

Basic Mechanisms of Psychotropic Drugs

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Summary: Many epilepsy patients, particularly those with complex partial seizures, also develop psychiatric disorders during the course of their illness and have to be treated with psychotropic drugs in addition to their antiepileptic medication. However, the brains of epileptic patients can be considered pathologically altered and psychotropic drugs may thus have profound and stronger effects on seizure threshold or unwanted side effects than in purely psychiatric patients. Thus, the

knowledge of the mechanisms of psychotropic drugs is necessary to predict their effects in epilepsy patients. In this review, current concepts of the mechanisms of neuroleptic, antidepressant, and anxiolytic drugs emerging from basic and preclinical research are summarized, and the potential impact of using these drugs in epilepsy patients is discussed. **Key Words:** Antidepressant—Anxiolytic—Benzodiazepine—Dopamine—Neuroleptic—Serotonin—Review.

Psychiatric conditions are more prevalent in epilepsy patients than in the general population. Treating epilepsy patients with psychotropic drugs is therefore a frequent necessity but it may bring potential problems. Thus, psychotropic drugs can influence the threshold for seizures. Conversely, the epileptic brain is physiologically and anatomically different from the normal brain, putting the patient at a higher risk for some side effects. For instance, epilepsy patients show psychotropic side effects to D-CPPene, a competitive antagonist of the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor developed as an anticonvulsant (AED), at a dose that produced no such effects in healthy volunteers (1).

Many drugs used in psychiatry modulate neurotransmission in monoaminergic systems (i.e., noradrenaline, dopamine, and serotonin). Besides noradrenaline, which is thought to express an antiepileptogenic effect, preclinical research revealed a surprisingly small effect of drugs acting on monoaminergic transmission in animal models of epilepsy (2). Nevertheless, the fact that epilepsy patients may react more or even differently to psychotropic drugs than other patients requires knowledge about the mechanisms of the prescribed drugs.

NEUROLEPTIC DRUGS

Symptoms of schizophrenia are diverse and include symptoms described as positive (e.g., delusions and hal-

lucinations), negative (e.g., flattened affect and social withdrawal), and cognitive-attentional (e.g., lack of sensory gating and impaired working memory). Accordingly, no single drug mechanism is likely to correct all of these symptoms, at least not without inducing concomitant unwanted side effects.

Several groups of neuroleptic drugs are in use to treat schizophrenia. Classic (or typical) neuroleptics, such as haloperidol, interact preferentially with dopaminergic neurotransmission. The antipsychotic potency of these conventional drugs directly correlates with their affinity to a subtype of postsynaptic dopamine receptors, the D₂ receptor (3). With the successful cloning of the dopamine receptors, it became clear that at least five subtypes exist, each of which has a unique pharmacologic profile (4). The D₁ and D₅ receptors are coupled to a stimulatory G protein that activates adenylyl cyclase, the enzyme that converts adenosine triphosphate (ATP) to the second-messenger cyclic adenosine monophosphate (cAMP) and are expressed mainly in the neocortex and the hippocampus. They have only low affinity to most typical neuroleptic drugs.

The D₂ receptor is part of a family that also includes D₃ and D₄ receptors. These receptors inhibit the adenylyl cyclase, thus reduce cAMP production, and are expressed at particularly high levels in the striatum, but also in limbic structures like the amygdala and the hippocampus. The dopaminergic innervation of the forebrain arises from the substantia nigra pars compacta and the ventral tegmental area in the midbrain. Schizophrenia, particularly the positive symptoms, is thought to arise from a hyperactivity or increased reactivity of the

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mesolimbic dopaminergic pathway, and the blockade of D_2 receptors in the ventral striatum by typical neuroleptic drugs, such as haloperidol, is thought to be responsible for the efficacy against positive symptoms (5). However, a number of schizophrenic patients remain refractory to typical neuroleptic treatment and show only unwanted extrapyramidal motor side effects, which are produced by concomitant antagonism of dorsal striatal D_2 receptors. Moreover, negative and cognitive symptoms of schizophrenia are usually little improved by typical neuroleptic drugs. These symptoms are thought to reflect diminished function of the mesocortical pathway impinging on D_1 receptors in the frontal neocortex, which is not restored by typical psychotropics (6).

This original dopamine hypothesis of schizophrenia has been challenged by the observation that the atypical neuroleptic drug clozapine is therapeutically effective at significantly smaller doses than would be predicted on the basis of its low affinity to the D_2 receptor (7). The observation that clozapine has a high affinity for the dopamine D_3 and particularly for the D_4 -receptor subtypes raised the possibility that the antipsychotic efficacy of clozapine may be attributed to D_4 -receptor antagonism (8). However, a number of facts argue against this hypothesis. Clozapine has no unique high affinity to D_4 receptors but shares this with a number of atypical, but also typical neuroleptic drugs, whereas other clinically effective atypical and typical neuroleptics have a low affinity to D_4 receptors (9). A major role of D_4 -receptor antagonism is further called into question by the absence of psychiatric abnormalities in individuals without functional D_4 receptors (10) and the lack of antipsychotic efficacy of the D_4 -selective antagonist L-745,870 in clinical trials (11).

An alternative concept to explain the antipsychotic efficacy of atypical neuroleptics emerged from the observation that besides a common downregulation of cortical D_1 receptors, both typical and atypical psychotropics upregulate D_2 receptors in the cortex and induce immediate-early gene activation in the nucleus accumbens (12). If D_2 receptors in the cortex are different from D_2 receptors in the striatum, this may explain the antipsychotic effect of clozapine, because clozapine blocks cortical D_2 receptors (and probably also in the nucleus accumbens) but not striatal D_2 receptors.

Alternatively, clozapine may exert its antipsychotic efficacy by interacting with a broad array of dopaminergic, serotonergic, and even adrenergic receptors, which could account for its distinct pattern of clinical activity (13). Most compelling in this respect is the antagonism at serotonergic 5-HT₂ receptors (neuroleptics fail to discriminate between 5-HT_{2A} and 5-HT_{2C} receptors) because lysergic acid diethylamide (LSD) and other psychedelic hallucinogens act on 5-HT_{2A} receptors. However, receptors of the 5-HT₃, 5-HT₆, 5-HT₇, and

even 5-HT_{1A} subtype have been implicated in the antipsychotic effect of clozapine (14).

From the psychosis produced by abuse of phencyclidine (PCP), another theory emerged. PCP is a low-affinity, noncompetitive blocker of the NMDA-subtype glutamate receptor (15). Thus, reduced activation of forebrain NMDA receptors may be involved in schizophrenia, and antipsychotic efficacy may be achieved by restoring this reduced glutamatergic transmission.

In summary, many different receptors may be involved both in the etiology of schizophrenia and in the antipsychotic efficacy of typical and atypical psychotropic drugs. This makes it difficult to predict if and in which direction the drugs change seizure susceptibility in epilepsy patients (i.e., can precipitate seizures). Assuming that dopaminergic receptors are the most important sites of action at least of typical neuroleptics (Table 1), our knowledge from experimental data in rat models of epilepsy suggests that activation of D_2 receptors is anti-convulsant, whereas activation of D_1 receptors is proconvulsant in limbic parts of the forebrain (2). Treatment of epilepsy patients with neuroleptic drugs that reduce activation of receptors of the D_2 family may thus bear the risk of increased seizure frequency, especially in patients with temporal lobe epilepsy or other types of epilepsy that arise in the limbic system.

ANTIDEPRESSANT DRUGS

Disorders of mood, categorized into unipolar depression and manic-depressive disorder, are characterized by disturbances of affect that are so severe that cognition, judgment, and interpersonal relationships are altered. Appetite, energy level, and sleeping patterns also can be profoundly disturbed. In the 1930s, electroconvulsive treatment of depressive patients was introduced and largely contributed, together with the serendipitous discovery of the first antidepressant drugs, to the decline in number of patients hospitalised in psychiatric institutions. Along with the progress in pharmacotherapy described later, the refinement in physical therapy was considerable. Electroconvulsive treatment is now effectively applied unilaterally under anesthesia and muscle relaxation. New perspectives were opened by the introduction of rapid transcranial magnetic stimulation in the therapy of patients with depression (16), and more recently, vagus nerve stimulation. Although these physical procedures have been proved to be much more satisfactory and acceptable for the patient, epilepsy patients are still considered a high-risk population for this kind of antidepressant therapy.

Insight into the basic mechanisms of pharmacotherapy of depression started with the discovery that iproniazid and other hydrazine derivatives are monoamine oxidase (MAO) inhibitors that effectively elevated the cere-

bral levels of noradrenaline and serotonin. The emerging monoamine hypothesis of depression was substantiated by the finding that imipramine and other tricyclic antidepressants inhibit the reuptake of monoamine from the synaptic cleft and thus increase their availability at the receptors (17). The common principle of action of both MAO inhibitors and tricyclic antidepressants was considered the elevation of the concentration of biogenic amines (noradrenaline or serotonin or both) in the synaptic cleft. However, there can be no simple relation between mood and monoamine concentration at the receptor because antidepressant drugs do not elevate the mood level in healthy subjects, and a treatment of ≥ 2 weeks with antidepressant drugs is necessary to alleviate depression in patients, although the reuptake of monoamines is reduced immediately (18).

A regulatory process that would account for the latency between onset of antidepressant treatment and therapeutic effect seems to be involved. From experimental data in rats, in which a downregulation of β -adrenergic receptors and decreased production of the associated second-messenger cAMP in the cortex after prolonged daily injection with antidepressant compounds was found, it was hypothesized that a downregulation of β -receptors underlies the clinical effect of antidepressant drugs (19). However, several newly introduced antidepressant drugs, particularly the selective serotonin reuptake inhibitors (SSRIs), did not downregulate β -adrenoceptors.

Because of their negligible effect on the noradrenergic system, the high clinical efficacy and the serotonin selectivity of reuptake inhibitors, like fluoxetine, sertraline, citalopram, and paroxetine, supported the serotonin hypothesis of depression. The latency between the beginning of treatment and the onset of the antidepressant effect was explained by the presence of 5-HT_{1A} autoreceptors on serotonergic neurons that inhibit the release of serotonin. Thus, the immediate net effect of the application of an SSRI would be zero because the increased concentration of serotonin in the synaptic cleft after SSRI application would result in increased activation of the inhibitory autoreceptors and a decreased release of serotonin (20). Under an elevated extracellular concentration of serotonin, 5-HT_{1A} receptors are downregulated, whereas postsynaptic 5-HT₂ receptors are upregulated after some time, so that prolonged application of an SSRI would result in a delayed net increase of serotonergic neurotransmission. This theory is substantiated by the observation that different antidepressant treatments, including electroshock therapy, either downregulate 5-HT_{1A} receptors or upregulate 5-HT₂ receptors in the long-term range. Furthermore, the theory suggested that the use of an SSRI together with a 5-HT_{1A}-receptor antagonist should shorten the onset of the antidepressant effect. Indeed, administration of pindolol,

a 5-HT_{1A} and β -adrenoceptor antagonist, accelerated the action of an SSRI (21). Even the clinical antidepressant efficacy of selective noradrenaline inhibitors like venlafaxine can be explained with this theory by the postulate of a downregulation of α_2 -heteroreceptors, which control the release of serotonin on serotonergic synapses (20). Antidepressant-induced downregulation of 5-HT_{1B/D} autoreceptors, which are expressed on the presynaptic side of serotonergic neurons, also may contribute to a delayed onset of a net increase of serotonergic transmission.

Although the action of antidepressants against unipolar depression was regarded as closely associated with monoamine neurotransmission during the last four decades, the possible role of neuropeptides in depression has recently been suggested. It has been discovered that drugs acting as antagonists on certain neuropeptide receptors have a considerable potential as antidepressants (22). For instance, substance P is released in response to stress and may have depressant actions via the tachykinin NK₁ receptor in the central nervous system. The development of nonpeptide antagonists yielded promising results for the treatment of depression in clinical trials (23). Usually neuropeptides are co-released with conventional neurotransmitters on strong stimulation and may serve as a modulator and adaptive process for biologically relevant strong stimulation.

However, they have a second important function that may be related to their role in mood control. Neuropeptides regulate the hormonal system. It has recently been described that central noradrenergic system and the hypothalamus–pituitary–adrenal axis are strongly activated or even dysregulated in depressed patients, suggesting that antagonists of the corticotropin-releasing hormone (CRH) may be helpful for the treatment of depression (24).

In summary, current antidepressant treatment involves the modulation of neurotransmission at a number of different receptors, serotonergic and noradrenergic receptors being probably the most important (Table 1). With regard to the treatment of depressed epilepsy patients, the result on seizure susceptibility is not easy to predict because it depends on the drugs' affinities to various receptors, type of epilepsy, and background of the patient. Increasing the transmitter concentration of serotonin by reuptake inhibitors may have both anticonvulsant and proconvulsant effects by increased activation of different receptors. Preclinical data in rat models suggest that the net outcome of such treatment is slightly anticonvulsant at best (2,25). Recent analysis of different serotonin-receptor knockout mice revealed that the 5-HT_{2C} receptor may be involved in the control of seizures (26).

Regarding the effects of increased noradrenaline concentration in the brain, we have the same problem with receptor heterogeneity as with the serotonergic system. Preclinical data from animal models, however, suggest

TABLE 1. Basic mechanisms of psychotropic drugs

Treatment/disorder	Typical drug	Receptor
I. Schizophrenia		
Typical neuroleptic	Chlorpromazine, haloperidol	Dopamine D ₂ (antagonist)
Atypical neuroleptic	Clozapine	Dopamine D ₃ /D ₄ (antagonist) (also 5-HT _{2A} , α_1 , H ₁ antagonist)
Drug abuse (psychotic)	Phencyclidine	NMDA (antagonist)
	LSD	5-HT _{2A} (agonist)
II. Depression		
Unipolar depression	Electroconvulsive therapy	?
	MAO inhibitors ^a	all: Adrenergic α_2 - β_1 (downregulation)
	Tricyclic drugs ^a	Serotonin 5-HT ₂ (upregulation)
	SSRI ^a	Serotonin 5-HT _{1A} , (downregulation)
Bipolar disorder	Li ⁺ salts	? (blocking IP ₃ metabolism)
	Carbamazepine, valproate, lamotrigine	? (Na channel)
III. Anxiety		
Generalized anxiety	Benzodiazepines	GABA _A (positive modulator)
	Buspirone	Serotonin 5-HT _{1A} (partial agonist)
Panic disorder	Tricyclic antidepressants	Monoamine transporter (inhibition)
Posttraumatic stress disorder	Clonidine	α_2 -adrenoceptor (agonist)
Obsessive-compulsive disorder	SSRIs	Serotonin reuptake transporter (inhibition)

The putative main mechanisms of actions of psychotropic drugs for treatment of schizophrenia and different types of depression and anxiety are summarized.

^a MAO inhibitors, tricyclic drugs, and SSRIs all acutely increase the extracellular concentration of monoamines or serotonin only by either reducing degradation (MAO inhibition) or blockade of reuptake from the synaptic cleft, but slow regulatory processes are necessary for the (delayed) antidepressant effect.

5-HT, 5-hydroxytryptamine (serotonin); GABA, γ -aminobutyric acid; IP₃, inositol triphosphate; LSD, lysergic acid diethylamide; MAO, monoamine oxidase; NMDA- *N*-methyl-D-aspartate; SSRI, selective serotonin reuptake inhibitor.

that by nonspecifically increasing noradrenaline in the central nervous system, activation of α_2 -adrenoceptor predominates and will result in a net anticonvulsant effect (2). Thus, from a mechanistic point of view, pharmacologic antidepressant therapy will put epilepsy patients at a lower risk of proconvulsant side effects than will neuroleptic therapy.

In patients with bipolar manic-depressive disorder, drug therapy includes lithium salts. The exact mechanism of this treatment is not yet clear but may involve a decreased responsiveness of the phosphoinositol diphosphate second-messenger system by blocking the degradation and regeneration of inositol triphosphate (27,28). From the pilocarpine model of temporal lobe epilepsy in rats, it is known that pretreatment with lithium strongly reduces the dose of the muscarinic agonist pilocarpine necessary for inducing complex partial seizures (29). This may be a secondary effect of enhancing the uptake of pilocarpine into the brain and does not necessarily mean an increased seizure susceptibility of epilepsy patients treated with lithium. Furthermore, some AEDs that are thought to act through a use-dependent blockade of voltage-activated sodium channels [i.e., carbamazepine (CBZ), valproate (VPA), and lamotrigine (LTG)] have been found to be useful against bipolar disorders and may be more appropriate for epilepsy patients with this type of mood disorder (30).

ANXIOLYTIC DRUGS

Disorders of anxiety are among the most frequent psychiatric conditions, producing profound distress and

social and occupational impairment. Since their introduction ~40 years ago, benzodiazepines (BZDs) have been proved safe and efficacious drugs for pharmacologic treatment of anxiety states. Besides chlordiazepoxide and diazepam (DZP), which were introduced in the late 1950s, more than a dozen compounds were developed; they differ primarily in their pharmacokinetics, rather than in their clinical effects.

In 1977, a high-affinity binding site for BZDs in the brain was identified (31,32), and it became clear that BZDs modulate γ -aminobutyric acid (GABA)_Aergic function by increasing the inhibitory action of GABA at the GABA_A-receptor complex (33). GABA_A receptors are thought to be a pentamer of different subunits forming a chloride channel. Binding of BZDs to this receptor complex in the presence of GABA increases the frequency of channel opening. The enhanced influx of chloride through the channel potentiates GABA_A receptor-mediated inhibition.

The situation with BZD becomes complicated by the fact that ≥ 16 different subunits of GABA_A receptors exist, and that BZDs do not bind to all combinations of different subunits (34). Most of the GABA_A receptors that were found in the mammalian brain consist of α , β , and γ subunits, and BZDs bind at the interface between the α and γ subunits (35). Sensitivity of GABA_A receptors to BZDs requires the presence of a γ_2 subunit and an adjacent α_1 , α_2 , α_3 , or α_5 subunit. GABA_A receptors containing α_4 or α_6 subunits are insensitive to BZDs because of a single amino acid difference at position 101 (36). Because BZD-sensitive GABA_A receptors are

found throughout the brain, anxiolytic treatment with BZDs often affects several important neuronal circuits and causes unwanted side effects like ataxia, amnesia, and potentiation of the effect of ethanol.

An advantage of the heterogeneous nature of GABA_A receptors is that the different effects can be mediated by different GABA_A-receptor complexes consisting of specific subunit combinations. Unfortunately, the available BZDs are not very selective, except for the fairly α_1 -selective zolpidem, which is clinically used as hypnotic drug, suggesting that α_1 subunit-containing GABA_A receptors cause sedation (34). If anxiolysis could be attributed to a different GABA_A receptor, this would open the possibility of developing anxiolytic drugs without sedative and probably other side effects.

A first approach of generating knockout mice lacking an α subunit was of no use because these mice died or had severe neurologic disorders (37,38). Recently another elegant approach used genetically engineered mice with altered α_1 , α_2 , or α_3 subunits. The clue was to render the subunits insensitive to BZDs by mutating the histidine in the 101 residue of the α subunit to arginine, a mutation that leaves the receptors' sensitivity to GABA and its natural physiologic function unchanged (39–41). Thus, it became clear that BZDs exert their anxiolytic effects at GABA_A receptors containing α_2 subunits, but not α_1 or α_3 subunits (39,41) and that BZD site ligands that do not affect GABA responses mediated by α_1 subunit-containing GABA_A receptors provide anxiolytic effects without sedation and ataxia (40). Interestingly, the α_2 subunit-containing GABA_A receptors that mediate anxiolysis are located mainly in the areas of the limbic system, striatum, and neocortex (42).

Besides anxiolysis, BZDs have anticonvulsant efficacy that should render them ideal drugs for treatment of anxiety in epilepsy patients. However, a major problem associated with the use of BZDs in epilepsy is the development of tolerance to the anticonvulsant effect, with the risk of exacerbation of the seizures after BZD discontinuation (43). Various pharmaceutical companies tried to develop new BZDs that have no or less potential to develop tolerance, but to date without success. Probably the 1,5-BZD clobazam (CLB) is less prone to developing tolerance (44) and may represent a drug of choice for epilepsy patients in psychiatry (see contribution of M. Trimble in this issue). It should be noted that other transmitter systems also have been implicated in the development of anxiety, particularly in specific subtypes of anxiety disorders, and new routes of anxiolytic treatment are currently under trial (Table 1). Although their interaction with seizure susceptibility in epilepsy patients is not clear at the moment, they may represent an alternative to BZDs for anxiolytic treatment in the future.

Acknowledgment: Professor Trimble and the members of the Commission for the Psychobiology of Epilepsy are very grateful to the International League Against Epilepsy for their financial support of the commission and for their help with the publication of this supplement.

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