Alternating and Postictal Psychoses: Review and a Unifying Hypothesis

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A comparison of the clinical and pathophysiological features of postictal psychosis and brief interictal or alternating psychosis was undertaken to examine if the underlying mechanisms are distinct in these 2 conditions. A selective review of the published literature in English on epilepsy and brief psychosis was carried out. The literature indicates that even though brief postictal and alternating psychoses are considered to be separate syndromes, they have a number of similarities. It can be argued that the underlying pathomechanisms are common, with the brain’s inhibitory processes in response to seizures playing a key role in the development of the psychosis. These homeostatic mechanisms manifest as electrophysiological, cerebral blood flow, and neurotransmitter and receptor changes. Both syndromes are likely to be associated with prolonged inhibition in limbic circuits, with further seizures modifying the psychosis depending upon whether it is associated with disinhibition or hypersynchrony involving enhanced inhibition. The neurotransmitter with a key role is GABA, although ionic currents, catecholamines, opiates, adenosine, glutamate, and nitric oxide play a role. Brief postictal and alternating psychoses provide an opportunity to understand the complex relationships between epilepsy and schizophrenia-like brief psychotic episodes, and this understanding can assist in their management.

Key words: alternating psychosis/brief psychosis/epilepsy/inhibition/interictal psychosis/postictal psychosis/schizophrenia

Introduction

The association between epilepsy and schizophrenia-like psychosis (SLP) has attracted the interest of psychiatrists for over a hundred years. While much of this interest has concerned the chronic psychoses, the presence of brief psychoses in epileptic patients has proven to be a productive area for speculation on the mechanisms involved. The categorization of these brief psychotic syndromes has traditionally been according to their temporal relationship to the seizures, as ictal, postictal, and interictal. A contrasting picture has usually been presented for brief interictal psychosis, usually referred to as alternating psychosis, and postictal psychosis. Definitions of these syndromes used in this review are presented in table 1. This contrast has generally been the basis for the seemingly inconsistent hypotheses of “affinity” and “antagonism” between the 2 disorders.

The 2 themes that have dominated psychiatric thought on the relationship between brief SLP and epilepsy are (1) they occur together more often than by chance (affinity), as evidenced by the occurrence of postictal psychosis following epileptic seizures and (2) they are antagonistic to each other, as indicated by the infrequency of seizures during alternating psychosis, and vice versa. The evidence suggests that both associations are possible, at least in a modified form, and the argument presented in this article attempts to resolve this paradox. It is suggested that the same pathomechanisms underlie both affinity as well as antagonism between brief SLP and epilepsy.

Methods

Articles were identified by searches of MEDLINE between 1966 and 2005 and references from relevant articles. The search terms “epilepsy,” “schizophrenia,” “schizophrenia-like psychosis,” “epileptic psychosis,” “interictal psychosis,” “postictal psychosis,” “alternating psychosis,” “cortical inhibition,” “cortical excitation,” and “neural networks” were used. Information was selectively reviewed from cross-references.

Postictal Psychosis

Clinical Features. The behavioral disturbances that may follow a seizure, or a bout of seizures, have received increased attention in the last 2 decades, and postictal psychosis may be regarded as a special instance of such a disturbance. Postictal psychosis usually follows seizure clusters or a recent exacerbation in seizure frequency that may be related to withdrawal of antiepileptic drugs, often as a part of the video electroencephalographic
Psychosis is a psychiatric disorder characterized by delusions, hallucinations, disorganized speech or thought, and/or grossly disorganized or catatonic behavior.

**Brief psychosis** is psychosis that lasts more than a day but generally less than 1 month. Some epilepsy-related brief psychoses may last up to 2–3 months. Psychoses lasting more than 6 months are chronic, and those lasting more than 3 months are tending to chronicity.

**Postictal psychosis** is psychosis that follows immediately after 1 or generally multiple seizures, but certainly within 1 week of the last seizure.

**Interictal psychosis** is psychosis that develops when the patient with epilepsy has not had a seizure for more than 1 week or is unrelated to the any recent increase in seizure activity. Brief interictal psychosis is sometimes considered broader than alternating psychosis, but the 2 terms are used synonymously in this review.

**Alternating psychosis** is psychosis that occurs when seizures have ceased or reduced significantly in frequency, often after change in dose or introduction of new antiepileptic drug.

**Forced normalization** is the occurrence of episodic behavioral disturbance in an epilepsy patient associated with a change in electroencephalogram (EEG) to relative normality compared with previous and subsequent EEG.

Postictal psychoses are common in epilepsy-monitoring facilities assessing patients with treatment-resistant complex partial epilepsy; 6.4% and 10% patients, respectively, developed this syndrome in 2 studies. If the psychosis develops gradually and in parallel with increasing seizure frequency, it may be referred to as perictal rather than postictal, but there is no reason to believe that this distinction is meaningful clinically or for its pathophysiology. A confounding factor in the evaluation of postictal psychosis in video EEG monitoring facilities is that these patients have often had a withdrawal of their antiepileptic drugs, and it has been suggested that this itself may result in psychopathology, even though psychosis is not usual in the absence of seizures.

Between the last seizure and the psychosis, there is usually a nonpsychotic period, which ranges from a few hours to a few days. It was 12–72 hours in the Kanner et al study and up to 1 week according to Lugsdail and Toone. Some clouding of consciousness is often present in this period, and it may extend to the initial period of psychosis or even the whole episode. The psychotic symptoms are pleomorphic (persecutory, grandiose, referential, somatic, and religious delusions, catatonia, hallucinations, etc.), and affective symptoms (manic or depressive) are often prominent. First-rank symptoms of Schneider can occur but are rare. Postictal psychoses resolve within a few days, with the mean duration in the study by Kanner et al being about 70 hours (range = 24–144), and all resolving within 1 month in the study by Savard et al. A few reports of longer duration of postictal psychosis have been published, but at which point the diagnosis should be changed to interictal psychosis is debatable. The proposal of the Subcommission on Classification of the International League Against Epilepsy Commission on Epilepsy and Psychobiology was that postictal psychosis lasting more than a month may require reconsideration of diagnosis and a change to interictal psychosis. Some authors have used 2 months as the longest duration of a postictal psychosis in their series, with the rare case lasting over 3 months. For the purpose of our discussion brief psychosis is less than 1 month, with duration of up to 3 months being uncommon. The resolution of postictal psychosis is generally spontaneous, and a further seizure may exacerbate the psychosis. The brief psychosis may recur, at a frequency of 2–3 episodes per year in 2 studies, and in some patients—15% in 1 study—these episodes may become chronic, ie, last over 6 months.

**Predisposing Factors.** The predisposing factors are not well understood. A question that has been frequently posed in the published literature is whether postictal psychosis is associated with a specific type of epilepsy, ie, that with a temporal focus, and whether independent bilateral disturbance is more commonly represented than unilateral abnormality. The majority of reported patients suffer from partial complex seizures that are secondarily generalized. Epilepsy has often been present for more than 10 years before the onset of psychosis. EEG abnormalities persist in the majority during the psychosis. In 1 case report, the patient with postictal psychosis demonstrated frequent bitemporal independent epileptiform discharges on depth recording that were maximal in the mesial limbic regions. On the other hand, another report presented 2 patients with postictal psychosis who had repeated EEGs during the psychosis which showed that their habitual focal epileptiform abnormalities were absent, suggestive of "forced normalization" (see alternating psychosis below). While Kanner et al found no specific predisposing factors that differentiated their psychotic group from a comparable nonschizophrenic epilepsy group, Savard et al were impressed with a high rate of ictal fear, bilateral independent discharges, and gross structural lesions (6 out of 9 patients), including the presence of alien tissue tumors. Kanemoto et al also noted frequent psychic auras, and Umbricht et al noted frequent bitemporal foci in their subjects. In contrast with the other literature, Devinsky et al found similar rates of postictal psychosis in partial and primary

### Table 1. Glossary of Terms

<table>
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<td>Psychosis</td>
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generalized epilepsies, although they did note bilateral independent interictal discharges in those with partial seizures. Postictal psychosis has also been associated with frontal lobe epilepsy, accounting for 3 out of 11 cases in 1 series.\textsuperscript{17} Five of the 14 patients studied by Logan-dail and Toone\textsuperscript{2} had abnormalities on brain computerized tomography. In the magnetic resonance imaging study of Kanemoto et al,\textsuperscript{8} postictal psychosis was most likely to occur in patients with resistant temporal lobe epilepsy stemming from mesial temporal sclerosis, especially on the left side. These patients with left-side mesial temporal sclerosis were also likely to have atrophy of the temporal neocortex. Mathern et al\textsuperscript{18} reported 2 patients, 1 of whom had unilateral postictal discharges, but on autopsy was found to have bilateral hippocampal neuronal loss even though the pathology was asymmetric. Some authors also report low intelligence as a predisposing factor for postictal psychosis,\textsuperscript{10,14} suggesting the presence of more widespread brain abnormality. In summary, the weight of the evidence supports a stronger association with complex partial epilepsy, especially of temporal lobe origin, in which there is bilateral pathology, although this relationship is not exclusive.

**Pathogenetic Mechanisms.** The pathogenetic mechanisms are poorly understood, even though the proximity of these psychoses to seizures and their frequent occurrence in epilepsy centers while patients are being monitored makes them ideal candidates for the exploration of underlying mechanisms. The finding of chronic frequent subictal discharges suggests that ictal activity in the temporal lobe may be directly related to this kind of psychosis. Changes in monoamines, particularly postsynaptic dopamine receptor sensitivity, have been suggested as the mediating mechanism.\textsuperscript{16} Some support for the dopamine mechanism came from a single-photon emission computed tomography (SPECT) study using $[\text{123I}]$iodobenzamide that demonstrated low levels of striatal dopamine D2 receptors in patients with perictal psychosis.\textsuperscript{19} Low folic acid levels have been suggested to have a role,\textsuperscript{20} but firm evidence is lacking. The significance of a report of hyponatremia in these patients is also unknown.\textsuperscript{7}

More importantly, it would be fruitful to examine postictal psychosis in the context of the homeostatic mechanisms that are brought about in the brain to control seizures. These have been divided into electrophysiological mechanisms, cerebral blood flow (CBF) changes, and neurotransmitter and receptor changes.\textsuperscript{4} Postictal psychosis in this context has been conceptualized as a phenomenon akin to Todd’s paralysis, indicating the postictal inactivation of cortical regions involved in the ictal event, which usually include bilateral medial temporal structures.\textsuperscript{21} A simple electrophysiological explanation that the postictal state is because of "neuronal exhaustion" is not supported by experimental evidence.\textsuperscript{22} A second possible explanation is that of neurotransmitter depletion because of repeated firing, evidence for which is again lacking.\textsuperscript{4} An important aspect of seizure termination is active inhibition, in which a number of mechanisms are involved. A hierarchy of inhibition is produced by fast inhibitory postsynaptic potential mediated by GABA\textsubscript{A} receptors, a later hyperpolarizing potential mediated by GABA\textsubscript{B} receptors,\textsuperscript{4} and after hyperpolarization produced by calcium-activated potassium currents. While these inhibitory mechanisms are brief, prolonged inhibition of neuronal activity can be produced by hyperpolarizing pumps, whose object is to restore the steady-state ionic balance after neuronal activity. Seizures lead to increased extracellular K\textsuperscript{+}, and levels higher than 20–30 mM produce a spreading depression and cessation of neuronal activity, which may account for the postictal state.\textsuperscript{23} Seizures also cause lactic acidosis and low pH, and the H\textsuperscript{+} ions compete with other ions at the ion channel associated with N-methyl-D-aspartate receptors.

Seizures cause a release of a number of other neurotransmitters which include acetylcholine, catecholamines, serotonin, opiates, adenosine, and nitric oxide (NO). Endogenous opiates appear to play a special role in the postictal state.\textsuperscript{24} Naloxone is noted to reverse postseizure catalepsy in rats subjected to electroshock,\textsuperscript{25} and to increase the rate of interictal spiking in humans.\textsuperscript{26} but the evidence is not entirely consistent.\textsuperscript{27,28} Adenosine and NO are neuromodulators that may act as endogenous antiseizure agents. It is possible that the repeated release of neurotransmitters during seizure activity leads to postsynaptic receptor changes, as has been demonstrated for benzodiazepine receptors,\textsuperscript{29} and this may be relevant to postictal psychosis.

Seizures lead to substantial changes in CBF, which may have a relevance to postictal psychosis, although the precise mechanism is unknown. Ipsilateral to the temporal lobe seizure, there is a rise of CBF to twice the baseline at about 5 minutes, but by 1 hour, the CBF is below baseline. A SPECT study of 4 patients with temporal lobe epilepsy and postictal psychosis demonstrated mesial frontal hyperperfusion during the psychosis.\textsuperscript{30} Another report from the same group suggested hyperperfusion in both temporal and mesial frontal regions and left lateral frontal region.\textsuperscript{31} Fong et al\textsuperscript{32} reported a marked right temporal and left basal ganglia hyperperfusion in postictal psychosis in 2 patients. It is worth considering that the CBF response in patients with postictal psychosis is aberrant, and this may in some way be related to the psychosis. A difficulty in the interpretation of these findings is created by the fact that seizures may uncouple cerebral perfusion from metabolic activity by altering cerebrovascular autoregulation, as has been demonstrated for postictal hemiparesis.\textsuperscript{33} Therefore, hyperperfusion in postictal psychosis cannot necessarily be construed as hypermetabolism, although regional variations after correction for global change in perfusion cannot be dismissed.
Moreover, increased perfusion is equally likely to be related to increased inhibition or excitation, and the primary disturbance may be local or remote. Metabolic studies, combined with neurotransmitter labels using positron emission tomography (PET), are more likely to help sort out these possibilities.

In summary, understanding the mechanisms of the postictal state can provide useful insights into the pathogenesis of postictal psychosis, which may further inform the pathogenesis of psychosis in general. Manipulation of some of these mechanisms with drugs may produce valuable strategies to prevent psychosis and other psychiatric and cognitive disturbances of the postictal state.

**Brief Interictal Psychosis or Alternating Psychosis**

**Clinical Features.** Brief psychotic episodes can also develop when seizures are infrequent or fully controlled. These psychoses last from days to weeks, they are often self-limiting, and their separation from postictal psychoses may be difficult. The phenomenology is characterized by paranoid delusions and auditory hallucinations, but multiple other features, including affective symptoms, may occur. The symptomatology is therefore very similar to postictal psychosis, although clouding of consciousness is more commonly reported in the early stages of postictal psychosis. Tellenbach pointed out the presence of premonitory symptoms such as insomnia, anxiety, feelings of oppression, and withdrawal as heralding the psychosis, and Wolf suggested that treatment with anxiolytic drugs at this stage may prevent development of the psychosis.

The relationship of alternating psychosis to seizures and EEG abnormality has received much attention. Interictal implies that these psychoses occur in-between seizures rather than in close proximity with them. The favored description is of a brief psychosis alternating with periods of increased seizure activity such that the seizures and psychosis appear antagonistic. Unlike postictal psychosis, this psychosis can be ameliorated by the occurrence of 1 or more seizures. Alternating psychoses are uncommon, and Schmitz and Wolf reported only 3 cases of alternating psychosis in 697 epilepsy patients.

**Pathogenetic Mechanisms and the Concept of Forced Normalization.** The concept of forced normalization (forcierte Normalisierung) was introduced by Landolt for the puzzling observation that the EEGs of epilepsy patients often looked less pathological when their behavior had deteriorated. This phenomenon, also called “paradoxical” or “spurious” normalization, has been documented by a number of authors with the additional observations that (1) the EEG may become more, rather than entirely, normal; (2) the manifestation is not always of psychosis, and other disturbances, such as affective symptoms, an anxiety or dissociative state, and behavioral disturbance, may be present; and (3) not all brief interictal psychoses manifest this phenomenon. Ramani and Gumnit observed forced normalization in only 1 of 9 epilepsy patients who became psychotic while being treated in hospital for their epilepsy. Forced normalization is not exclusive to alternating psychosis and has been occasionally described with postictal psychosis, suggesting a complex relationship between seizure activity and psychosis. Interestingly, Landolt described this phenomenon in relation to childhood absence seizures, and some authors have suggested that it is more likely to occur with primary generalized epilepsy.

The neurophysiological basis of forced normalization is not fully understood. One suggestion is that it reflects ongoing subcortical or mesial temporal epileptic activity with enhanced cortical inhibition. This has been referred to as an “inhibitory surround” in response to on-going seizures. This explanation argues that ongoing epileptic activity is necessary for the maintenance of inhibition as well as the development of psychosis. While the role of inhibition in response to seizure activity, as a homeostatic mechanism against ictal activity, is an appealing hypothesis to explain forced normalization, it is possible that it does not represent ongoing epileptiform activity but is a prolonged response to preceding epileptiform activity. It is known that occasionally patients may develop prolonged unconsciousness after a seizure or a series of seizures, especially in elderly or ill patients. Todd’s paralysis has been reported to last for up to 36 hours. Therefore, it is possible that inhibition after a seizure or a series of seizures may be fairly prolonged. It is also important to understand the sources of the EEG abnormalities. The scalp EEG is a reflection of groups or populations of neurons that fire in a synchronous manner. The pyramidal neurons of layers IV and V of the cortex are considered to be responsible for scalp EEG activity, but both radially and tangentially oriented currents may make a contribution to the EEG signal. Sources of EEG abnormality in epilepsy may lie close to the surface or be deep in the brain, and the latter are less likely to be picked up on the scalp. The inhibitory events described above are most likely to occur in close proximity to the seizure focus, thereby reducing the electrical current generated from the focus. This may be the basis for the normalization. Even a reduction in the frequency of epileptic events will produce a relative normalization.

Patients with alternating psychosis have been reported to suffer from either complex partial epilepsy or primary generalized epilepsy. While a temporal lobe onset is common, Wolf argued that all these patients also had generalized seizures. Kanemoto et al reported the frequent presence of mesial temporal sclerosis in patients with interictal psychosis, who were also likely to have experienced the onset of epilepsy before the age of 10 years. Ictal fear and autonomic aura have been more commonly reported in patients who develop alternating psychosis, but this is not invariably supported.
Special relationships between brief interictal psychosis and 2 drug classes should be highlighted.

Psychosis and Antiepileptic Drugs. Antiepileptic drugs have been reported to precipitate psychosis, although the published literature is confounded by the inclusion of affective and confusional psychoses or delirium in this category. The facts that the control of seizures may induce psychosis in a few patients and that neuroleptic drugs, which are proconvulsant, are useful in treating such a psychosis are consistent with the concept of alternating psychosis and forced normalization. Gibbs first drew attention to this in relation to phenacetylurea, and Landolt implicated the succinimides. Wolf further emphasized the relationship with ethosuximide and reported that valproate did not produce the same result. Others have reported psychosis in association with clobazam, phenytoin, carbamazepine, barbiturates, and benzodiazepines. Psychosis related to vigabatrin, a new antiepileptic drug that is an irreversible inhibitor of GABA aminotransferase, has excited much interest, but the psychoses reported are multiformal, and only 4 out of 14 cases in 1 report met the description of alternating psychosis. Topiramate has been associated with forced normalization and psychosis, especially in patients who were concurrently on vigabatrin. Forced normalization has also been reported with levetiracetam but is rare with lamotrigine and gabapentin. Another group of drugs that are potent antiepileptic drugs in animal models is the N-methyl-D-aspartate (NMDA) antagonists, eg, MK-801, ketamine, and phencyclidine, and these drugs also have a propensity to cause psychosis.

Antipsychotic Drugs and Epilepsy. All antipsychotic drugs have the propensity to cause paroxysmal EEG abnormalities and induce seizures, and the effect is related to drug type and dose. The phenothiazines have been the most widely studied for their seizure propensity. They have been reported in 9% of patients who received high-dose phenothiazines (≥1000 mg/day chlorpromazine or its equivalent), 0.7% of patients who received moderate doses, and 0.3% of patients who received low doses (≥200 mg/day chlorpromazine or its equivalent). From the published literature, the relative risk of seizures with the various typical antipsychotics is difficult to establish, but the risk is considered to be lower with haloperidol, trifluoperazine, pimozide, and molindone. The newer antipsychotics are not free of this effect, and in fact, clozapine is the most epileptogenic of the antipsychotics, with myoclonus or frank seizures reported in 0.3%–5% of patients treated with therapeutic doses. Interestingly, clozapine is also regarded as the most effective antipsychotic drug currently available. In the premarketing studies of clozapine, the overall incidence of seizures was 2.9%, being 4.4% with high doses (600–900 mg/day), 2.7% with moderate doses (300–599 mg/day), and 1.0% with low doses (299 mg/day or less). A subsequent postmarketing surveillance study of 5629 patients reported a rate of 1.3%, which was again dose dependent. The rates are lower with the other atypical drugs, with a seizures rate of 0.9% reported for olanzapine and quetiapine (cf. 0.5% for placebo) and 0.3% for risperidone.

Are Postictal and Brief Interictal Psychoses Distinct? The Excitation-Inhibition Imbalance Hypothesis of Psychosis

The above descriptions suggest that the classical distinction between postictal psychosis and alternating psychosis, with the former being closely related to a flurry of seizures while the latter occurring during a period when seizures are relatively quiescent, may be arbitrary and stemming from clinical convenience. Phenomenologically, the 2 syndromes are very similar, although the postictal psychosis is likely to be briefer in duration. The interval between the last seizure and the occurrence of postictal psychosis can vary considerably, and the criterion of up to 1 week is an arbitrary one. The predisposing factors and neurophysiological correlates for the 2 syndromes appear to be similar as well. While forced normalization is usually associated with alternating psychosis, it is not invariably in this syndrome and can occur in postictal psychosis. Patients who experience both postictal psychosis and alternating psychosis have been said to have "bimodal psychosis," and in these patients either syndrome may appear first.

Neurophysiological Mechanisms. An examination of possible neurophysiological factors underlying the psychosis suggests that alternating psychosis and postictal psychosis share common mechanisms. Epilepsy is a state of imbalance between excitation and inhibition that predisposes a local or widespread brain region, involving 1 or more neuronal networks, to become hyperexcitable and hypersynchronous. The focus in brief epilepsy-related psychosis should be on inhibitory mechanisms in the brain that are closely related to the epileptic activity. The inhibitory processes mentioned above not only bring about the postictal state but are also necessary for maintaining the interictal state. The consequent imbalance of excitation and inhibition, when it affects certain neuronal networks, is likely to produce psychotic symptoms. The usual association of alternating psychosis and postictal psychosis with limbic epilepsy is consistent with this hypothesis, as dysfunction in these regions is widely hypothesized as the basis for psychosis. As the development of seizures may be due to either disinhibition or hypersynchrony involving enhanced inhibition, the occurrence of a seizure during psychosis may have different pathogenetic mechanisms and may indicate either disinhibition or increased inhibition. The effect on psychosis of a seizure could thereby be either an amelioration of symptoms or their exacerbation. This may explain why seizures during postictal psychosis often exacerbate the psychosis.

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whereas those during alternating psychosis may improve the psychiatric status. Different patterns of excitation and inhibition may also explain why the EEG may show “forced normalization” in some cases of interictal psychosis, and this is not exclusive to alternating psychosis. However for most cases, this hypothesis suggests that alternating psychosis and postictal psychosis are related to increased inhibition in limbic neuronal networks. In postictal psychosis, this is the brain’s homeostatic response to frequent seizures. In alternating psychosis, the relevant brain regions are already in that state, and the occurrence of seizures is a sign of disinhibition, which also signals the improvement from psychosis.

Molecular Mechanisms of Excitation and Inhibition. The molecular basis of these mechanisms has been briefly described above, with an emphasis on GABAergic mechanisms, but contains contributions from other neurotransmitters which include acetylcholine, catecholamines, glutamate, serotonin, opiates, adenosine, and NO. Brief epilepsy-related psychosis must be distinguished from schizophrenia, but it is important to recognize that GABAergic interneurons have been suggested to have an important role in the psychoses in general.65 These interneurons are the principal cortical targets of dopaminergic and serotonergic projections, play a role in cortical development, and are involved in the binding together of cortical networks. The complexity of these interneurons is only beginning to be understood. For eg, the hippocampus, a region which is considered to have an important role in psychosis, has at least 3 types of interneurons—basket cells, axo-axonic cells, and oriens-lacunosum-molecular cells—which exhibit distinct, state-dependent patterns of activity and contribute differentially to hippocampal network states.64 As we understand more about the physiological and behavioral correlates of activity in these interneurons, it may be possible to develop more proximate models of psychotic states.

Abnormalities of cortical inhibition have been described in schizophrenic patients as well. Most of this evidence suggests reduced cortical inhibition, although the net effect could be an excitation-inhibition imbalance leading to abnormal network states that underlie the psychotic symptoms. The prepulse inhibition paradigm has been applied to demonstrate impaired sensorimotor gating in schizophrenia which has been attributed to reduced cortical inhibition.65 Patients with schizophrenia have impaired inhibition of event-related potential responses to paired auditory stimuli.66 Morphological changes in GABA interneurons have been described in neuropathological studies on schizophrenic patients.67 Finally, transcranial magnetic stimulation has been used to demonstrate impaired cortical inhibition in schizophrenia.68

If GABA is the principal inhibitory neurotransmitter in the brain, the main excitatory neurotransmitter is glutamic acid. Disruption of glutamatergic circuits in the brain has been implicated in both epilepsy and psychosis. Enhanced glutamatergic activity, particularly at the NMDA receptors, is proconvulsant.69 Seizure activity, in turn, leads to long-lasting but not permanent changes in NMDA receptor currents.70 On the other hand, antagonism of NMDA receptors with drugs such as ketamine and phencyclidine, leads to the development of psychotic symptoms, particularly hallucinations.71 This is consistent with the glutamate receptor dysfunction hypothesis of schizophrenia.72

The concept of an excitation-inhibition imbalance may seem too nonspecific to explain such complex symptoms as delusions and hallucinations, but it lies at the heart of the notion that the genesis of these symptoms is related to activity-dependent neuronal communication in cortico-cortical and cortico-subcortical circuits. There are many cell types in the cortex using excitatory, inhibitory, and modulatory neurotransmitters, but the overall activity is balanced out.73 Imbalance between excitation and inhibition will potentially lead to an excess of output or input and thereby an altered activity state of the network. Alteration in membrane potentials that follow produces changes in the spontaneous firing patterns and the incidence and properties of various neuronal classes, with alterations in behavior.74 Because the neuronal networks are nonlinear states, abrupt changes in their dynamics can occur due to changes in input, with major behavioral consequences. The key regions involved in psychosis have been hypothesized to be the entorhinal cortex,75 the basolateral amygdala,76 and other limbic regions,62 and these are the regions most vulnerable to seizure-induced plasticity.77

Other Molecular Mechanisms. Dopamine has of course received prominent attention in the discussions of molecular mechanisms of psychosis. As discussed above, dopamine antagonists are proconvulsant and antipsychotic, while dopamine agonists are the reverse. It is possible that the antagonism between epilepsy and psychosis may be related to catecholaminergic mechanisms, with dopamine playing a prominent role. Dopamine has been demonstrated to be involved in pharmacological kindling. The repeated administration of dopamine agonists in small doses leads to an increasing behavioral response, which results in sensitization and is conditionable.78 Dopamine is also involved in the long-lasting NMDA-dependent shifts in excitability that are part of neuronal plasticity.79

Another area of much interest in the pathogenesis of epilepsy relates to genetic factors that cause recurrent abnormal synchronization of neuronal networks. Many of the genes implicated code for calcium, sodium, and chloride ion channels which lead to abnormalities in membrane excitability. Most of the mutations involved have been related to rarer forms of epilepsy, but ion channels are involved in the common forms of epilepsy.
as well. The field is moving rapidly, but it is as yet not understood what role channel abnormalities play in the common forms of temporal lobe and primary generalized epilepsies and how they are regulated to produce spontaneous cessation of seizures. The effect of ion channel abnormalities on neurotransmitter release and their role in the pathogenesis of psychosis are not understood and are important areas for future studies.

Clinical Implications. The consequences of the excitation-inhibition imbalance model of epilepsy-related brief psychoses are apparent in the treatment strategies employed. In postictal psychosis, there is an incomplete control of seizures, and attempts to optimize this control are recommended. In alternating psychosis, however, the brain regions are already in a state of overinhibition, and withdrawal of antiepileptic drugs may sometimes be recommended to permit the occurrence of a seizure and the possible amelioration of psychosis. The development of psychosis probably needs bilateral and extensive inhibition to occur, which is only likely to occur if seizures are generalized. The therapeutic goal is to achieve an optimal balance of excitation and inhibition, and this situation may favor the continuation of infrequent seizures due to an underlying epilepsy-prone neural network.

The long-term consequences of brief psychosis are not well understood. These psychoses often recur and do not stay true to themselves, i.e., patients with alternating psychosis may have postictal psychosis and vice versa. There are some plastic regenerative changes in response to the repeated occurrence of seizures\(^7\) and psychosis,\(^8\) with a proportion of patients developing chronic psychosis on follow-up. The consequences may be somewhat different depending upon whether seizures occur in childhood or adulthood. There may also be genetic susceptibility to brain changes.\(^7\) It has been shown that stimulation of the hippocampus leads to an anomalous axonal sprouting from dentate granule cells before the development of seizures.\(^8\) Expansion of glutamatergic presynaptic mossy fibers and an increase in perforated postsynaptic densities on granule cell dendrites have been demonstrated in temporal lobectomy specimens,\(^8\) changes possibly produced by increased expression of messenger RNA for c-fos and nerve growth factor by recurrent limbic seizures. In addition, there is neurogenesis as well as neuronal loss, in varying combinations. There is also activation and proliferation of glial cells. Synaptic function and ion channel function may be altered.\(^7\) The aberrant regeneration and the resultant “miswiring” alone or in combination with other morphological and functional changes interact with the baseline neuropathology. This may be the underlying basis for chronic SLP in some patients with repeated brief psychosis. The superimposition of seizures on this may further modify the expression of the psychopathology, producing both exacerbations and remissions depending upon their nature and frequency.

Future Directions

An examination of the relationship between brief postictal psychosis and alternating psychosis presents the best opportunity to examine some of the underlying pathophysiological mechanisms for epilepsy-related brief psychosis. Because many postictal psychosis occur in hospital while patients are being monitored, they present an excellent opportunity to examine whether brain’s inhibitory processes play a key role in their generation. Techniques such as transcranial magnetic stimulation and prepulse inhibition may be used to investigate various aspects of cortical inhibition. The processes can be examined at the molecular level using in vivo microdialysis techniques\(^8\) in patients as well as in animal models of epilepsy. Functional imaging with SPECT and PET, using appropriate ligands, is likely to be valuable. Longitudinal studies of patients with postictal psychosis and alternating psychosis should help determine long-term outcome, and because some of these patients proceed to surgery, neuropathological studies of excised tissue would be instructive. Furthermore, network models of psychosis and other psychiatric disorders are just beginning to be developed\(^8\) as techniques for large-scale recording of neuronal ensembles become available,\(^7\) and these could be applied to brief psychosis of epilepsy.

Many answers remain enigmatic. Why is it that only some patients with recurrent complex partial epilepsy become psychotic? Is it the “right mix” of inhibition and excitation that is responsible? Is it the involvement of key anatomical structures and thereby neuronal assemblies or networks? Does the development of psychosis require a substratum of a structural abnormality on which the interplay of these processes comes about? Is it the activity of particular interneurons that is crucial in the determination? We must consider all these questions to help move this field forward.

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References


