down-regulation of the cholinergic receptor in the temporal lobe of epileptic patients, has also been described [39], which may be a homeostatic mechanism for decreasing excitatory input.

(b) Serotonine (5HT): This neurotransmitter has been linked with regulation of impulses related to hormonal secretion, sleeping, mood, eating, drinking, and sexual drive. It causes the activation of hyperpolarising currents capable of stopping spontaneous neuronal discharges [90]. It may also produce: (1) depolarisation by blocking sustained K^+ currents, as in muscarine receptor activation [91]; (2) blockade of pos-discharge hyperpolarisation (post-hyperpolarisation), as muscarine or beta-adrenergic receptors [92]; (3) blockade of slow IPSP obtained in CA1; and (4) blockade of fast IPSP and increased spontaneous and evoked IPSP in CA1 [93].

It is accepted that 5HT delays seizure generation, while a reduction in 5HT promotes their appearance [94]. The 5HT depletion with *p*-chlorophenylalanine decreases the discharge threshold in rats pre-treated with pentylenemetrazol [95], while administration of precursor 5HTP increases it [96]. Browning suggests that 5HT attenuates the tonic component of maximal electroshock seizures [97]. 5HT and ACh effects as neurotransmitters and neuromodulators are complex, assuming at a postsynaptic level al least five different effects for ACh and four for 5HT, as well as additional actions mediated at presynaptic sites. A preponderance of inhibitory actions for 5HT and excitatory ones for ACh is assumed, although receptor $5HT_2$ would play a major role in amygdaloid kindling acquisition.

(c) Noradrenaline (NA): A large body of work has attempted to correlate NA levels with epileptic seizure susceptibility. According to Brière et al., a reduction in $alpha_1$ receptors in tissues removed from temporal epileptic patients may be the background of a noradrenergic hypofunction, which in turn may reduce inhibition of epileptic foci [98]. Adrenaline, noradrenaline and homovanillic acid concentrations in CSF increase after a generalised tonic–clonic seizure [99], perhaps as an inhibitory compensatory reaction, or simply due to higher overall activity.

On studying amygdaloid kindling in rats injected with 6-hydroxydopamine in ascending noradrenergic fibres, Corcoran and Masson [100] found that animals with NA depletion, rapidly developed generalised seizures. In rats with audiogenic attacks, a reduction was found in $alpha_1$ and $alpha_2$ receptors concomitantly with seizure susceptibility [101]. In another rat model, there is an increase in receptors, $alpha_2$ agonists proving proconvulsant and $alpha_2$ antagonists, anti-convulsivant [102]. $Beta_2$ receptor activation may be anticonvulsivant, acting through cAMP.

In rats, locus coeruleus stimulation may delay amygdaloid kindling development [103]. It is assumed that NA acts as an inhibitory neurotransmitter within the brain, partly facilitating GABAergic transmission. In animals the higher monoamine level produced by monoamine oxidase inhibitors, protects them against seizure susceptibility.

(d) Dopamine (DA): DA applied by iontophoresis in hippocampal slices can provoke and/or prolong hyperpolarisation, which could be associated with an anti-epileptic action [104]. Quesney and Reader have suggested that photosensitive epilepsy could be related to a cortical deficit in DA transmission, a condition which could be counteracted by apomorphine administration [14]. Johnson et al. [105] indicate that cortical DA contents are reduced in photosensitive recessive autosomal homozygote chickens. DA administration by microiontophoresis on the frontoparietal or the occipital cortex in rats or cats usually decreases evoked discharges [106]. Opposite actions are attributable to D_1 and D_2 receptors. The former may be proconvulsant and the latter may be found to be anticonvulsant.

5.3. Second messengers

(a) Cyclic nucleotides (cN): cAMP elevation commonly develops subsequent to epileptic seizures, while cGMP elevation could be related to seizure triggering mechanisms [107].

Aminophylline inhibits cAMP accumulation in different cerebral regions and promotes a faster development of tonic attacks induced by pentylenemetrazol [107].

The reason of cAMP increment at seizure onset would be to avoid discharge propagation and may respond to raised adenylate cyclase mediated by adenosine and/or biogenic amines. In turn, depolarisation and Ca^{2+} entry into cells, may activate guanylate cyclase that regulates cGMP levels [107].

Hoffer et al. demonstrated that cGMP applied by iontophoresis excites and induces epilepsy in pyramidal neurones of grafted hippocampus [108]. In contrast, cAMP invariably diminishes spontaneous and evoked activity in guinea pig hippocampal slices in vitro [107].

Isobutylmethylxantine, which raises cGMP and reduces

cAMP, increases spontaneous and evoked potential duration [107].

cAMP may be the second messenger for biogenic amines and adenosine, and may prove to be responsible for the anticonvulsant action of these compounds. In contrast, cGMP could be responsible for the initiation and maintenance of epileptic discharges. Regulatory G proteins, binding to guanine nucleotides, are involved in kindling epileptogenesis. Iwasa et al., reported an increase in G_i 2 alpha mRNA on the side of stimulated cortex, 24 h after the last generalised seizure, persisting 3 or 4 weeks, in rats undergoing amygdaloid kindling [109].

(b) Phosphoinositides (PI): The phosphoinositides (PI) makes up another system which, as cyclic nucleotides, may act as the second messenger in cerebral neurones (Fig. 5).

According to Dubeau and co-workers, PI turnover is significantly reduced in active epileptic cortex vs. inactive cortex, as defined by electrocorticography, suggesting a PI cycle uncoupling that would prevent modulation of neuronal activity [110]. The main function of this system is to prevent excessive Ca^{2+} accumulation in endoplasmic reticulum. Cholinergically induced PI formation is reduced by epileptic activity, as also seen in the kindling model by noradrenergic and cholinergic deactivation [111]. Likewise, stimulation by excitatory aminoacids tends to reduce the efficiency of this cycle in the epileptic cortex [110]. The importance of this second messenger system is illustrated by the fact that it appears to be related al least with 17 different receptor subtypes. Among these, the muscarine receptors (M_1 and M_2), alpha $_1$ (adrenergic), H_1 (histaminergic), $5HT_2$ and AMPA stimulate the cycle, while D_2 receptors as well as adenylate cyclase prove to be inhibitory [112].

Epileptic seizures increase diacylglycerol (DAG) by IP2 [113]. DAG accumulation activates PKC, which phosphorylates alpha$_1$ receptors, inhibiting its response, thus disrupting the cycle. Bradichinine, a strong activator of the PI cycle, produces a biphasic response comprising transient initial hyperpolarisation followed by a depolarisation. Intracellular application of IP3 mimics the initial phase through a calcium-sensitive K^+ current, and may be subsequent to calcium mobilisation from its intracellular stores [114].

(c) Calcium (Ca^{2+}): Calcium provokes repetitive sustained discharges, through its entry to the neurones, by voltage-dependent currents and/or by NMDA receptor channel (see Fig. 2). There are various types of voltage-dependent Ca^{2+} channels: the presynaptic N channel, related to receptors and G proteins, the L channel in neuronal soma and the T channel, whose dysfunction was mentioned in relation with epileptogenic mechanisms of generalised absences, among other channels (P, Q, R).

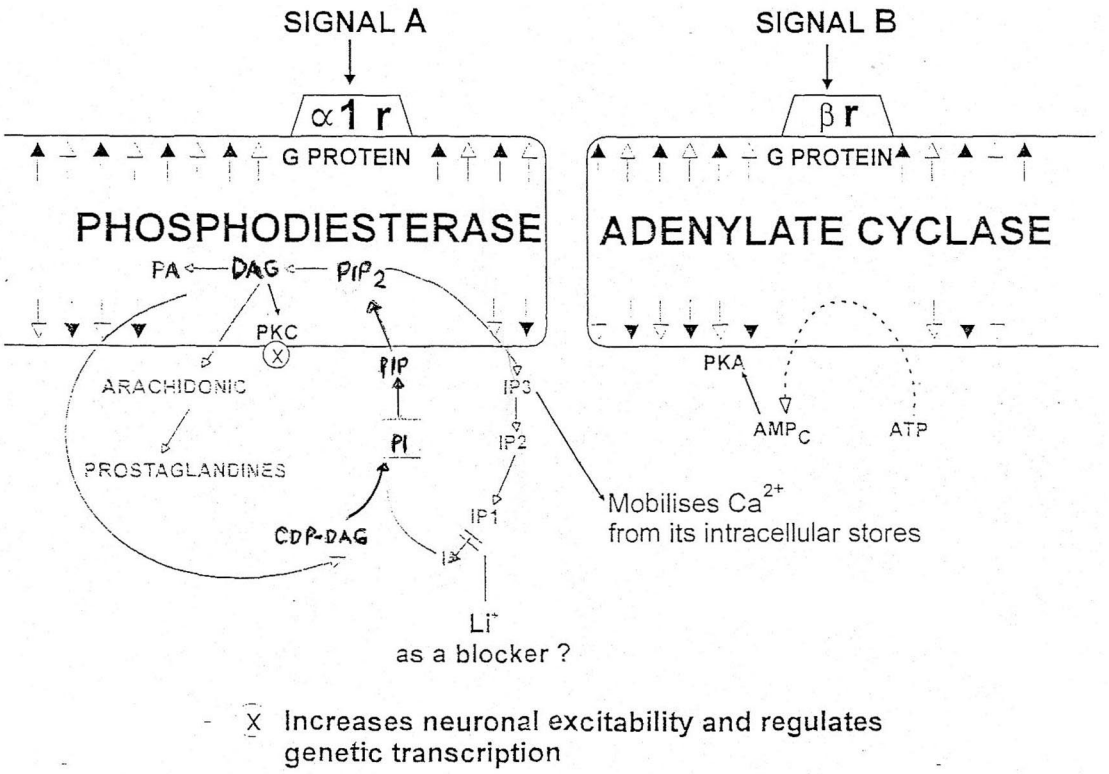

Fig. 5. Transmembrane signalling systems: phosphoinositide (PI) cycle. PI, phosphatidyl inositol; PIP, phosphatidyl inositol 4 P; PIP2, phosphatidyl inositol 4-5 diP; DAG, 1-2 diacylglycerol; PA, phosphatidic acid; PKC, proteinkinase C; IP 3, D-myo-inositol 1-4-5 triP; IP 2 D-myo-inositol 1-4 diP; IP 1, D-myo-inositol 1-P; I, D-myo-inositol; CDP–DAG citidine diphospho–diacyl-glycerol; PKA, proteinkinase A. Modified from Hirasawa K and Nishizuka Y. Phosphatidylinositol turnover in receptor mechanism and signal transduction. Ann Rev Pharmacol Toxicol 1985; 25: 147–170 [165].

Channel N is important for neurotransmitter release and is exclusive of neurones. Little is known about the L and T channels, that appear to be related to control of neuronal excitability. It should be recalled that, as in the case of cyclic nucleotides and PI, calcium is an intracellular transducer of signals coded by membrane receptors, that function with such receptors and with their configuration changes (second messengers). Ferrendelli et al. demonstrated the ability of phenobarbital, phenytoin and carbamazepine to block voltage-dependent Ca^{2+} entry to isolated nerve ending preparations, which is also valid for BDZ [115].

Calcium activation by NMDA receptors generates fast and long-lasting currents, leading in some instances to fast depolarisation and persistent neuronal changes [116].

The discovery of a binding calcium protein calmoduline (CaM) was the first step in understanding the mechanism postulating Ca^{2+} as a second messenger. CaM binds Ca^{2+} and is, in turn, attacked by CaMK2. Anti-convulsant drugs antagonise the system by activating the enzyme CaMK2, which inhibits CaM [117]. CaMK2 levels are impaired in hippocampal neurones in animals undergoing kindling [118]. PKC is another protein regulating neuronal excitability and influenced by Ca^{2+}. Calcium, by itself, is a powerful modulator of the PI system [114].

PKC is the convergence site of second messengers. The enzyme can interact with both pre-synaptic and post-synaptic membranes, regulating neurotransmission and genetic transcription. Multiple subtypes have been characterised. PKC activation inhibits several types of K^+ channels, thus increasing neuronal excitability, perhaps through phosphorylation of G_i, an inhibitory G protein, that depresses adenylate cyclase and therefore, decreases bi-directional modulation exerted by cAMP on neurotransmission. It also can reduce sodium currents by phosphorylation of the alpha subunit of the sodium channel protein itself [119].

In experimental epilepsy, paroxysmal discharges are accompanied by a reduction in Ca_e^{2+} level [120], which occurs in human epileptic tissues. Such Ca^{2+} mobilisation may operate as a common path for the execution of epileptic discharges.

5.4. Other neuromodulator substances

(a) Purines: During epileptic seizures, adenosine is released, acting as a powerful endogenous anti-convulsant [121]. In vitro studies have shown the anti-convulsant effect of adenosine in audiogenic attacks [122], seizures induced by maximal electroshock [107] and biochemically induced seizures [123]. Adenosine uptake inhibitors reduce severity and duration of seizures induced by amygdaloid kindling [124].

In hippocampus preparations, adenosine reduces the synaptic transmission, acting on pre- and post-synaptic receptors [125] and decreasing the release of excitatory neurotransmitters [126]. In slices, adenosine suppresses the synaptic transmission of CA3 to CA1 by Schaffer collaterals and the stimulation of dentate granular cells by the perforant tract [114], an effect perhaps mediated by A_1 receptors. It may be concluded that adenosine precludes the initiation and maintenance of epileptic discharges [127].

(b) Opioid peptides: A variety of experiments support the role of opioid peptides as proconvulsant or anticonvulsant. In favour of their epileptogenic actions: (1) beta-endorphin and leukoencephaline administered IV induced ictal EEG activity in the rat [128,129]; (2) mu and delta receptors are likewise pro-convulsant [130]; and (3) morphine causes generalised seizures [131] and can antagonise this effect [132]. Conversely: (1) naloxone shortens the postictal state that follows kindling or electroshock [133,134]; and (2) various kappa agonists show anti-convulsant activity against seizures induced by ECT o fluorotil, while dinorphine shares the same effect.

Lanerolle et al. reported increased immunoreactivity for dinorphine A in granular cells of human hippocampal epileptic foci [135]. However, the interpretation of this finding and of other neuropeptide alterations remains uncertain. Mayberg et al. documented a significant increase in mu receptor binding in epileptic temporal cortex [136]. The anti-convulsant effect of the peptide ACTH should be mentioned, but the explanation of its anti-epileptic action remains controversial.

The role of opioid systems in the suppresion of seizures in a variety of experimental models of epilepsy is better documented than is the role of opioid systems in the initiation of the attacks. Current evidence suggests that the anti-convulsant effects of peptide and non-peptide opioids can be mediated through mu, delta or kappa opiate receptors. Frost has suggested that non-mu opiate receptors are elevated in temporal lobe epilepsy [137].

6. Anti-epileptic therapy

6.1. Drugs in use

Better known anticonvulsant drugs generally act: (1) by increasing GABAergic action mechanisms, that are predominantly inhibitory; (2) by depressing excitatory glutamate neurotransmission; (3) by depressing voltage-dependent Ca^{2+} mobilising mechanisms; or (4) by depressing Na^+ conductance, which is also voltage-dependent.

According to Macdonald, the Na^+ channel blockade is an important action in phenytoin, CBZ and valproate, less important in phenobarbital and clonazepam and null in ethosuximide. The blockade of T calcium channels is significant for valproate and ethosuximide, doubtful for clonazepam and CBZ, and null for phenobarbital and phenytoin. Finally, the GABA channel activation is important in the clonazepam action, less but still significant

for phenobarbital, debatable in the case of valproate and null for phenytoin, CBZ and ethosuximide [138].

Drugs acting against Na^+ channels provide the treatment of choice for generalised and partial tonic–clonic seizures; those acting at the T calcium channel level afford satisfactory therapy for generalised absences, and those acting at GABA receptors are useful to treat myoclonic seizures.

This brief discussion has not reviewed the action of more recently available drugs, such as oxcarbazepine, vigabatrin, lamotrigine, phelbamate, gabapentin, topiramate and zonisamide, among others. Their use may benefit patients otherwise categorised as refractory. However, their mechanisms of action remain controversial.

6.2. New therapeutical approaches

(a) Genetic studies: There is a bulk of recent research about genetic linkage studies in familial epilepsies with special reference to the following clinical forms: autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), autosomal dominant lateral temporal lobe epilepsy (ADLTE), familial partial epilepsy with variable foci (FPVEF), benign familial neonatal convulsions (BFNC), familial febrile convulsions (FFC), benign epilepsy of childhood with centrotemporal spikes (BECTS) and juvenile myoclonic epilepsy (JME).

ADNFLE: All families reported show that there is an autosomal dominant inheritance with incomplete penetrance. Affected individuals develop predominantly nocturnal seizures with frontal lobe semiology. Phillips et al. [139] pointed out that the gene for ADNFLE maps to chromosome 20q13.2–q13.3 and found a second locus at 15q24 [140].

A missense mutation in the gene for the alpha-4 subunit (CHRNA4) of the neuronal nicotinergic acetylcholine receptor (nAChR) was described in an Australian family [139] and another mutation in the same gene in a Norwegian family [141]. This gene maps in the same region of 20q. The missense mutation replaces serine with phenylalanine at codon 248, in the second transmembrane domain. The gene is expresssed in all layers of the frontal cortex [142].

ADLTE: This syndrome is inherited in an autosomal dominant mode, with a penetrance of about 80%. It is characterized by rare partial seizures, usually secondary generalized, arising mostly during sleep. The partial component, the interictal EEG abnormalities and the results of SPECT studies suggest a lateral temporal lobe origin. The genetical analysis found linkage to chromosome 10q [143].

FPEVF: This group differs from the other inherited partial epilepsies because the clinical features of the seizures and interictal EEG foci differed among family members and include frontal, temporal, occipital and centroparietal seizures. A suggesting of linkage was found on chromosome 2q [144].

BFNC: It is a rare autosomal dominant form of epilepsy. Genetic heterogeneity is reported with a first suggested locus on chromosome 20q and a second one on chromosome 8q [145].

FFC: Wallace et al. [146] reported linkage of a putative autosomal dominant febrile convulsion gene to chromosome 8q13–21, and Johnson et al. [147] reported another autosomal dominant febrile convulsion gene on chromosome 19p13.3 between loci D19S591 and 19S395.

BECTS: Neubauer et al. [148] found evidence for linkage of BECTS to a region on chromosome 15q14. This disorder is genetically heterogeneous.

MJE: Weissbecker et al. [149] reported confirmation of a JME locus to the HLA region of chromosome 6p. More recently, chromosomal regions harbouring genes for nAChR subunits were tested for linkage to the JME trait in 34 pedigrees. Significant evidence for linkage with heterogeneity was found to polimorphic loci encompassing the region in which the gene encoding the alpha 7 subunit of nAChR maps to chromosome 15q14 [150].

(b) Regulatory events at the genetic level: Second messenger systems interact with proteins controlling genetic transcription. Thus, a ''third messenger'' has been postulated acting in the cell nucleus in order to control genetic expression. These are proteins translated from protooncogenes. Phorbol esters, by activating PKC, induce protooncogene transcription as Fos and Jun. These genes exert regulatory functions interacting in adaptative responses to environmental stimuli or biologic stress, e.g., epileptic seizures. Within this regulation, it is possible to include neuronal metabolism, as well as neurotransmitter synthesis and degradation. A second cascade of regulatory events may involve not only the number of receptors, but also their subtypes as well as the coupling to the receptor-G protein second messenger.

Thus, mRNA of various genes with early inmediate response, initially identified in fibroblasts, are rapidly increased within the brain after convulsive seizures [151] (c-fos, c-jun, jun-b y zif/268). PKC could raise mRNA levels for these transcriptional factors [152]. This mRNA increase occurs mainly in granule cells of the dentate gyrus [114].

According to Sprengel et al., the genetic mechanism of RNA editing appears to be involved in the control of rapid glutamate-elicited postsynaptic Ca^{2+} transients. Analysis of the Glu-R-B gene subunits transcripted in mice which were genetically engineered to harbor one allele incapacitated for editing, revealed that 30% of the GluR-BmRNA occurred in its unedited form, which was predictive of an increase in the Ca^{2+} permeability of AMPA receptors, and may lead the mice to have seizures [153].

New pharmacological designs must consider ''second and third messenger'' processes, in order to control epileptic seizure physiopathology.

(c) The control of neurotransmitters, their receptors an ionic flux: In generalised absences, pharmacological approaches attempt to achieve: (1) NMDA receptor inactiva-

tion; (2) GABAB receptor inactivation; and (3) inactivation of low threshold T calcium currents.

In focal epilepsy, with or without secondary generalisation, and in primary generalised epilepsy, the pharmacological approaches attempt to achieve: (1) blockade of Na^+ conductance that promotes repetitive voltage-dependent discharges; (2) blockade of voltage-dependent Ca^{2+} currents; (3) inactivation of NMDA receptors and other types of the GluR superfamily; (4) an increase in K^+ conductance; (5) an increase in Cl^- entry; (6) activation of GABAergic receptors; (7) interactions with cyclic nucleotide and PI systems (second messengers); and (8) Na^+, K^+–ATPase stimulation.

(d) Surgical control of epileptic discharges: Surgical procedures are in vogue for treatment of partial epilepsies and temporal lobe epilepsies (e.g., focus surgery, amygdalohippocampectomy, anterior temporal lobectomy or total lobe resection), unilateral hemispherical lesions e.g., Rasmussen syndrome or hemimegalencephaly (hemispherectomy or hemispherotomy) and uncontrollable Lennox syndrome (corpus callosum section) [154]. Subpial transections are performed when other techniques are not recommended in order to spare the eloquent areas (e.g., Landau-Kleffner syndrome). These procedures, as well as vagal o thalamic stimulation, have succeeded where medical treatment has failed.

A global survey on epilepsy surgery which covers a period of ten years, reported by the International League Against Epilepsy (ILAE) provided the following data: In adults: (1) Anterior temporal lobectomies were performed in 71% of the surgical patients and there was a reduction or suppresion of seizures in almost 90% of them; (2) selective amygdalo hippocampectomies were done in 10% of the intervened patients with marked post-operative improvements in almost 80% of them; (3) frontal lobe resections in another 10% were less effective to render the patients seizure-free; and (4) parietal and occipital resections were done infrequently and their results were a little better than the frontal lobe resections but no so effective as temporal lobe resections. In children: (1) anterior or complete callosotomies were performed, leading to a marked reduction of seizures, although the children were not completely seizure-free in more than 90% of the cases; and (2) hemispherectomies were performed in almost 24% of the patients and their results were much better than the callosotomies, which were performed in order to render the children seizure-free [155].

7. Conclusions

The basic mechanisms of the epilepsies were considered separately in: (a) convulsive primary generalised epilepsy; (b) non-convulsive primary generalised epilepsy; and (c) partial epilepsies.

(a) The discharge synchronisation mechanisms generating this seizure type are poorly understood, but correlate with epileptogenic circuits in the brain stem (tonic phase?) and/or the limbic system (clonic phase?).

(b) The model of SW complex at 3–6 cycles/s, generated in the cat after parenteral injection of penicillin, shows an alternate sequence of depolarisation–hyperpolarisation, in which the spike (S) corresponds to an EPSP and the slow wave (W) to an IPSP [156]. There are cycles in the thalamocortical complexes that include: (1) NMDA activation; (2) activation of GABA receptors; (3) activation of T calcium channels; and (4) restarting of the cycle. Perhaps these concepts may be extrapolated to generalised absences suffered by human epileptic patients.

(c) Partial transition to seizures is a dynamic intracellular and network event which closely correlates with the paroxysmal depolarisation shifts (PDS), considered a giant EPSP triggered by increased excitatory input in neurones that undergo one or more abnormalities. These are as follows: (1) proliferation of recurrent axonal collaterals; (2) excess of Ca^{2+} conductance; (3) GluR hyperactivity, in one or various subtypes (NMDA, Ka, AMPA, mGluR, among others); (4) impaired $GABA_A$ receptor activity; (5) alterations in the extracellular compartment with K^+ accumulation or Ca^{2+} and/or Mg^{2+} depletion; (6) functional deficits in ATPases involved with cationic transport against chemical gradients; (7) deficient aerobic metabolism of the neurone itself; (8) sudden changes in pH and/or osmolality (alkalosis and hyponatremia favour the appearance of seizures); and/or (9) genetic abnormalities, etc. An example of GluR hyperactivity is the region CA3 of the hippocampus, which has the highest density of Ka receptors [157] and is a pacemaker of interictal spikes in chronic epileptic foci. It has been claimed that circulating autoantibodies react with GluR3 in Rasmussen encephalitis [158].

Regarding the influence of neurotransmitters and neuromodulators, other than glutamate and GABA, in relation to neuronal excitability, let us speculate as follows: (a) glycine is mainly an excitatory agent and taurine is an inhibitory agent; (b) Ach is predominantly excitatory; 5HT is predominantly inhibitory; (c) the adrenergic receptors are $alpha_2$ excitatory; $alpha_1$ and β inhibitory; (d) the dopaminergic receptors D_1 agonists are pro-convulsant and the D_2 agonists are anti-convulsant; (e) adenosine with inhibitory effects as cAMP, while cGMP has opposite effects; (f) opioid peptides with contrasting effects: β-endorphin and leukoencephaline excitatory, naloxone and dinorphine inhibitory, while morphine presents dual effects; and (g) Zn^{2+} exerts dual effects.

Besides regulating ionic channels by the action of voltage and by neurotransmitter-receptor coupling, a transmembrane signalling system (Fig. 5) helps the neurones to regulate their excitability by binding the receptor inside the membrane to G protein which in turn binds cyclic nucleotides and PI. These substances and calcium (Ca^{2+}) make

up three systems of second messengers that have been thoroughly studied.

Several receptors operate with these systems, including $GABA_B$ and mGluR. $GABA_B$ receptor exerts antagonic effects; it inhibits presynaptic release of GABA, thus proving excitatory, but it also inhibits presynaptic release of glutamate, thus proving inhibitory. Besides, it also prolongs postsynaptic hyperpolarisation by K^+ efflux and the appearance of Ca^{2+}-dependent spikes in experimental models of absence seizures. According to Mody et al. new evidence demonstrates that mGluR are involved in the regulation of cortical and hippocampal excitability, long time potentiation and epileptogenesis [159].

According to Vornov and Coyle [157] ''multiple neurotransmitters may modulate the same mechanism of second messengers, but an isolated neurotransmitter may activate different second messengers''. Second messenger systems converge in PKC, membrane enzyme that regulates cell excitability but also promotes transcriptional changes which can operate in the regulation of neuronal metabolism, neurotransmitter synthesis and transport, receptor density and their eventual coupling to G protein. A ''third messenger system'', is currently envisaged, having mRNA as subject [160], whose level increases after electrical stimulation or convulsive seizure.

Factors such as morphological changes, electrophysiological abnormal responses, failure in neurotransmitter functioning or in metabotropic receptors coupled with second messengers systems or genetic mutations could be combined [161] in relation with a genetic charge favouring epileptogenesis [153,162] and acquired lesion [16,26] or a combination of both, decreasing the discharge threshold which in turn will drive Na^+ and Ca^{2+} into the nerve cells, a common path for the execution of epileptic discharges.

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