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Modulation of Ligand-gated Ion Channels by Antidepressants and Antipsychotics

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Abstract It is generally accepted that antidepressants and antipsychotics mediate their therapeutic effects via specific interaction with processes related to synaptic neurotransmission in the central nervous system. Besides their well-known classical mechanisms of action, antidepressants and antipsychotics show widely unknown effects, which might also contribute to the pharmacological profile of these agents. There is growing evidence that an interaction of these drugs with allosteric modulatory sites of ligand-gated ion channels (LGICs) might represent a yet unknown principle of action. Such interactions of psychopharmacological drugs with LGICs might play an important role both for the therapeutic efficacy and the side effect profile of these agents. In this review, we focus on the direct interaction of antidepressants and antipsychotics with LGICs, which may provide a basis for the development of novel psychopharmacological drugs.

Keywords Antidepressants · Antipsychotics · Ligand-gated ion channels · Psychopharmacological drug · Antagonist · Allosteric · Modulator · Synaptic transmission

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Introduction

Psychopharmacological drugs are widely used in the clinical treatment of affective disorders and psychotic disturbances. Their therapeutic effect is assumed to be mediated by interactions with G-protein-coupled receptors (GPCRs), neurotransmitter transporters (neurotransmitter uptake/release processes), and different enzymes. In view of the frequently similar efficacy of substances belonging to the same class of drugs, potential side effects have become the most important criterion for the selection of a specific drug. Significant adverse effects may occur through interaction with other receptors believed not to be directly related to the therapeutic action, primarily GPCRs, such as the muscarinic acetylcholine receptor (Ach_M), the histamine-1 (H1) receptor, and the α_1- and α_2-receptors.

Classical attempts to improve psychopharmacological drugs have concentrated on developing more potent and selective substances for known neurotransmitter receptors, subtypes thereof or neurotransmitter uptake/release processes. However, it is becoming increasingly clear that many therapeutically successful psychopharmacological compounds also interact with mostly uncharacterized allosteric sites at ligand-gated ion channels (LGICs) and it seems likely that this mechanism of action is responsible, at least in part, for both the therapeutic effects and side effect profile of such agents. These findings cast doubts on the classical approach of simply trying to improve potency and selectivity for known binding sites for classical neurotransmitter systems. In fact, several investigations from recent years indicated that psychopharmacological drugs can act as functional antagonists at ionotropic neurotransmitter receptors localized on synaptic membranes.

In this review, we focus on the direct interaction of antidepressants and antipsychotics with LGIC.

Antidepressants

Inhibition of serotonin (5-HT) and/or noradrenaline (NA) reuptake or the inhibition of monoamine oxidase [1, 2] are mechanisms of action shared by most antidepressants. In addition, second messenger systems (cAMP), transcription factors such as the cAMP responsive element binding protein, the brain-derived neurotrophic factor [3], and components of the hypothalamic-pituitary-adrenal system [4] have been identified as targets for antidepressants. Undesired side effect arises most importantly through the activation of certain GPCRs, such as the Ach_M [5], the histamine-1 (H1) receptor, and the α_1-receptors. In an attempt to reduce anticholinergic side effects, a major problem with tricyclic antidepressants, more specific compounds have been developed. These include selective 5-HT reuptake inhibitors (SSRIs, e.g., fluoxetine), selective NA reuptake inhibitors (SNARIs, e.g., reboxetine), selective 5-HT and noradrenergic reuptake inhibitors (SNRIs, e.g., venlafaxine and milnacipran), and noradrenergic and specific serotonergic antidepressants (NaSSAs) such as mirtazapine [1–3, 6]. A direct interaction of antidepressants with such LGIC would challenge the concept of target specificity claimed so far for these drugs and might represent a novel principle of antidepressant drug action.

Glutamatergic Receptors

Glutamate is the major excitatory neurotransmitter in the brain and primarily acts on three types of ionotropic receptors, namely, the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, kainate receptors, and *N*-methyl-D-aspartate (NMDA) receptors (for review, see [7]). The past decade has seen a steady accumulation of evidence supporting a role for glutamate and its receptors in depression and antidepressant activity [8, 9]. To date, evidence has emerged indicating that NMDA receptor antagonists and positive modulators of AMPA receptors have antidepressant-like activity in several preclinical [10–13] and some clinical studies [14]. NMDA receptor antagonists mimic certain effects of clinically effective antidepressants. For example, it has been demonstrated that chronic administration of NMDA receptor antagonists to rodents results in a downregulation of cortical beta-adrenoceptors, a phenomenon also observed after chronic treatment with many antidepressants. Moreover, it has been shown that a wide range of antidepressants alter radioligand binding to NMDA receptors in a fashion consistent with a reduction in NMDA receptor function (see review in [15]). This was reflected by an increased IC_{50} of glycine to inhibit [^{3}H]5,7-dichlorokynurenic acid binding to strychnine insensitive glycine receptors, and a reduction in the proportion of high affinity, glycine-displaceable [^{3}H]CGP 39653 (a competitive NMDA receptor antagonist) binding sites [16, 17]. In a more recent study, rats were subjected to chronic stress in combination with tianeptine treatment. Whereas stress increased NMDA-receptor-mediated excitatory postsynaptic currents (NMDA-EPSCs), concomitant pharmacological treatment with tianeptine prevented the stress-induced increase of NMDA-EPSCs. Exposing hippocampal slices in vitro to tianeptine resulted in an increase of the amplitudes of NMDA- and AMPA-receptor-mediated EPSCs. However, this enhancement of EPSCs involved a postsynaptic phosphorylation cascade rather than a direct interaction on glutamatergic receptors [18].

Although data showing a functional interaction of antidepressants with AMPA or NMDA receptors are scarce, some evidence exists for an antagonistic effect of these agents on NMDA receptors. In the CA1 region and the dentate gyrus of hippocampal slices, the tricyclic antidepressants imipramine, desipramine (DMI), and amitriptylin inhibited the NMDA-receptor-mediated epileptiform activity and the induction of long-term potentiation at equal concentrations, thereby suggesting that these effects are mediated by inhibitory actions on NMDA receptors [19].

The first evidence for a direct pharmacological interaction between NMDA receptors and tricyclic antidepressants was described in 1989 [20]. In mouse hippocampal neurons, DMI was a potent, selective antagonist of responses to NMDA with an IC_{50} of 10 μM. The strong voltage-dependency of this effect and the decrease in the open time and burst length distributions after single channel analysis suggested that the action of DMI on NMDA receptor channels is similar to that of MK-801 and does not reflect binding to other domains such as the regulatory sites for Zn^{2+} and glycine.

Another functional antagonistic effect of an antidepressant against NMDA receptors composed of ξ1, ε1 subunits (the mouse homologs of NMDAR1A and NMDAR2A), expressed in *Xenopus* oocytes has been shown recently [21]. The SNRI milnacipran inhibited NMDA-induced currents, however, with a concentration range of 100- to 500-fold greater than the concentrations required to inhibit the reuptake of 5-HT and NA. At standard clinical doses the steady-state plasma concentrations of milnacipran are reported to be in the order of 0.2 μM and even peak plasma concentrations do not exceed 0.5 μM [22]. Thus, the concentrations required to inhibit the LGIC receptors are 75- to 300-fold greater than those encountered clinically. Indeed these considerations render it unlikely that NMDA antagonism contributes to the antidepressive effect of milnacipran.

$GABA_A$ Receptors

Gamma aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the central nervous system (CNS). Its action is exerted in the brain through $GABA_A$,

$GABA_B$, and $GABA_C$ receptors. The $GABA_A$ and $GABA_C$ receptors belong to the family of LGIC (for review, see [23, 24]); however, in this review, we concentrate only on the $GABA_A$ receptor. $GABA_A$ receptors consist of various subunits and are targets for benzodiazepines, barbiturates, neuroactive steroids, and distinct anticonvulsive agents. There is considerable evidence that a dysfunction of $GABA_A$ receptors plays an important role in the pathophysiology of panic disorder [25]. Antidepressants, especially SSRIs, meanwhile comprise a first-line treatment in the pharmacotherapy for panic disorder [26]. They interfere with the synthesis of endogenous neuroactive steroids and induce an increase in the concentration of endogenous neuroactive steroids such as 3α, 5α-tetrahydroprogesterone (THP) and 3α, 5β-THP [27, 28]. These steroids are potent allosteric modulators of $GABA_A$ receptor function (for review, see [29]). In a clinical investigation it has been demonstrated that depression induces an increase in steroids, which antagonize $GABA_A$-receptors, whereas those which increase GABA-induced currents were reduced [30]. After treatment with fluoxetine, steroid concentration shifted to normal values. These effects may also contribute to the pharmacological profile of antidepressants.

Fluoxetine also exerts direct pharmacological effects on a variety of recombinant $GABA_A$ receptors expressed in human embryonic kidney (HEK)-293 cells [31]. Fluoxetine increased the response of the receptors to submaximal GABA concentrations but did not alter the maximum current amplitude. Among the six subtypes, only the α_5-subunit conferred reduced sensitivity to fluoxetine. However, because of the low potency of this effect with an EC_{50} at 128.1 μM for the potentiation of GABA-induced currents through the $\alpha_1\beta_2\gamma_{2L}$ isoform, it is unlikely that the necessary concentration are reached under clinical conditions.

The delayed therapeutic effect contrasts with the rapid action of the antidepressants on biogenic amine uptake. Therefore, it is of interest whether antidepressants also have other sites of action, which can result in enhancement of GABAergic neurotransmission. The MAO inhibitor phenelzine increases GABA levels in the whole brain by inhibiting GABA transaminase in a dose-dependent manner [32], whereas perfused imipramine enhances GABA release from rat thalamus in a Ca^{2+}-dependent manner [33]. Therefore, both imipramine and phenelzine enhance the amount of GABA available for interaction with $GABA_A$ receptors via the GABA binding site. In contrast to a direct pharmacological interaction, albeit with similar effects on the modulation of $GABA_A$ receptor function, chronic stimulation of $GABA_A$ receptors by agonists or modulators might result in changes in the pharmacological properties of the receptor concomitantly with alterations in the expression of specific $GABA_A$ receptor subunits. Long-term exposure to the antidepressant imipramine produced an increase of rat brainstem levels of $GABA_A$ receptor α1-, β2-, and γ2-subunit RNAs. Phenelzine decreased α1-subunit RNA and increased β2- and γ2-subunit RNAs levels. Interestingly, these changes in gene expression were different from those produced by the nonantipanic anxiolytic buspirone, which induced a decrease of the three $GABA_A$ receptor subunit mRNA levels [34].

$5\text{-}HT_3$ Receptors

5-HT receptors constitute a complex receptor group with at least seven families comprising 14 structurally and pharmacologically distinct mammalian subtypes [35]. They are mostly GPCRs, but one member of this group, the $5\text{-}HT_3$ receptor, is a ligand-gated nonselective cation channel [36]. Activation of $5\text{-}HT_3$ receptors causes membrane depolarization and an increase in intracellular Ca^{2+} [37]. Postsynaptic $5\text{-}HT_3$ receptors are mainly present on GABAergic interneurons mediating fast synaptic neurotransmission in the CNS [38, 39], whereas presynaptic $5\text{-}HT_3$ receptors modulate the release of several neurotransmitters in various brain regions [36, 40, 41]. Evidence for $5\text{-}HT_3$ receptors expressed on principal neurons are scarce. One cue is provided from [42] showing $5\text{-}HT_3$-mediated currents in cultured principal neurons of the hippocampal CA1 region. Within the CNS, $5\text{-}HT_3$ receptors are highly expressed in the area postrema, hippocampus and the amygdala [43, 44]. Rapid excitatory neurotransmission mediated by $5\text{-}HT_3$ receptors results in neurotransmitter release, especially of dopamine, in mesolimbic pathways [38]. Based on animal models and preliminary clinical studies, it has been suggested that $5\text{-}HT_3$ receptor antagonists display anxiolytic properties [45, 46].

It has been a long-term current belief that SSRIs, SNARIs, SNRIs, and NaSSAs, with the exception of mirtazapine, do not interact preferentially with neurotransmitter receptors. However, preliminary investigations suggested that fluoxetine also acts as a functional antagonist at $5\text{-}HT_3$ receptors localized on neurons of rat nodose ganglia [47]. More recent electrophysiological data indicate that the antagonistic effect of fluoxetine is probably conferred by a noncompetitive mechanism of action [48]. In a more detailed study [42], it has been demonstrated that different classes of antidepressants act as functional antagonists at the human $5\text{-}HT_3$ receptor stably expressed in HEK-293 cells and at endogenous $5\text{-}HT_3$ receptors of rat hippocampal neurons and N1E-115 neuroblastoma cells. The tricyclic antidepressants DMI, imipramine, and trimipramine, the SSRI fluoxetine, and the SNRI reboxetine noncompetitively reduced the 5-HT-induced Na^+ and Ca^{2+} currents in a dose-dependent fashion in the lower micromolar range. Interestingly, moclobemide and carbamazepine had no effect on $5\text{-}HT_3$ currents.

It is still unclear how the lipophilic antidepressants exert their noncompetitive effects on receptor proteins. One possi-

bility might be that the functional antagonistic effects of antidepressants at the 5-HT_3 receptor may be explained by an enhancement of receptor internalization. Receptor internalization is of major importance for receptor recycling and is an important determinant for the availability of functionally active membrane-bound receptors [49–51]. However, a recent study demonstrated that the noncompetitive antagonism of antidepressants at the 5-HT_3 receptor was not conferred by an enhancement of receptor internalization [52] as shown by immunofluorescence studies, assessment of receptor density in clathrin-coated vesicles, and electrophysiological recordings after coexpression of a dominant negative mutant of dynamin I, which inhibits receptor internalization.

Disordering of the bulk lipid phase of membranes might be another attractive hypothesis because it provides a possible mechanism by which lipophilic agents could affect membrane proteins such as ion channels via an action on membrane lipids. However, detailing the effects of different classes of antidepressants on steady-state diphenylhexatriene fluorescence anisotropy of purified plasma membranes from HEK-5-HT3A cell showed no correlation between the effects of antidepressants on membrane anisotropy and their inhibition of the 5-HT-induced cation current [42]. Thus, the inhibitory effects of antidepressants at this LGIC presumably are not merely secondary to their effects on membrane fluidity.

Recent studies showing that detergent-resistant membrane fragments can be isolated from cells suggest that biological membranes are not always in a liquid-crystalline phase. Sphingolipid and cholesterol-rich domains may exist as phase-separated "rafts" in the membrane. Lipid rafts have been characterized as detergent-resistant membranes with low buoyant density in a sucrose gradient and make a specialized signalling platform with higher concentrations of different signalling molecules compared with nonraft regions. Moreover, lipid rafts are enriched in axonal terminals [53] and dendrites [54] and may play a role in the polarized sorting and/or trafficking of ion channels [55]. Many pre- and postsynaptic proteins are enriched in the raft fraction [54–58] and there appear to be more rafts in synaptosomal membranes [59]. Thus, it is possible that enrichment of psychopharmacological agents within lipid rafts is crucial for exerting noncompetitive effects on ionotropic receptors and that specifically those psychopharmacological agents, which are exerting noncompetitive effects on ionotropic receptors, are enriched within lipid rafts.

Compatible with this idea are recent findings showing that the 5-HT_{3A} receptor protein expressed in HEK-293 cells and in N1E-115 neuroblastoma cells is located exclusively in the low buoyant density fractions in a sucrose gradient, which also contain caveolin-2 and flotillin-1, which are proteins that are preferentially associated with lipid rafts [52]. Thus, these low buoyant density fractions indeed represent raft-like domains. Similar to the 5-HT_3 receptor, only antidepressants such as DMI, fluoxetine, and reboxetine, which are capable to act as noncompetitive functional antagonists at the 5-HT_3 receptor, were enriched in lipid rafts (Fig. 1). In contrast, carbamazepine and moclobemide, which are devoid of antagonistic properties at this LGIC, and the competitive antagonist mirtazapine, did not reach substantial concentrations within these membrane microdomains (Fig. 1). In addition, the concentrations of psychopharmacological drugs within low buoyant density fractions were strongly associated with their inhibitory potency against 5-HT-induced cation currents. These data provide strong evidence that an accumulation of antidepressants might be important for the functional antagonistic effects of these drugs at the 5-HT_3 receptor.

5-HT_3 receptors, which share structural features with the $GABA_A$ receptor, are also targets for modulation by neuroactive steroids, which is an important principle for the regulation of neuronal excitability. Whole-cell voltage-clamp recordings revealed that the gonadal steroids 17β-estradiol and progesterone also act as noncompetitive antagonists at the 5-HT_3 receptor stably expressed in HEK-293 cells [60]. Functional antagonistic properties at this LGIC could also be shown for 17α-estradiol, 17α-ethinyl-17β-estradiol, testosterone, and allopregnanolone but not for pregnenolone sulfate and cholesterol, indicating that the modulation of 5-HT_3 receptor function by steroids is dependent on their respective molecule structure. The modulation of the 5-HT_3 receptors by steroids cannot be attributed only to their lipophilic properties. This is supported by the observation that not all steroids display an antagonistic effect at this LGIC and that the alcohols ethanol and phenol are devoid of antagonistic properties. It has been proposed from this work that gonadal steroids probably interact allosterically with the 5-HT_3 receptor at the receptor-membrane interface.

nACh Receptors

Nicotinic acetylcholine receptor (nAChRs) are diverse members of the neurotransmitter-gated ion channel superfamily (for review, see [61–64]). nAChRs are found throughout the nervous system, where they play critical and diverse physiological roles. Each nAChR subtype has a distinctive subunit composition, and each nAChR subunit is encoded by one of at least 16 different genes (α1–α9, β1–β4, γ, δ, and ε). It is common for vertebrate nAChRs to be classified as either "muscle type" or "neuronal" depending on whether they are expressed at the neuromuscular junction or within the central or peripheral nervous system. Muscle type nAChR consists of α1, β1, γ, δ, and ε, whereas the neuronal type comprises the subunits α2–α8 and β2–β4 (for review, see [65]); the most recently identified vertebrate nAChR subunits (α9 and α10) are

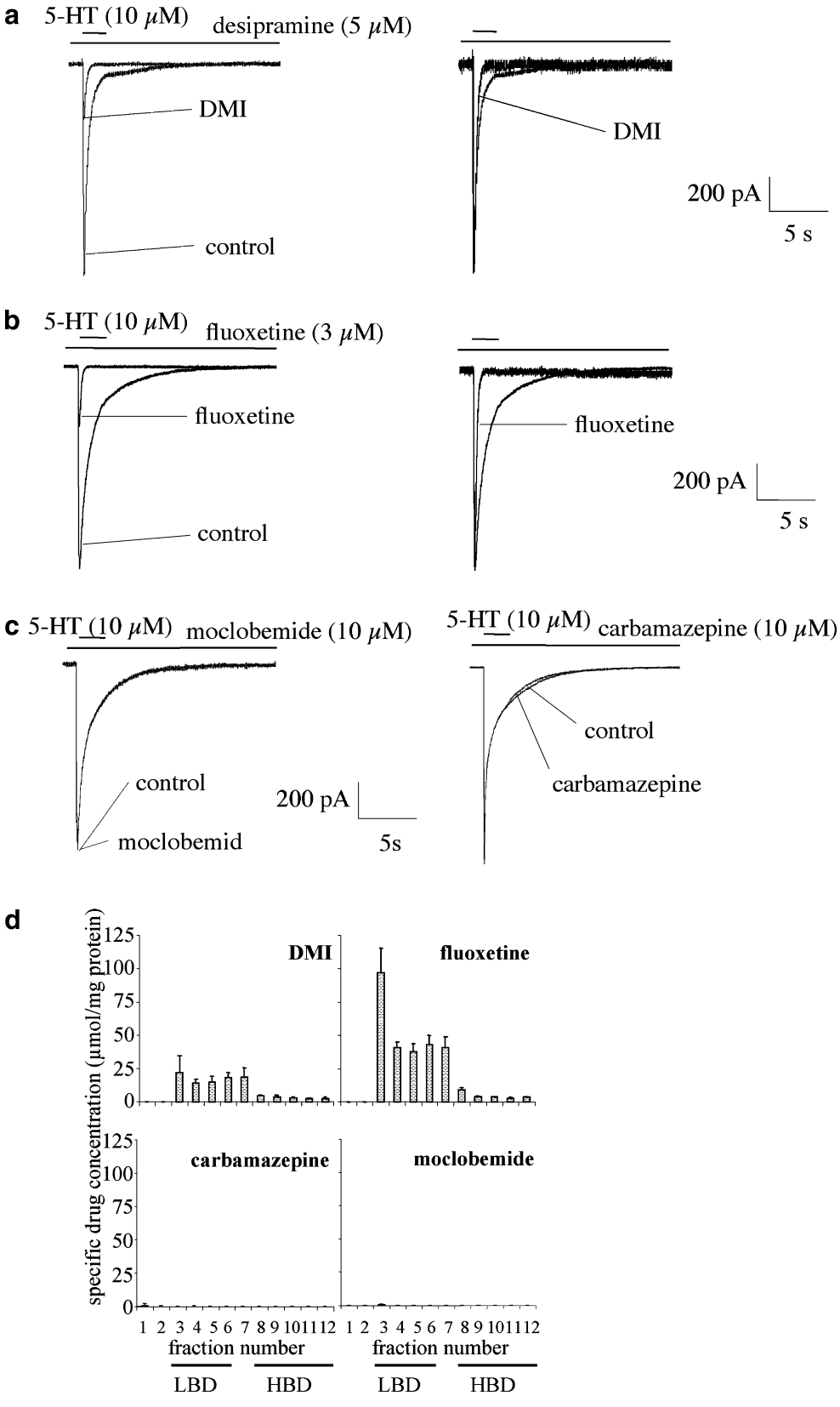

Fig. 1 Effects of different types of antidepressants on the 5-HT-evoked Na^+ current in HEK-5-HT_{3A} cells. Representative recordings of 5-HT-evoked Na^+ currents after application of DMI (**a**) and fluoxetine (**b**) at the respective IC_{50} concentrations. Left panels represent the original traces. To delineate effects of the antidepressants on the kinetics of 5-HT-evoked Na^+ current, the reduced peak amplitude was adjusted to the control peak (right panel). The upper bar indicates the application of 10 μM 5-HT; the lower bar indicates the presence of the respective antidepressant at its IC_{50} concentration. Moclobemide and carbamazepine (**c**), both without inhibitory effects, were tested at a 10 μM concentration. **d** Concentration of DMI, fluoxetine, moclobemide, and carbamazepine in low buoyant density and high buoyant density fractions of HEK-5-HT_{3A} cells. Sucrose density fractions were prepared as described in [52]. Drug concentrations were determined by high-performance liquid chromatography. Results are expressed as specific concentrations (μmol/mg protein) and represent the mean±SD of four independent experiments. Fractions 3–6 represent low buoyant density fractions; fractions 8–12 represent high buoyant density fractions. The figure subpanels were modified according to [52]

expressed primarily in mechanosensory hair cells of sensory epithelia (the cochlea and vestibular labyrinth) and, consequently, do not fall conveniently into the conventional classification of muscle-type and neuronal nAChRs). There is considerable evidence that hypercholinergic neurotransmission, which is associated with depressed mood states, may be mediated through excessive neuronal nicotinic receptor activation and that the therapeutic actions of many antidepressants may be in part mediated through inhibition of these receptors [66]; for review, see [67].

Over the past 20 years, the anticholinergic effect of antidepressants is well documented, employing different methodological approaches. Several groups have reported inhibitory actions of classic tricyclic antidepressants, including imipramine [68–70], nortriptyline, amitriptyline [66, 71, 72], and DMI on the nAChR [69]. More recent studies have characterized newer, more selective monoamine reuptake inhibitors, including fluoxetine [73, 74], sertraline, paroxetine, nefazodone [75], nisoxetine, citalopram, nomifensine [76], and reboxetine [77] as nAChR antagonists.

Electrophysiological studies are of particular interest to specify the pharmacological effects of antidepressants on nAChR expressed in different cell systems or cell lines. Among various antidepressants, norfluoxetine was the most potent functional antagonist for neuronal α2β4 and muscle AChRs in the *Xenopus* oocytes expression system [78]. More detailed analysis of imipramine and DMI revealed a noncompetitive antagonism against nAChRs expressed in *Xenopus* oocytes and human neuroblastoma cells with their IC_{50}s in the lower micromolar range [78]. The mechanistic bases for the noncompetitive action of tricaroboxylic acids on AChRs has been identified by rapid perfusion technique on outside-out patches and the analysis of single channel currents [79]. Doxepine, imipramine, and amitriptyline increased the decay rate of currents, inhibited the activation of resting channels, and decreased the cluster duration of single channel currents.

Sertraline, paroxetine, nefazodone, and venlafaxine have been shown to exert noncompetitive antagonism against human muscle-type nAChR (α1/β1 γδ), human autonomic nAChR (α3/β4, α5/β2), or chick α7-nAChR expressed in various cell systems. IC_{50}s were in the low to intermediate micromolar range, and functional blockade of chick α7-nAChR was produced in the intermediate to high micromolar range. Fluoxetine appears to antagonize dose-dependently both muscle (α1/β1 γδ) and neuronal (α2/β4 or α3/β4) nAChR either by increasing the rate of receptor desensitization and/or by channel blockade [73]. Perhaps one of the most interesting antidepressants demonstrated to have nAChR inhibitory activity is the atypical antidepressant bupropion [75, 80, 81]. Bupropion is unique because it is a relatively weak reuptake inhibitor of both NE and DA with little or no direct action on serotoninergic neurotransmission. Moreover, like the potent nicotinic receptor antagonist mecamylamine [82, 83], bupropion blocks the acute effects of nicotine in animals [80] and is an effective smoking cessation drug [84].

The concentration of antidepressants that inhibit nAChRs are consistently in the low micromolar range and resemble those reached in the brain during clinically effective treatment. Whereas the prominent monoaminergic effects of these drugs occur at much lower concentrations, it has been argued that concentrations required to inhibit nAChRs are comparable to those accumulated in the brain within the time frame when these drugs begin to be therapeutically active [76, 81].

Antipsychotics

In recent years important progress has been made in basic schizophrenia research. The dopamine hypothesis of schizophrenia postulates a dopaminergic hyperactivity in this disorder, which has for a long time been supported only by indirect pharmacological evidence [85]. This hypothesis has now received more direct support by means of PET and SPECT imaging techniques [86–89]. This dysregulation appears to be related to positive symptoms. These data are consistent with the observation that all antipsychotic drugs (APDs) provide at least some degree of dopamine type 2 and 4 receptor blockade and that these drugs improve positive symptoms [90]. Negative symptoms respond poorly to both typical and to some degree to atypical antipsychotics. Because neuroleptics exert also antagonistic effects at 5-HT_2 receptors, histamine receptors, muscarinic acetylcholine receptors, and α-adrenoceptors [91], the question has been raised whether dopamine is the only neurotransmitter showing dysfunction in schizophrenia. Modulation of other systems such as glutamatergic, GABAergic, serotonergic, cholinergic, and opioid system have also been implicated to contribute to the therapeutic potential of antipsychotics.

Glutamatergic Receptors

In recent years considerable interest has focused on the possible role of glutamate in schizophrenia [92, 93]. This is based on the discovery that phencyclidine (PCP, "angel dust") can induce a psychotic condition mimicking schizophrenia, perhaps even more closely than amphetamines. PCP is a powerful antagonist on one of the glutamate receptor subtypes, namely, the NMDA receptor. This receptor is equipped with an ion channel regulating the penetration of calcium and other cations into the neuron. PCP binds to a specific site in this channel, thereby blocking the function of the receptor. Hence, it is generally

accepted that in schizophrenia there is hypofunction of the glutamatergic system [94–96]. As a consequence, therapies enhancing glutamatergic transmission might be predicted to be useful antipsychotics. In fact, there are a number of clinical studies (some uncontrolled) indicating that glycine, a coagonist of NMDA receptors, improves negative symptoms in schizophrenic patients [97, 98], in particular, depressive and cognitive symptoms.

Recently, many pharmacological strategies involving glutamate receptors have been suggested and novel compounds acting on glutamatergic neurotransmission are currently under evaluation: (1) augmentation strategies improving NMDA-R transmission (glycine, D-serine, D-cycloserine, and glycine transporter inhibitors); (2) ampakines, positive modulators of AMPA receptor complex; (3) agonists of glutamate metabotropic receptors; and (4) drugs involved in subcellular adaptation both at pre- and postsynaptic sites.

Preclinical studies indicate that the three ionotropic glutamate receptors are altered by treatment with APDs, although the direction of reported changes has been inconsistent. Different studies report increases, decreases, or no change in levels of these receptors after long-term treatment with various APDs [99–103]. Moreover, contradictory and often opposite findings have been reported in the expression of subunits composing different glutamate receptors after chronic administration of APDs [104, 105]. Typical neuroleptics such as haloperidol and the atypical antipsychotic agent clozapine were commonly used in these studies. Long-term treatment with olanzapine, quetiapine, or risperidone significantly decreased NMDA receptor levels in caudate–putamen [103], but increased AMPA receptor levels in same region [106, 107]. Olanzapine and risperidone but not quetiapine also reduced NMDA receptor labeling in hippocampal CA1 and CA3 regions. Kainate receptors were unaltered by either treatment in the brain regions examined. The inability of olanzapine, risperidone, and quetiapine to alter kainate receptors suggests a minor role of these receptor in mediating CNS actions of these drugs. The atypical APDs clozapine and olanzapine and the typical APD haloperidol strongly modulate AMPA receptor and NMDA-receptor-mediated glutamatergic transmission after prolonged treatment [108]. An early publication provided evidence for the typical antipsychotic chlorpromazine affecting glutamate receptors in frog spinal cord motoneurons [109].

The APDs haloperidol, clozapine, and olanzapine effectively facilitated NMDA-induced [110–112] responses in pyramidal cells of the rat medial prefrontal cortex. In the nucleus accumbens, clozapine (100 nM) also potentiated NMDA-evoked currents, selective for NR2B subtype-containing NMDA receptors and glutamatergic EPSCs [113]. Other atypical antipsychotics showed similar biphasic dose–response curves [110]. The estimated EC_{50} value for clozapine was 14 nM [111, 114, 115], for olanzapine 2.9 nM [112], whereas haloperidol showed an EC_{50} value of 38 nM [111]. Furthermore, haloperidol but not clozapine produced a concentration-dependent inhibition of AMPA-induced current with an EC_{50} value of 37 nM [111]. Although antipsychotics apparently affect glutamatergic transmission, the observed effects are rather attributed to the involvement of protein kinase C and Ca^{2+}/calmodulin-dependent kinase II signal transduction pathways, dopamine release, and postsynaptic activation of D1 receptors than to a direct pharmacological effect [110, 113, 116–118].

Nevertheless, a few reports showed direct pharmacological effects of antipsychotics on NMDA and AMPA receptors. Haloperidol and clozapine inhibited subtype-specific currents through NMDA receptors expressed in *Xenopus* oocytes. Haloperidol selectively blocks NR1A/2B subunit combinations (IC_{50}=3 μM; maximum inhibition, approximately 85%) in a voltage-independent fashion, whereas the other subunit combinations are less sensitive (IC_{50}>300 μM; [119]). The splice variant combinations NR1b/2B and NR1e/2B are also blocked by haloperidol. About 30–100 μM haloperidol induces potentiation of NR1a/2A receptor responses. Clozapine inhibits the NMDA receptor, being significantly more effective at receptors containing NR2A and NR2B than at those containing NR2C. Interestingly, the inhibition required pretreatment with clozapine before activation of the receptor with NMDA [120].

In summary, these data show some modulatory effects of antipsychotics on ionotropic glutamate receptors and glutamate-mediated synaptic transmission. Whether these contribute to the therapeutic potential still has to be elucidated.

$GABA_A$ Receptors

In the last decade substantial evidence has implicated impaired GABAergic neurotransmission to the neuropathology of schizophrenia [121]. Various abnormalities of $GABA_A$ receptors have been identified. Autoradiographic studies using [^{3}H] muscimol (which has high affinity for GABA binding sites) have found a significant increase of $GABA_A$ receptor density in the dorsolateral prefrontal cortex [122, 123], anterior cingulate cortex [124–126], and hippocampus [127, 128] in patients suffering from schizophrenia compared to control subjects. Because of long-term antipsychotic treatment before death, these findings may reflect not only the consequences of schizophrenia but also effects of medication. The evaluation of long-term effects of APDs in animal models enabled a differential characterization of these possibilities. A modu-

lation of $GABA_A$ receptor density has been shown for haloperidol, clozapine, chlorpromazine, and olanzapine in many brain regions [128–130]. Besides these long-term effects of antipsychotics, which could account in part for the delayed onset of the pharmacological response, a direct interference with $GABA_A$ receptors has been described for phenothiazines (PTZs). Electrophysiological studies have shown that trifluoperazine, chlorpromazine, and thioridazine noncompetitively block the responses evoked by exogenous application of GABA in the lower micromolar range [131] and reduce the amplitude of IPSCs [132]. Analysis of miniature IPSCs suggests that the effects of PTZs are caused by a reduction in binding and increase in unbinding rates of the agonist to $GABA_A$ receptor channel [133]. The effects of CPZ on mIPSCs could be seen at micromolar concentrations similar to those attained in the brain of psychotic patients [134]. Interestingly, haloperidol was ineffective against GABA at concentrations up to 100 μM [131].

It has also been shown that clozapine can interact with the $GABA_A$ receptor [129]. The possibility that GABAergic receptors could be a relevant target for clozapine appears to be of interest because dopaminergic neurons such as those in the ventral tegmental area (VTA) are known to be regulated by the activity of GABAergic neurons both of local origin and from areas such as the nucleus accumbens [135–137]. Most evidence in favor of an interaction between clozapine and GABA receptors has originated from binding studies. It has been demonstrated that clozapine in the micromolar range can reverse the inhibitory effect of GABA on the binding of ^{35}*S*-*t*-butylbicyclophosphorothionate ([^{35}S]TBPS; a competitive $GABA_A$ receptor antagonist and a reliable predictor of $GABA_A$ receptor blockade) to rat brain membranes [129]. A clozapine metabolite, *N*-desmethylclozapine, seems to have the same effect [138]. The same authors have suggested that, in addition to clozapine, other APDs such as chlorprothixene may also act as antagonists at $GABA_A$ receptors [139, 140]. These observations have been confirmed by Korpi et al. [141], who found that clozapine at 10 μM significantly reduced GABA-mediated Cl^- influx in brain vesicles. However, in the same study, clozapine antagonizes GABA inhibition of [^{35}S]TBPS binding in brain sections only at concentrations in the higher micromolar range. Finally, using a system allowing the expression of various combinations of recombinant $GABA_A$ receptor subunits, this same group has demonstrated that clozapine preferentially interacted with $GABA_A$ receptors containing $\alpha1\beta2\gamma2$ and $\alpha6\beta1\gamma2$ subunits, an effect that is not seen with haloperidol [141]. Physiological evidence has been provided by Michael and Trudeau [142], demonstrating that clozapine dose-dependently reduced evoked IPSCs and GABA-induced currents and thus acts as an antagonist at both synaptic and extrasynaptic $GABA_A$ receptors on VTA neurons.

5-HT_3 Receptors

Because 5-HT_3 receptors are highly expressed in the caudate nucleus, putamen, hippocampal, and amygdala regions [35, 41], it has been suggested that selective 5-HT_3 receptor antagonists may have psychotropic effects [143]. Early animal studies suggest that 5-HT_3 receptor antagonists, in addition to their well-recognized antiemetic use, might be clinically useful for the treatment of anxiety, schizophrenia, drug and alcohol abuse, depression, cognitive disturbances, Alzheimer's disease, cerebellar tremor, Parkinson's disease treatment-related psychosis, treatment of inflammatory pain, and appetite disorders [35, 41, 143]. The dopamine hypothesis of schizophrenia suggests an enhanced mesolimbic activity of dopaminergic neurotransmission [144]. Behavioral, neurochemical, and electrophysiological investigations indicate that 5-HT_3 receptors modulate dopaminergic activity in mesolimbic and nigrostriatal pathways [35]. 5-HT_3 receptor activation increased dopamine release from slices of rat nucleus accumbens [145] and striatum [145, 146]. Vice versa, 5-HT_3 receptor antagonists induced a significant reduction in the number of spontaneously active dopaminergic neurons in the VTA and substantia nigra compacta [147], and attenuated dopamine-mediated hyperactivity of the nucleus accumbens [148, 149]. This profile suggests that 5-HT_3 receptor antagonists mimic certain inhibitory effects of neuroleptic drugs on the dopaminergic system and prompted their use in schizophrenia [41, 150]. However, clinical trials with specific 5-HT_3 receptor antagonists as a monotherapy were not encouraging so far [91]. If neuroleptics are functional antagonists at 5-HT_3 receptors, this might contribute to the pharmacological profile of these antipsychotic agents.

Functional antagonistic properties of the atypical neuroleptic clozapine have been reported previously for endogenous rat and recombinant mouse 5-HT_{3A} receptors with even higher potency (IC_{50}=10 nM; [151, 152]) compared to recombinant human 5-HT_{3A} receptors (IC_{50}=680 nM; [153]). Binding studies revealed that clozapine displaced the selective competitive 5-HT_3 receptor antagonist [^{3}H] GR65630 from the 5-HT binding site with low to moderate affinity from human (K_i=3.6 μM; [153]) and murine 5-HT_{3A} receptors (K_i=100 nM; [152]). In line with such a competitive antagonistic action, the effect of clozapine is mainly reflected by the reduction of the peak current, comparable to the effect of the competitive 5-HT_3 receptor antagonist ondansetron. The pronounced discrepancy between the lower binding affinity and potent antagonism against cation currents for human and murine 5-HT_3 receptors is difficult to interpret solely by a competitive mechanism of action of clozapine. It is likely that clozapine interacts also allosterically with the 5-HT_3 receptor. Evidence for this hypothesis is provided by studies on the colocalization of antipsychotics with 5-HT_3 receptors in

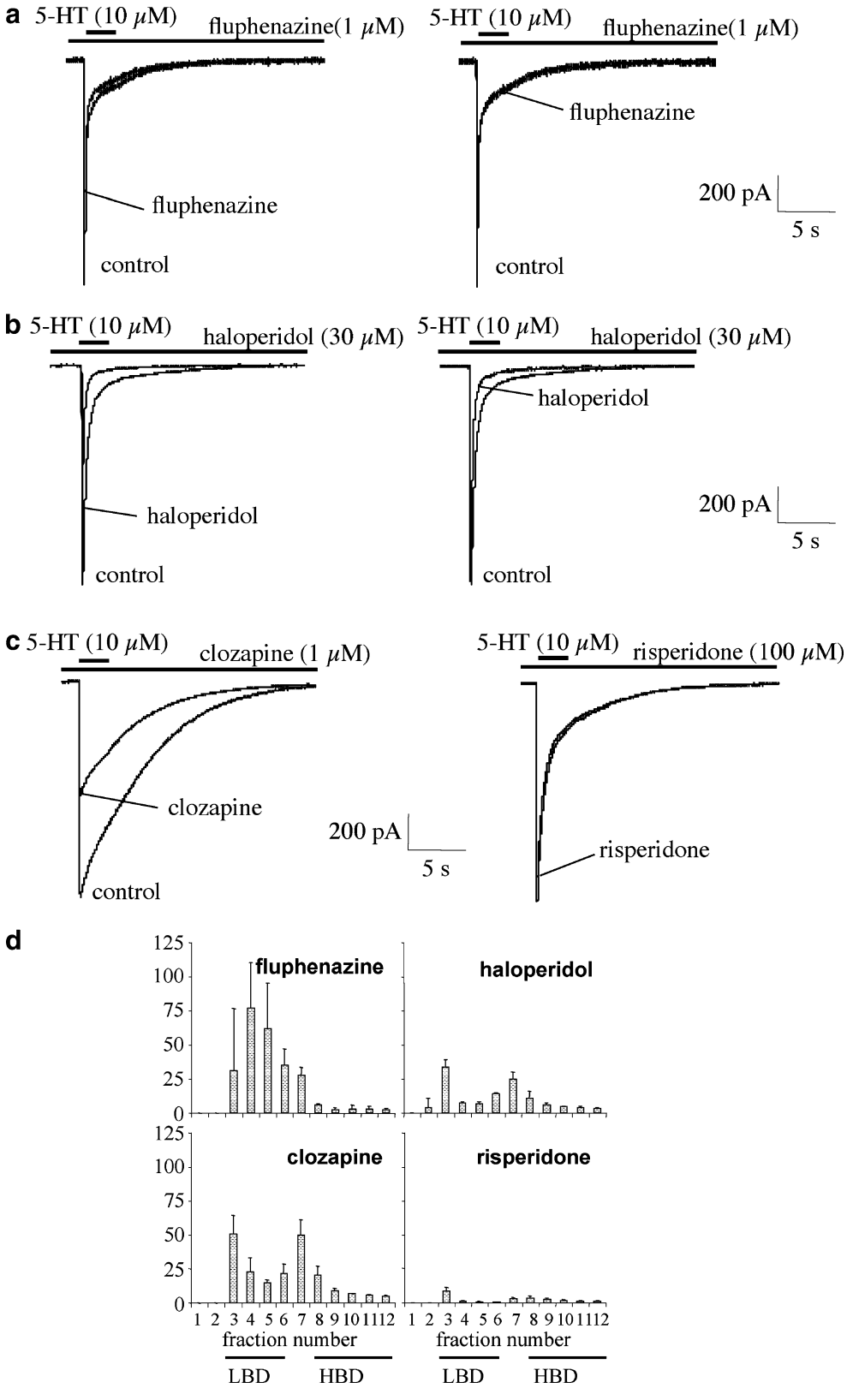

Fig. 2 Effects of different types of antipsychotics on the 5-HT-evoked Na^+ current in HEK-5-HT_{3A} cells. Representative recordings of 5-HT-evoked Na^+ currents after application of fluphenazine (**a**), haloperidol (**b**), clozapine (**c**, left), and risperidone (**c**, right). Left panels represent the original traces. To delineate effects of neuroleptics on the kinetics of 5-HT-evoked Na^+ current, the reduced peak amplitude was adjusted to the control peak (right panels). The upper bar indicates the application of 10 μM 5-HT; the lower bar indicates the presence of the respective neuroleptics at their IC_{50} concentration, with the exception of risperidone, where 100 μM were used. **d** Concentration of the same antipsychotics in low buoyant density and high buoyant density fractions of HEK-5-HT_{3A} cells. Sucrose density fractions were prepared as described in [52]. Drug concentrations were determined by high-performance liquid chromatography. Results are expressed as specific concentrations (μmol/mg protein) and represent the mean±SD of four independent experiments. Fractions 3–6 represent low buoyant density fractions; fractions 8–12 represent high buoyant density fractions. The figure subpanels were modified according to [52]

raft-like domains. When considering the competitive antagonists mirtazapine and clozapine, only clozapine is enriched in low buoyant density fractions, whereas mirtazapine is not. This would be compatible with the idea that mirtazapine acts solely as a competitive antagonist at the 5-HT_3 receptor, whereas clozapine, in view of its relatively low binding affinity, might act as a simultaneous competitive and noncompetitive antagonist.

A noncompetitive antagonism against endogenous neuronal 5-HT_3 receptors and human 5-HT_{3A} receptors stably expressed in HEK-293 cells has also been found for other antipsychotics. Flupentixol, fluphenazine, thioridazine, levomepromazine, and haloperidol, but not risperidone, reduced voltage-independent Na^+ and Ca^{2+} currents in micromolar concentrations [153]. The usage of flupentixol and fluphenazine analogs showed that the lipophilic side chain may play a role for a potent antagonism against Na^+ and Ca^{2+} currents. In contrast to antidepressants, fluphenazine and haloperidol affected membrane anisotropy at concentrations below their IC_{50} values, indicating that a change in membrane anisotropy might contribute to their antagonistic effect at the 5-HT_3 receptor. The inhibitory potency against 5-HT-induced cation currents was strongly correlated with the concentrations of psychopharmacological drugs within raft-like domains [52] (Fig. 2). Risperidone, which is devoid of antagonistic properties at this LGIC [153], is not accumulated in these membrane microdomains (Fig. 2). In conclusion, as it has been demonstrated for antidepressants, only those antipsychotics, which reach substantial concentrations within lipid rafts, are capable to act as noncompetitive functional antagonists at the 5-HT_3 receptor [52].

The inhibitory effects of neuroleptics at 5-HT_3 receptors might contribute to the antipsychotic potential of these compounds, as 5-HT_3 receptor antagonists reduce dopaminergic neurotransmission (for review, see, [41]). Indeed, first clinical investigations suggested an anxiolytic and antipsychotic potency of specific 5-HT_3 receptor antagonists [35, 143, 144]. However, systematic clinical studies could not demonstrate sufficient antipsychotic effects of selective 5-HT_3 receptor antagonists in schizophrenia [91, 143, 144, 154]. Nevertheless, the 5-HT_3 receptor antagonistic properties might contribute to the pharmacological profile of distinct neuroleptics.

nACh Receptors

Several recent findings suggest that nAChR system abnormalities are responsible for a number of schizophrenia-related neurophysiological deficits [155–157] and that the expression of α7 receptor is decreased in schizophrenia. Moreover, nAChRs are located on cell bodies and terminals of the hippocampal NE pathway [158] and the nigrostriatal DA pathway [159], which are brain regions involved in the pathophysiology of schizophrenia.

An interference of antipsychotics with nAChR has been shown only for chlorpromazine [160] in patch-clamp recordings of a mouse muscle cell line. Chlorpromazine noncompetitively decreased the mean channel open time of the nAChR in a concentration- and voltage-dependent manner. This pharmacological effect of chlorpromazine argues in favor of an open-channel block and supports the notion that chlorpromazine binds to a site within the nAChR ionic channel.

Conclusion

Both antidepressants and antipsychotics may modulate the function of various LGICs via direct and/or indirect mechanisms. Moreover, they may regulate the expression of distinct subunits of these neurotransmitter receptors. These largely unknown mechanisms of action orchestrate a much more complex picture of the pharmacological profile of these psychopharmacological agents than would be obtained by focusing only on their classical mechanisms of action. It has to clarified in the future whether the effects of antidepressants and antipsychotics on LGICs are of clinical relevance in that they may contribute to the therapeutic efficacy of these drugs. In addition, such effects may also help to explain the side effect profile of these compounds, e.g., the enhancement of seizure liability by antidepressants or antipsychotics. Finally, it has to be determined whether the accumulation of these drugs in raft-like domains and the modulation of LGICs may also help to identify novel psychopharmacological agents with a pharmacological profile distinct from that of already known antidepressants and antipsychotics.

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