An intercalation mechanism as a mode of action exerted by psychotropic drugs: results of altered phospholipid substrate availabilities in membranes?

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Abstract Patients respond differently to psychotropic drugs, and this is currently a controversial theme among psychiatrists. The effects of 16 psychotropics on cell membrane parameters have been reported. These drugs belong to three major groups used in therapeutic psychiatry: antipsychotics, antidepressants, and anxiolytic/hypnotics. Human platelets, lacking dopamine (D₂) receptors (proposed targets of most psychotropics), have been used as a cell model. Here we discuss the effects of these drugs on three metabolic phenomena and also results from Langmuir experiments. Diazepam, in contrast to the remaining drugs, had negligible effects on metabolic phenomena and had no effects in Langmuir experiments. Psychotropic drugs may work through intercalation in membrane phospholipids. It is possible that the fluidity of membranes, rich in essential fatty acids, the content being influenced by diet, could be a contributing factor to the action of psychotropics. This might in turn explain the observed major differences in therapeutic response among patients.

Keywords Human platelets · Psychotropic drugs · Cholesterol · PUFAs · NSAIDs · PLA₂ · PPI cycle · MLC · Solid-state NMR · PET · fMRI · SPECT

Classification: membrane-active psychotropics

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Abbreviations

AA	arachidonic acid
AMI	amitriptyline
ASA	acetyl salicylic acid
BDs	benzodiazapines
BDR	benzodiazepine receptor
CAT	computed axial tomography
CLO	clozapine
CNS	central nervous system
cPLA ₂	cytosolic phospholipase A ₂
CPZ	chlorpromazine
CTM	citalopram
DMSO	dimethylsulfoxide
DPPC	1,2 dipalmitoyl phosphatidylcholine
DPPS	1,2 dipalmitoyl phosphatidylserine
DZP	diazepam
EPS	extra pyramidal side effect
GABA	gamma amino butyric acid
GFP	gel-filtered platelets
HPD	haloperidol
H _{II}	inverted hexagonal phase
IMI	imipramine
MLC	myosin light chain
MLCK	myosin light chain kinase
mma	mean molecular area [Å ²]
MRI	magnetic resonance imaging
NE	norepinephrine
NSAID	non-steroidal anti-inflammatory drugs
OLP	olanzapine
PA	phosphatidic acid
PC	phosphatidylcholine
PE	phosphatidylethanolamine
PG	phosphatidylglycerol
PET	positron emission tomography
PS	phosphatidylserine

PCP	prochlorperazine
PI	phosphatidylinositol
PIP	phosphatidylinositol-4-phosphate
PIP ₂	phosphatidylinositol-4,5-bisphosphate
PKC	protein kinase C
PLA ₂	phospholipase A ₂
PLC	phospholipase C
PMZ	pimozide
PPI	polyphosphoinositide
PRP	platelet-rich plasma
PUFAs	poly-unsaturated fatty acids
QTP	quetiapine
RSP	risperidone
sPLA ₂	secretory phospholipase A ₂
SPECT	single photon emission computed tomography
SSRI	selective serotonin re-uptake inhibitor
TFP	trifluoperazine
ZIP	ziprasidone

Introduction

Amphiphilic preparations like psychotropic drugs and anesthetics intercalate in the membranous phospholipid bilayer of mammalian cells such as neurons. This phenomenon causes metabolic changes in the cells, firstly, by disturbing the alignment of integral receptor-proteins, via altering the potency of signaling cascades which in turn leads to deviation of the anticipated response, and secondly, by changing the activity of membrane-associated enzymes via altering the availability of their substrates. Human cells have many such enzymes, e.g. PLC, PLD, and PLA₂. According to the membrane-pacemaker theory, membrane fluidity is necessary for normal physiological function which is dependent on an abundance of dietary poly-unsaturated fatty acids (PUFAs). Amphiphilic psychotropics have a tendency to interact electrostatically with acidic glycerophospholipid sn-2 fatty acids, which are usually unsaturated and normally of the essential type and thus affect membrane dynamics.

The therapeutic efficiency of psychotropic drugs is thus influenced by the level of PUFAs especially in the neuronal membrane. Here we review different aspects of membrane function and integrity in relation to the use of psychotropic drugs in psychiatric diseases.

Prelude to human psychiatric disorders

Recent studies have shown that many psychiatric diseases are actually accompanied with abnormalities of the brain, and some somatic diseases are affected seriously by psychological factors. “Psychiatric disorders have been considered as mental rather than physical illnesses, because

they manifest with disordered psychological functioning in the areas of emotion, perception, thinking, and memory, and/or have no established biological basis” [15]. There are today two main methods used to classify psychiatric disorders in medical practice, that is the American Psychiatric Association’s Diagnostic and Statistical Manual (4th edition), or DSM-IV, and the World Health Organization’s International Classification of Disease (10th edition), ICD-10. These two systems are actually very similar, but ICD-10 is more widely applied outside of the USA.

Epidemiology of psychiatric disorders

Psychiatric disorders are among the most prevalent human illnesses in medical practice in western societies, including Scandinavia. In general, depression, anxiety, and adjustment disorders are the most common (10%) and psychosis is rare (less than 1%). In general hospitals, organic disorders such as delirium (10% in the elderly) are especially common; however, in specialist psychiatric services, psychoses are among the most common disorders seen [15]. An American study aided by statistical data estimated via the National Co-morbidity Survey of psychiatric disorders showed that the most common disorders were major depressive episodes, alcohol dependence, social phobia, and simple phobia [92]. In a similar Norwegian study taking into consideration the socio-economical factors and the difference of life style between rural and urban areas as a predisposing factor to the etiology, one could show that the prevalence of mental disorders was considerably lower in rural areas than in the cities. However, the same basic pattern of mental illness was observed, with alcohol abuse/dependence and major depression being the most common disorders on both sides. The gender pattern showed higher values for women in both rural and urban citizens, except that alcohol and drug abuse was higher in men [95].

Etiology of psychiatric disorders

The etiology of psychiatric disorders is actually multifactorial, so it is difficult to focus on a single factor to be the underlying cause for a certain psychiatric case. It is therefore fair to look at the etiology of these debilitating illnesses from all aspects because many factors go hand in hand to result in the basic cause of these disorders. Most of these are biological factors, and some of them are presented here briefly, because they are of relevance to this review.

• Genetic factors

Genes are a causal factor in many psychiatric disorders, including schizophrenia [30, 31, 86, 94] and bipolar affective disorders [122, 164]; major depressions [185,

[192], phobias, and anxiety neurosis [163, 167]. In psychiatric disorders multiple genes are involved.

- Brain structure and function

In psychiatric disorders, brain structure, as a rule, appears normal, although one can see generalized atrophy in Alzheimer's disease and enlarged ventricles in schizophrenia. In patients with affective disorders, magnetic resonance imaging (MRI) findings have indicated an increased ventricle/brain ratio and other signs of cerebral atrophy, as well as an increased frequency of so-called "signal hyper-intensity lesions" in the brains of unipolar and bipolar patients [181]. Positron emission tomography (PET) studies in major depressive disorders have shown reduced blood flow and metabolism in the prefrontal cerebral cortex of patients who exhibit psychomotor retardation, similar abnormalities are found in the anterior cingulate gyrus and the basal ganglia [182]. Diffusion tensor imaging investigations in schizophrenia have demonstrated the presence of several major white matter tracts in the brain compared to brains of healthy controls. These changes are due to a demyelination process affecting the white matter of the brain [152]. Other studies have shown that induction of the demyelination process in rat brain could be stopped by chronic administration of quetiapine (QTP; a second generation antipsychotic drug) [188]. This observation can give an indication of the effect of antipsychotic drugs on brain lipids. Our results in [131] both confirm and strengthen these findings, in that QTP and all other antipsychotics and antidepressants investigated, caused as inhibition of cPLA₂ in platelets. Cerebral white matter demyelination was also observed in the depressive phase of multiple sclerosis [60]. In another study, computed axial tomography (CAT) revealed the existence of extensive lesions in the white matter and cerebral atrophy in depressive patients due to the demyelination process [109]. Reduction in the gray matter (neuronal somal size) of different areas of the cerebral cortex has been demonstrated using MRI studies in schizophrenic patients [16, 32, 136]. Brain function is commonly altered; there may be changes in the level of neurotransmitters, such as dopamine, norepinephrine, and 5-hydroxytryptamine (serotonin) [53]. A recent review demonstrates the existence of interactions (interplay) between serotonin and dopamine both at anatomical and functional levels [186]. Consequences of brain damage as a result of head injury [12, 56, 68, 142] and inflammation [84, 110, 189, 191] which can cause changes in brain structure and function, may thus contribute to psychiatric illness. Other modern techniques in radiology have shown differences in regional activity of the brain e.g. single photon emission computerized tomography [124, 150, 168, 183] and functional magnetic resonance imaging scans [33, 35, 88, 96]. PET is one of the new methods to study the binding of compounds including psychotropic drugs to dopamine and

serotonin receptors of interest in biological psychiatry [64, 121]. PET is a useful tool to investigate schizophrenia [17, 133] or predict those who are prone to get the disease because of high genetic risk by studying the receptor status and comparing them to healthy controls [98]. Compared to controls, there is a loss of symmetry in D₂ receptors in the putamen of those at increased risk of schizophrenia.

- Influence of dietary fatty acids

An important role for dietary fats in mental diseases is becoming obvious. The relationship between food, mood, and behavior is documented [36]. Persistent negative correlations between high n-3 PUFA consumption and depression have been shown by large-scale population studies [73, 155, 172, 173]. Low n-3 PUFA levels and low n-3/n-6 ratios in plasma have been shown in patients with depressive disorders [176]. In the literature one can find numerous studies reporting lower levels of n-3 and n-6 PUFAs in membrane phospholipids of people suffering depression and schizophrenia (see Table 1 in [55]). These deficiencies were primarily observed in erythrocyte membranes [135] although adipose tissue of depressed subjects [114] as well as phospholipids of post-mortem brain samples of schizophrenics have shown similar deficiencies [190].

- Mitochondrial dysfunction

Mitochondria are the organelles where important steps of fatty acid metabolism are carried out. The process of oxidative phosphorylation cannot be performed in these subcellular organelles without having sound structure and function, which insures normal neuronal function. There is evidence showing that many depressive patients have dysfunctional mitochondria [59, 93]. Mitochondrial dysfunction in schizophrenia has in fact been known since 1954 [171]. This malfunction was judged to be a part of the pathophysiology behind schizophrenia [10]. Alterations in several metabolic pathways in the brains of schizophrenic patients leading to decrease of carbohydrate and lipid biosynthesis were involved in myelin degradation in the white matter of these patients [140].

- Abnormal phospholipid turnover rate

Patients with psychosis and depression are among the patient groups that have disturbances in the balance of membrane lipid metabolism, that is to say phospholipids, and this is mainly due to overactivity of neuronal phospholipases. Phospholipase A₂ with its two major forms (cytosolic and secretory) has been suggested to be the cause of these disturbances. Abundant references are available in the medical literature proving this statement [5, 13, 128, 144]. As a matter of fact the cornerstone of this review is where the effects of psychotropic drugs on the structure and metabolism of membrane glycerophospholipids was studied

[130–132]. The integrity of these phospholipids through inhibition of the function of phospholipase A₂ (c PLA₂) is thoroughly discussed in [131].

Treatment of psychiatric disorders

The multifactorial origin of the majority of psychiatric disorders means that there are multiple targets that should be considered in their treatment. Many forms of interventions are available in the treatment of psychiatric disorders; the most important are the biological forms, which include the psychotropic drugs (drug treatment) and electro-convulsive therapy, drug treatment is discussed briefly here:

- Antipsychotic agents

The term “psychosis” denotes a variety of mental disorders of which schizophrenia is a particular category, where the patient has a clear sensorium but has a marked thinking disturbance [90]. In the psychotic state, the patients lose some of their reality testing ability. They may suffer from hallucinations and/or illusions, and besides there may be a tendency towards the more bizarre manifestations of psychiatric disturbances as a common finding [184]. Antipsychotic drugs have been used in medicine for more than 50 years. Reserpine and chlorpromazine were the first drugs found to be effective in schizophrenia. Although phenothiazines are still sometimes used for the treatment of psychoses, many new agents are more tolerable and have replaced these forerunner drugs [90]. Antipsychotic drugs can cause different clinical effects such as:

1. Sedation of psychomotor agitation and aggressiveness in psychotic patients.
2. Reduction of hallucinations and abnormal insights or terminate them.
3. They activate chronic asthenic schizophrenic patients.
4. They can cause different neurological side effects like Parkinsonism.
5. They can cause different endocrinological disturbances.

Because of the above-mentioned, it is very difficult to give a precise and short definition of the word “antipsychotic drug” [105].

- Antidepressant drugs

Depression is the state of sustained depressed disturbance of mood that needs therapy to avoid serious consequences like mental and functional disabilities, melancholia, and suicides [15]. The first demonstration of the euphoriant effect of a drug was isoniazide (INAH), an antibiotic used to treat tuberculosis. Since then a large number of monoamine oxidase inhibitors (MAOI) have been developed [165, 184]. Monoamine oxidase inhibitors are now

rarely prescribed in many countries because of their dangerous interactions with drugs like amphetamine and foods rich in tyramine such as cheese and red wine. MAOI drugs can cause an accumulation of amines in the systemic circulation potentially causing a fatal hypertensive crisis [14, 15].

- Sedative drugs

Anxiety is the major symptom/sign in anxiety disorders. It is also a common coexisting feature in almost all psychiatric disorders like depression, bipolar disorders, and psychosis [105]. Anxiety is often clinically manifested via somatic symptoms and signs such as tachycardia/hypertension, palpitation, sweating, dryness of the mouth, dilated pupils, headaches, diarrhea/epigastric discomfort/nausea, and frequency of micturition [184]. Sedative drugs are usually prescribed to treat anxiety, with benzodiazepines being the main drug. Not all forms of anxiety respond efficiently to benzodiazepines. Antipsychotics and antidepressants also have a place in the treatment of anxiety, especially when comorbidities like depression and psychosis are coexisting [18].

Schizophrenia

This disease has an incidence of 0.85–1% in the western society, the prevalence is similar worldwide [15, 184]. It is a syndrome in which specific clinically recognizable psychological manifestations are found. Schizophrenics also have peculiar ways of thinking and behaving and perceive their environment in an abnormal way.

When the syndrome was described for the first time by Kräpelin in 1913, it was thought to be a sort of early onset of dementia and that is why it was given the name “Dementia Praecox”. The name schizophrenia was applied by Bleuler in 1950 [184].

According to M.C Sharpe and S.G Potts (chapter 10 in [15]), the disease is manifested clinically by two ranks of symptoms. The first is observed more obviously in acute attacks of the disease and these include:

- Auditory hallucinations, second or third person (écho de la pensée)
- Broadcasting, insertion/withdrawal of thoughts
- Controlled feelings, impulses, or acts (‘passivity’ experiences/phenomena)
- Delusional perceptions (a particular experience is bizarrely interpreted)

And the second are the negative symptoms including:

- Flattened or blunted affect
- Avolition, which is apathy and loss of drive
- Poverty of speech
- Poor self-care

Depression

Depression is a disorder in which the mood resembles sustained sadness or grief, unlike the transitory mood changes that many people experience in response to various forms of stress, or from one part of the day to another. The important thing here is that the grief or sadness is sustained and it exceeds the ordinary mood variation both quantitatively and qualitatively [15, 184]. Depression is a common disorder; in general practice consultation rates have been calculated at 31 per 1,000 for neurotic depression, while population surveys suggest even higher rates of up to 15%.

Anxiety

Anxiety is a universal phenomenon in which the subject experiences a feeling akin to fear or apprehension usually accompanied by autonomic disturbances (sympathetic overactivity). Morbid anxiety is different because it is a maladaptive response, and serves no useful purpose; it pervades the mental life of the individual and becomes a rein, not a spur. The patient knows that these fears are irrational and groundless but helplessly magnifies, scrutinizes, and mulls over the content of his or her anxiety [184].

Psychotropic drugs, target receptors, mechanism of action, and side effects

Three types of psychotropic drugs are discussed in this review, and these are antipsychotics, antidepressants, and anxiolytics.

Antipsychotic drugs

For more than 30 years ago it was recognized that diseases or drugs that increase dopamine production will enhance or produce positive psychotic symptoms. Stimulants like amphetamine and cocaine release dopamine. If these stimulants are taken repetitively, they can cause paranoid psychosis which may be difficult to distinguish from schizophrenia [7, 46, 63, 66]. Besides, all known antipsychotics capable of treating positive psychotic symptoms, are, in reality, blockers of dopamine receptors, particularly of the D₂ type [74, 120]. The affinity of antipsychotic drugs to dopamine receptors (D₂/D₃) has been confirmed by PET [91]. This is sometimes referred to as the dopamine hypothesis of schizophrenia. Antipsychotics are effective against positive psychotic symptoms in about 70% of patients within 6 weeks. Clozapine, however, has greater efficacy, the onset of action is gradual, over 1–2 weeks [69]. Antipsychotics are also used in the prevention of relapse of psychosis, in delirium tremens, and in psychotic depressions.

Classification of antipsychotic drugs

Antipsychotics (neuroleptics, also called major tranquilizers) are the mainstay of treatment for schizophrenia and all other psychoses. There are [two] main methods to classify antipsychotics; the first is to distinguish them into older typical (conventional) antipsychotics and the newer (atypical) ones. The basis for this classification is that the typical ones give obvious extra pyramidal side effects (EPS), while the atypical ones do so to a lesser degree, if at all within therapeutic doses. Clozapine is special here since it was the first atypical antipsychotic medicine that was known to have this property, namely not producing EPS [69]. These atypical drugs affect the dopaminergic system to a lesser extent than typical (conventional) antipsychotics and in addition inhibit serotonergic, muscarinic, histaminergic, and α_1 adrenergic receptors [27, 28, 154], where each agent has its own unique receptor profile. Atypical antipsychotic drugs have a more widespread and moderate impact on neurotransmitter systems and brain regions, and they offer some advantages over conventional (typical) drugs with lower EPS side effect profiles. Most of them show only transient prolactin elevation in contrast to typical (conventional) antipsychotic agents. We have to mention here also that these atypical drugs have been proven to be more effective in treatment of patients resistant to traditional (typical, conventional) agents [99]. The second form of classification is to group them into first and second generation antipsychotic drugs. This method of classification is currently in use in the medical literature because the first method (typical and atypical) is gradually losing ground. Haloperidol (HPD) belongs to the first generation or “typical neuroleptics”. According to many pharmacologists an older classification categorized neuroleptics into two major groups that is phenothiazine and non-phenothiazine neuroleptics, where HPD is not a phenothiazine compound therefore it was regarded as an atypical one (this is a matter of major controversy). The third and last method which is believed to solve all these controversial arguments about the form of classification is to classify them according to their chemical structure, thus avoiding the use of unnecessary nomenclature such as typical, atypical, first, and second terminologies. According to chemical structures, these agents are as follows: (a) Phenothiazine derivatives, (b) thioxanthene derivatives like thiothixene, (c) buterophenone derivatives like HPD, and (d) miscellaneous structures, including almost all the newer preparations including pimozide (PMZ) which is sometimes classified with the typical antipsychotics [90]. The classification system for the neuroleptics included here is a sort of adaption of all these three methods rather than use of first and second generation antipsychotics in order to avoid complications. The major issue here is that all antipsych-

chotics (as mentioned in “**Antipsychotic drugs**”) work primarily by blocking D₂ dopamine receptors. This reverses the excessive dopamine activity in the mesolimbic system that is thought to cause symptoms of psychosis. The D₂ receptor blockade also contributes, along with antagonism at other receptors, to their side effects.

Typical antipsychotic drugs (first generation) included in this review are:

1. Phenothiazines (chlorpromazine, trifluoperazine, prochlorperazine, and promethazine).
2. Buterophenones (haloperidol)
3. Diphenylbutylpiperidines (pimozide)

Atypical antipsychotic (second generation) drugs are:

1. Benzisoxazole (risperidone and ziprasidone)
2. Dibenzodiazepines (quetiapine and clozapine)
3. Thienobenzodiazepines (olanzapine)

Side effects of (typical, conventional, or first generation) antipsychotics

These are many and serious [69]. Their prevalence and severity varies from one drug to another, depending on their pharmacological profile.

Extrapyramidal side-effects are a major problem. EPS are motor abnormalities related to the dopaminergic receptor blockade in the basal ganglia. They are four types:

1. *Acute dystonia*
2. *Parkinsonism*
3. *Acathisia (akathisia)*
4. *Tardive dyskinesia*

Other side effects Electrocardiography changes and neuroleptic malignant syndrome.

Atypical antipsychotic drugs (second generation), advantages and disadvantages

Atypical antipsychotics are increasingly being used as first-line agents instead of the conventional drugs because of several probable advantages like long-term efficacy, fewer EPS side effects, greater overall tolerability, possible higher efficacy against depressive symptoms, and more greater against cognitive symptoms. We have to bear in mind their potential side effects [69] like:

1. Weight gain
2. Development of type II diabetes
3. Increased risk of a stroke
4. Agranulocytosis (clozapine)

Regarding clozapine, which is considered by some psychopharmacologists as a drug class in itself [165], it should be reserved for schizophrenic patients who have not responded to, or do not tolerate at least two other neuroleptics. Regular blood screening for white cell count could be mandatory to avoid this disastrous adverse effect which can be encountered with the administration of this “so called” second generation or atypical antipsychotic agent [69]. This illustrates the importance of developing new drugs to avoid such undesired effects, as suggested in this review.

Antidepressants

Antidepressants are effective drugs to treat depression as a first-line measure. Some of these drugs are also used to treat other disorders, especially selective serotonin reuptake inhibitor (SSRI) preparations [2, 3, 157]. The efficacy of antidepressants is documented and established. Sixty percent of the patients for whom tricyclic antidepressants (TCA) and SSRI have been prescribed drugs respond to the drug therapy after about 6 weeks, while 30–40% over the same period respond to placebo [69]. Antidepressants either cause down-regulation of key neurotransmitter receptors or they preserve the neurotransmitters from degradation or re-uptake from the receptors of post-synaptic junctions in the brain. The time course of doing so determines the onset of action of these agents. This fact might be the reason behind why antidepressants need 4–6 weeks to start induction of their therapeutic action. Besides, the patient needs many months for full recovery, that is, almost 6 months continuous therapy is recommended after the depressive symptoms have subsided. The benefit of the prolonged course is to decrease the chances of relapse [69]. So the situation in depression is that the neurotransmitter is depleted and as a compensation and consequence, then post-synaptic receptors are up-regulated [165]. So the strategy in the treatment of depression is to boost the neurotransmitters by mono amino oxidase inhibition, or by blocking re-uptake pumps for monoamine neurotransmitters (serotonin). This results in the down-regulation of post-synaptic neurotransmitter receptors with a delayed time course, more closely related to the timing of recovery from depression. This also explains why most antidepressants usually do not exert their action immediately. Up-regulation of three types of post-synaptic neuroreceptors has been thought to explain the biochemical basis of depression, and these are norepinephrine (NE), dopamine (DA), and serotonin (5HT). Each group of these receptors has its own neurotransmitter catecholamine (NE and DA)/indolamine (5HT) that attaches to them after they are released (exocytosed) from the pre-synaptic neurons. Noradrener-

gic receptors are of many subtypes but the most important in this respect are α_1 , α_2 , and β_1 . Concerning dopamine (D) receptors, a plethora of them actually exist and they play a role in many psychiatric diseases. They are of many subtypes and have several molecular isoforms like D₁, D₂, D₃, D₄, and D₅. That most extensively investigated is the D₂ receptor, as dopaminergic antagonists for treatment of Parkinson's disease, and blocked by dopamine antagonistic narcoleptics for the treatment of schizophrenia. Serotonergic receptors are also of many pharmacological subtypes. There are four major categories of serotonergic receptors, each further subtyped depending upon pharmacological or molecular properties, and they are 5HT_{1A}, 5HT_{1D}, 5HT_{2A}, 5HT_{2C}, 5HT₃, and 5HT₄. The most important of these is perhaps 5HT_{2A}, which is also called the 5HT₂ receptor [165].

Classification and side effects of antidepressants

Antidepressants are of four types:

1. Selective serotonin re-uptake inhibitors
2. Non-selective monoamine re-uptake inhibitors (tricyclic antidepressants)
3. Monoamine oxidase inhibitors
4. Others

Selective serotonin re-uptake inhibitors

They selectively inhibit synaptic 5-HT re-uptake transporters, thereby increasing the synaptic 5-HT concentration. This group is now considered as first-line antidepressants, compared to the tricyclic antidepressant, which was previously the main class used. SSRIs have several advantages, like practical usage (single daily dose) and they need a shorter period to induce their antidepressant efficacy [78]. They also have disadvantages, like abstinence after withdrawal of the drug (this should be therefore done gradually), they may increase seizures in epilepsy and there is some evidence that suggests a small increase in suicide risk with SSRI [54, 85, 137, 141].

Non-selective monoamine re-uptake inhibitors (tricyclic antidepressants)

Tricyclic antidepressant drugs still have an important role in drug treatment of depression, despite the overall advantages of SSRIs, and especially in people who are intolerant or unresponsive to SSRIs, besides they might have slightly greater efficacy in severe depression and could be used as an analgesic in the treatment of chronic pain [148]. They are referred to as heterocyclic antidepressants by some pharmacologists, simply because not all

of them have three rings in their chemical structures. Generally these medicines inhibit presynaptic NE and 5-HT transporters and unlike SSRIs they also block various receptors, contributing to their wide profile of side effects [165].

Human platelets

Human platelets, a mammalian cell model

Human platelets have long been thought to lack D₂ receptors [143], which are the primary target for antipsychotic drugs. However, it has recently been reported that human platelets contain D₂-like receptors that mediate potentiation of ADP-induced aggregation [149]. Therefore, if there is any effect induced, which modulates biological phenomena, then this could not be only due to these receptors. Human platelets are abundantly available following gel filtration of platelet-rich plasma obtained from hemochromatosis patients after therapeutic phlebotomy. They may serve as a probe to provide additional information on psychiatric diseases like schizophrenia [61]. See also the introduction in [132].

Effects of psychotropic drugs on human platelets

It is evident from the literature that the effects of psychotropic drugs have been studied by many groups, both in human platelets and other cells [42, 62, 100, 123, 147, 166]. Many groups studied the effects of psychotropic agents on mammalian platelets [100] and human platelets before 1984 [147, 166]. Others investigated the effects of psychotropic agents (antidepressants in particular) on serotonin transport in human platelets, which is reviewed, in more detail in paper [132]. Our group was one of the pioneers in investigating the effects of these psychoactive drugs in human platelets. The work was initiated by Holmsen et al. in 1984 [76] when they observed that TFP reduces liberation of [³H]arachidonate and reduces myosin light chain (MLC) phosphorylation in thrombin-activated human platelets. Later, Tysnes et al. [180] found that CPZ disturbs the physiological PPI metabolic pathway in thrombin-stimulated human platelets labeled with [³²P] orthophosphate. Then Tharmapathy et al. examined the effects of cationic amphiphilic drugs on human platelets, where they studied the dose-dependent effects of eight cationic amphiphilic drugs on human platelets activated by (0.2 U/ml) thrombin. They found that at concentrations below 25 μ M, the drugs simulated secretory responses, while at concentration in the ranges of 25–50 μ M they inhibited these responses. At concentrations above (50–100 μ M) the same drugs

caused permeabilization of the platelet plasma membrane [174]. The same group noticed the stimulatory effects of venlafaxine on routine centrifugation of platelet-rich plasma, thus they could determine an important cause for contraindication of venlafaxine in acute myocardial infarction and acute cerebrovascular accidents [175].

Antidepressants and serotonin uptake by platelets

Platelets from most mammalian species, including man, effectively transport serotonin across the plasma membrane and store the amine in the dense granules [39]. The plasma membrane uptake requires extracellular anions, particularly chloride [102, 106–108], and has since 1960 been known to be inhibited by tricyclic antidepressants, such as IMI [116]. Later, other antidepressants such as amitriptyline (AMI) [38], nucleotide triphosphate (NTP) [113], and citalopram (CTM) [1] (which have been used in the papers cited in the present review) and many other drugs have also been shown to inhibit serotonin uptake in platelets. The uptake of serotonin by human platelets follows Michaelis–Menten kinetics and the inhibition by most antidepressants, except clomipramine, is competitive [103]. However, the mechanism of inhibition is not clear, as some studies find no correlation between binding of radiolabelled imipramine and serotonin uptake in human platelets [187], while others find a good correlation [146]. Thus, it is uncertain whether at least IMI inhibits serotonin uptake by binding to the serotonin transporter. Findings in the papers discussed in this review show that IMI powerfully distorts the structure of phosphatidyl serine monolayers [131], suggesting that alterations in the plasma membrane structure may be part of the inhibitory mechanism.

Biomembranes

Phospholipids

Phospholipids play a critical role in membrane structure and function. The ability of these lipids to assemble non-covalently into bilayers is due to their amphiphilic character. They have a polar region that is hydrophilic and orients towards the aqueous phase, and a non-polar hydrophobic region that avoids contact with water and forms the inner part of the bilayer. In addition to forming a permeability barrier between two aqueous environments, the lipidic bilayer also functions as a matrix for integral proteins and peripheral proteins. They are particularly important in signal transduction by receptor-mediated phospholipid-derived second messengers such as arachidonic acid (AA), diacylglycerol (DAG), inositol polyphosphates, and prostaglandins. The importance of phospholipids in biological processes is manifested by the

diversity of the lipid composition in membranes of different tissues and organelles.

Lipid composition

The lipid composition of biological membranes of cells is both complex and constant, reflecting the importance of lipid complexity in the cell. According to their chemical nature, membrane lipids can be classified into two major groups. One group that consists of open-chain compounds with polar head groups and long non-polar tails includes sphingolipids and glycerophospholipids. The second major group consists of fused-ring compounds, the steroids. An important representative of this group is cholesterol. The most abundant of the polar lipids, are the 1,2-diacylphosphoglycerolipids (phospholipids). These have a polar alcohol attached to C-3 of glycerol through a phosphodiester bond and two fatty acids that are ester-linked in the C-1 and C-2 positions. All glycerophospholipids are derivatives of phosphatidic acid (PA) and are named according to their polar head groups. The major classes are: phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylinositol (PI), and phosphatidylserine (PS). At pH 7, PA, PG, PI, and PS are negatively charged (-2 , -1 , -1 , and -1 , respectively) while PC and PE have a net zero charge (zwitterions; see Fig. 1).

Lipid distribution and symmetry

Membrane lipids show non-random distributions between and within organelles [77, 145, 151, 193]. The mammalian plasma membrane is rich in cholesterol, sphingolipids, and saturated glycerolipids, which, due to their high packing densities, promote bilayer rigidity and impermeability [77]. In addition, the biological membranes have an asymmetric lipid arrangement [145]. The external leaflet of the plasma membrane is enriched in choline-containing lipids, PC, and sphingomyelin (SM). The amine-containing phospholipids, PE and PS, are located preferentially on the cytoplasmic leaflet. In addition, phospholipids such as PA, PI, phosphatidylinositol-4-monophosphate (PIP), and phosphatidylinositol-4, 5-bisphosphate (PIP₂) are also enriched on the cytofacial side of the membrane. Some mammalian cell membranes such as, those of the erythrocyte membrane, is well characterized with respect to lipid asymmetry. For example, it has been shown that the outer leaflet of this membrane contains 75–80% of PC and SM, 20% of PE, PA, PI, and PIP₂, and no detectable PS or PIP [21, 26, 129, 145]. The maintenance of transbilayer lipid asymmetry is essential for normal membrane function, and disruption of this asymmetry is associated with cell activation or promotion of diseases. It is the selective

Fig. 1 Formulas of PS, PE, PC, PI, PG, and PA. These are 1, 2-diacylphosphoglycerolipids (phospholipids), in which the hydrophobic regions are composed of two fatty acids in C-1 and C-2 positions and an esterified phosphate group in C-3 position joined to a glycerol backbone. Phospholipids are divided into two groups (acidic and neutral) depending on the chemical group bound to the phosphate in the third position. At pH 7.4, PC and PE are neutral while PS, PI, PA, and PG are negatively charged

synthesis of different phospholipid species for each leaflet of the cell membrane that keeps the turnover of this asymmetry. While lipids can move freely within the same plane of the bilayer, their movement from one leaflet to another (“flip-flop”) is thermodynamically restricted. There are three known groups of enzymes that catalyze this sort of movement, the first is scramblase, a calcium-dependent enzyme, which has a bidirectional function [4, 81] (see Fig. 2), the second is flippase which has cytofacially directed function and it is ATP dependent, and the third is floppase, this has an exofacially directed function and again it is an ATP-dependent protein [40]. As we have stated above, the asymmetric distribution is a central part of normal cell function. It is vital for processes such as

intracellular fusion, exocytosis, phospholipid–protein interactions, and signal transduction pathways [89]. However, cell activation or apoptosis may cause the lipid asymmetry to be perturbed by a non-specific transfer of phospholipids between the two layers, exposing more PS in the external leaflet [195].

Molecular species of phospholipids

In a given type of cell, membrane phospholipids may account for more than 1,000 molecular species according to variability of the two fatty acids bound in the *sn*-1 and *sn*-2 positions of the glycerol backbone [79]. The fatty acid in the 1-position is usually saturated, whereas the one in the 2-

Fig. 2 A cartoon showing scramblase, adapted from H. A. Steinberg's molecular graphics

position is normally unsaturated (see Fig. 3). The chain length can vary between 14 and 24 carbons atoms, and can have up to six *cis* carbon–carbon double bonds. The enormous repertoire of membrane phospholipids indicates that systemic studies of lipids with well-defined compositions are thus relevant and important in describing and understanding the structure–function relationship of the lipid component in cell membranes.

Membrane fluidity

The membrane bilayer arrangement is held together by non-covalent interactions such as van der Waals forces and hydrophobic interactions. The arrangement of the hydrocarbon interior of the membrane bilayer can be ordered and rigid (gel phase) or disordered and fluid (liquid-crystalline phase). The fluidity of the membrane bilayer depends on its composition, that is, the fatty acid composition of diacylphosphoglycerols and cholesterol. In saturated fatty acids, a linear arrangement of the hydrocarbon chains leads to close packing of the molecules in the bilayer, and thus to rigidity. In unsaturated fatty acids there are kinks in the hydrocarbon chain at/around the *cis* double bonds. The kinks cause disorder in the packing of the chains with a more open structure than would be possible for straight saturated chains. The disordered structure, due to the presence of unsaturated fatty acids, causes greater fluidity in the bilayer. The fluidity of a cell membrane which is caused by the existence of PUFAs (n-3 and n-6) is

essential for normal functions of neurons and other cell types in the tissues of human organs. These functions include cell growth, solute transport, signal transduction and membrane-associated enzyme activities [52, 134, 170]. Membrane fluidity optimizes the metabolic rate within the cells, and by doing so contributes to the prevention of metabolic syndrome and mental diseases via the so called “membrane-pacemaker” theory of metabolism [82]. Each lipid has a specific transition temperature, T_i , that increases with alkyl chain length and decreases with the degree of unsaturation [79]. In addition to temperature, conditions such as level of hydration, pH, and electric field will affect phase transition [125]. The presence of cholesterol may also enhance the order and rigidity [65, 125]. The fused-ring structure of cholesterol stabilizes the extended straight-chain arrangements of saturated fatty acids by van der Waals interactions and lowers the chain orders near the lipid headgroup [6]. Cholesterol is the most studied sterol in models and natural membranes. As a matter of fact this lipid has a dual action to keep cell membranes in their normal physiological dynamic state, despite temperature changes within certain ranges. Membrane dynamics is a must for cellular life. There is an amazingly delicate balance between a loose fluid membrane causing great permeability and a rigid membrane forbidding any transfer across the bilayer. In other words cholesterol has an “ordering–disordering” action. This is best identified in model membranes, in its absence the membrane undergoes a phase transition from a fully rigid state (solid-ordered phase) at low temperature to a very fluid state (liquid-disordered phase) at high temperature [49].

Lipid polymorphism and membrane curvature

Fatty acids and lysophospholipids can adopt a micellar arrangement in an aqueous milieu, whereas phospholipids such as PC adopt the form of a bilayer. For instance, unsaturated phosphatidylethanolamine, which constitutes a significant proportion of membrane lipids, will in isolation adopt the inverted hexagonal phase (H_{II}). The H_{II} phase is promoted by increasing acyl chain unsaturation and increasing temperature [101]. Lysophospholipids, which

Fig. 3 Chemical structure of a membrane phospholipid with a 16:0 saturated fatty acid (R_1), in sn-2 position (R_2) 18:1 (unsaturated fatty acid). Phospholipids are divided into subgroups depending on the chemical group bound to the phosphate in the (R_3) position

have only one acyl chain, have a large head group area compared to the hydrocarbon area, and therefore comprise a cone-like geometry. These will self-assemble into micelles and thereby display positive membrane curvature. Cylindrically shaped lipids, having nearly equal headgroup to hydrocarbon area, will self-assemble into lipid bilayers. Lipids with small head group areas form “inverted” lipid phases such as an inverted (H_{II}) phase or cubic phases and therefore show negative membrane curvature. Hence, mixtures of micellar lipids and nonbilayer H_{II} phase-preferring lipids can adopt bilayer phases [75, 112]. The lipid phase behavior can be modulated by changes in hydration, state of ionization, presence of divalent cations, and temperature [45].

Lipid domains in biomembranes

Singer and Nicolson have proposed the fluid mosaic model of biomembranes, where integral transmembrane proteins float freely in the lateral plane of a “fluid” homogeneous sea of lipids [158]. In a controversial debate, the focus has changed towards a view in which membranes are not randomly distributed, but instead adopt local heterogeneity. Domains of laterally segregated lipid phases in the fluid matrix are known as “lipid rafts”. Relating to cell function, these domains are of great interest. Besides, it is currently understood that these submicroscopic domains (though not all) of rafts are depleted in unsaturated phospholipids and many transmembrane proteins. However, these domains are enriched in cholesterol, sphingolipids, and certain lipid-anchored proteins [24, 37]. It is well accepted that protein-stabilized membrane domains such as caveolae and clathrin-coated pits do exist in cell membranes. Nevertheless, the existence of lipid raft membrane domains in vivo remains controversial [51, 118, 119, 126, 156], despite successful reconstitution experiments in vitro [47, 111]. Micro-domain composition, size, and lifetime are questions that have still not been answered convincingly. In the literature one can find an increasing number of papers reporting an involvement of lipid rafts in a variety of membrane-mediated events including platelet activation [72], immune cell signaling [50], viral entry [115], and prion protein folding pathogenesis in neurons which causes Creutzfeld-Jacob disease (mad cow disease) [87].

Membrane lipids and cell signaling

When a transmitter, hormone, cytokine, or growth factor binds to a receptor on a neuron or any other cell type, it initiates a series of events described under the general term of cell signaling or signal transduction. The two main tasks of lipids are constitution of a membrane “scaffold” in which receptor and membrane proteins are embedded,

and secondly to participate directly in cell signaling. The latter signaling process usually involves activation via a G-protein/protein kinase mechanism of one or more phospholipases. Thus, membrane lipids play a crucial role in signal transduction, intracellular membrane trafficking, and control of cell growth and survival. The complexity is enormous and offers a range of opportunities for dysfunction.

Phosphoinositides

Phosphoinositides are involved in the regulation of cellular processes via receptor-mediated membrane signaling. These signal molecules affect the intracellular membrane trafficking, cytoskeletal regulation, cell growth, apoptosis, exocytosis, endocytosis, neuronal signaling, regulation of intracellular calcium, and cAMP concentrations as well as leptin intake [43, 117, 177, 178]. The most abundant phosphoinositide derivatives in mammalian cells are PIP and PIP₂. The latter is the source of three second messengers: inositol 1, 4, 5-*tris*phosphate, DAG, and phosphatidylinositol 3, 4, 5-*tris*phosphate, and is responsible for a wide range of membrane-related phenomena. Phosphatidylinositol phosphorylation is catalyzed by phosphoinositide kinases and phosphatidylinositol phosphate kinase, whereas the degradation is mediated by the lipid phosphatases.

Polyphosphoinositide metabolism

This cycle is one of the important metabolic pathways in mammalian cells including those of the brain and human platelets. The cycle starts with the phosphorylation of the 4-hydroxy group of PI by ATP catalyzed by PI 4-kinase and forming PIP. This phosphate, however, is split off by a phosphohydrolase. PIP is in turn phosphorylated in the 5-position by ATP, thus forming PIP₂, and this 5-phosphate is also split off by a phosphohydrolase. Thus, both PIP and PIP₂ exist in the cell as typical steady state levels and their monoester phosphate groups have high turnover. This cycle turns over slowly in non-stimulated platelets. It increases tremendously, however, when the platelets are activated with an agonist like thrombin for example. This cycle is explained in more detail in [130].

Phospholipase A₂ and arachidonate metabolism

Phospholipase A₂ belongs to a super family of enzymes catalyzing the cleavage of fatty acids in the sn-2 position of phospholipids [179]. Among more than 19 different isoforms of PLA₂ in the mammalian system, recent research has focused on group IV cytosolic PLA₂ (cPLA₂), group IIA secretory (sPLA₂), and group VI Ca²⁺-independent

PLA₂ (iPLA₂), which are involved in a complex network of signaling pathways like linking receptor agonists, oxidative, and proinflammatory agents to the release of AA and synthesis of eicosanoids. We have to mention here that all major groups of PLA₂ exist in the central nervous system (CNS). Information about the precise role of each one still needs to be investigated in detail [169]. In human platelets, several different forms of this enzyme have been detected and all found to mediate the release of arachidonic acid. For simplicity they are subdivided into two functional locations, that is secretory PLA₂ (s PLA₂; 13–17 Kd calcium-dependent protein) which is located in secretory (α -granules), secreted to the cell environment during activation and cytosolic PLA₂ (cPLA₂; 85 Kd protein) that is located in the cytosol and activated during platelet activation [57]. There exists another classification for these subdivisions, that is, according to their catalytic sites: histidine or serine [161].

Arachidonic acid is liberated from platelets upon stimulation of PLA₂ with an agonist like thrombin. It is the precursor for the biosynthesis of all eicosanoid messengers, i.e. prostaglandins, thromboxanes, leukotrienes, lipoxins, and hydroxyeicosatetraenoic acids [20, 58, 162]. Release of AA from membrane phospholipids makes it accessible for oxidative metabolism by several enzyme systems including cyclooxygenases, lipoxygenases, and cytochrome P450 enzymes [194]. Arachidonic acid and its metabolites play an important role in several biological processes such as inflammation, cellular proliferation, and intracellular signaling [20, 58, 162].

General discussion

In papers [130–132], 16 psychotropic drugs were tested in human platelets *in vitro*, as a human cell model, in order to study their effects on three biological phenomena (PLA₂ and AA metabolism, PPI cycle and MLC phosphorylation). The drugs were chosen from three different major groups; that is, to treat psychosis, depression, and anxiety. Many of these drugs are currently in therapeutic use in clinical psychiatry. Trifluoperazine (a typical antipsychotic and a major tranquilizer) is no longer used in Norway because of its very broad spectrum of side effects. All the 15 remaining drugs are currently in use here in this country; even so, the order of priority of use of these drugs is changing because an evaluation of advantages and disadvantages is being made. Serious side effects, encountered in clinical practice, observed by psychiatric health care staff, and also by the patients themselves, have encouraged drug design and psychopharmacological scientists to try to create better drugs with least possible side effects. The amphiphilic nature of many psychotropic drugs, like CPZ for example,

is because the chemical structure of this compound has two different moieties (see Fig. 4): the tricyclic hydrophobic ring which intercalates into the hydrophobic phase of the membrane bilayer system, while the hydrophilic tertiary propylamine tail (the hydrophilic moiety) interacts with the polar head group regions of the membrane bilayer [97]. The most obvious and common feature of these amphiphilic agents (psychotropic drugs) is their ability to cross the blood–brain barrier.

In [130], the effects of PCP, TFP, QTP, HPD, PMZ, and CLO on the PPI cycle were studied. All these drugs disturbed the normal PPI metabolism. Typical antipsychotic drugs (PCP, TFP, and HPD) are most effective, while PMZ and QTP were the least. This disturbance could reflect side effects or therapeutic action of these drugs or both. Those that disturbed the PPI cycle most also produced EPS side effects ranging from medium to very high. Apart from CPZ they have high clinical potency, low sedative action, and a low tendency to cause hypotension [90]. These drugs are generally potent agents (except CPZ) and have less selective receptor induced action therefore have more side effects of certain categories like EPS and endocrine side effects like elevation of prolactin [165]. More than this it might be difficult to generalize the findings of PPI cycle and Langmuir monolayer studies and correlate them to side effects or therapeutic actions spectra. What needs to be emphasized here is that the cationic amphiphiles that intercalate most are expected to alter the biophysical properties of biomembranes in such a way that they might soften the membrane, thus increase its fluctuation, and thereby disturb the normal membrane curvature (see Fig. 5). As an anticipated consequence, they cause disturbance of the normal three-dimensional spatial positions (alignment) of many receptor types leading to alteration of their availability to interact with their specific agonists (hormones, neurotransmitters etc.; see Fig. 6); consequently, leading to changes in normal functions of receptor-proteins [153] or probably inducing adverse effects, or both. Regarding chemical structures, these drugs are cationic amphiphiles (see Scheme 1), that is, they can intercalate in-between molecules of acidic glycerophospholipid to a high degree (see Fig. 5). This was also obvious in the Langmuir monolayer studies. In [132] the effects of the other five drugs on the PPI cycle were studied, these drugs were PRZ, CTM, ZIP, RSP, and DZP. All these drugs (apart from the anxiolytic/anticonvulsant DZP) also disturbed the normal pathway of the platelet PPI cycle. The disturbance was proportional with the degree of intercalation into the lipid monolayer investigated by the Langmuir mini-trough technique. So, the level of disturbance, arranged in decreasing ranking order for the drugs used was as following: PCP > TFP > PRZ > ZIP = RSP > CTM = HPD = PMZ > CLO > QTP > DZP = 0 [130, 132] (see Table 1).

Fig. 4 Chemical structure of chlorpromazine

If we take a close look at the ranking order we can understand why QTP (serequel) (the atypical, or second generation antipsychotic drug) which intercalates less than first generation antipsychotic agents, disturbs the spatial positioning of integral receptors less than typical or first generation antipsychotic agents, has low clinical potency, very low EPS toxicity, low-medium hypotensive action, and medium sedative action, that is, opposite to CPZ apart from that both have low clinical potency [90]. The situation for DZP is totally different, simply because this drug does not exert its effects through intercalation. It does so, most

Fig. 5 Substrate availability and membrane curvature disturbances as a result of intercalation of psychotropic drugs in the inner leaflet of the membrane phospholipid bilayer

Fig. 6 Schematic illustration of the possible mechanism of action of psychotropic drugs. This hypothesis implies that these drugs not necessarily only interact with receptor-protein, but may change the function of the receptor-protein indirectly by binding to and intercalating in the membrane that surrounds the receptors

Adapted from Anja Underhaug-Gjerde

probably, through a receptor-dependent mechanism. This is thoroughly discussed in [132].

Concerning PLA₂ and arachidonate metabolism, this was also inhibited to a greater extent by the drugs that intercalate to a high degree in the membrane phospholipids and cause the greatest increase in the mean molecular area (mma) of a pure acidic phospholipid monolayer. It was therefore expected that DZP would not cause any inhibition in the activity of a membrane-associated enzyme like cPLA₂, but interestingly it actually increased the activity of PLA₂ which was manifested by a significant increase in the amount of ³H labeled AA liberated (see Table 1). So if the inflammation theory of psychiatric disorders is true [9, 19, 23, 67, 191], especially the mild encephalitis hypothesis (the autoimmune mild encephalitis), then this explains the improvement of patients taking cyclooxygenase II blockers (Cox-II-blockers) [8]. In doing so, antipsy-

chotic and antidepressant agents which have been in use in work described in this review, all without exception, yet with different potencies, inhibited phospholipase A₂ in a way that might be similar to acetylsalicylic acid (ASA). NMR studies have shown that PLA₂ in vitro can be inhibited irreversibly by ASA, where the drug binds to the catalytic site of the enzyme [159]. Diazepam did not show this property, so according to these findings, and reviewing the results discussed in [131], we can say that DZP may contribute to the deterioration of the clinical picture in such situations. As a consequence, it should be avoided in the treatment of psychosis and depression at least as a sole drug of first-line treatment, simply because according to psychopharmacological knowledge, DZP is neither an antipsychotic nor an antidepressant when it is used alone. No clinical evidence exists today, however, to confirm these claims. In contrary DZP still has clear

Scheme 1 Chemical structures of the drugs

indications for use in clinical psychiatry, especially in the catatonic phases of schizophrenia [71, 80] and depression [83] besides its applications as an adjuvant to other antipsychotic drugs or alone [11, 29, 104, 138] to treat psychosis.

The decreasing ranking order of the drugs in PLA₂ inhibition was as follows: PCP > TFP > CPZ > NTP > PMZ > IMI > ZIP > CTM ≥ PRZ ≥ RSP ≥ AMI > HPD > QTP > OLP > CLO [131, 132] (see also Table 1).

The decrease was statistically significant with PCP, TFP, CPZ, NTP, PMZ, IMI, CTM, and RSP; while DZP in contradiction to all other drugs used caused a

significant increase in the activity of PLA₂ as mentioned above.

The calmodulin-dependent process of myosin light chain phosphorylation in thrombin-activated human platelets [41, 70] is also an important tool to study the difference in effects of psychotropic drugs on mammalian cells, including neurons. This biological phenomenon is not proportional to the degree of intercalation of psychotropic drugs into a membrane phospholipid bilayer. This is because the enzyme, which catalyzes the phosphorylation of MLC, is not membrane associated. MLC kinase exists in the cytoplasm and it does not translocate to the platelet

Table 1 Effects of 16 psychotropic drugs on PPI and PLA₂ metabolism in human platelets and their effects in Langmuir mini-trough studies

Drugs		PPI metabolism ^a (mean ranking order)	PLA ₂ metabolism ^b (%) decrease from control)	Langmuir ^c (PS) γ at 10mN/m (mma % increase above control)
CPZ	ND		25.3	30
TFP	5.0		22.1	31
PCP	6.0		13.6	27
HPD	3.0		81.8	41
PMZ	3.0		48.7	56
QTP	1.5		84.0	48
CLO	2.5		94.1	36
OLP	ND		92.1	31
NTP	ND		13.6	30
AMI	ND		77.3	40
IMI	ND		64.1	31
PRZ	4.0		76.73	154.6
ZIP	3.5		65.31	39.84
CTM	3.0		76.16	185.41
RSP	3.5		77.05	28.6
DZP	1.0		120.27	2.88

mma mean molecular area, γ surface tension, *mN/m* milli Newton per meter, *PS* phosphatidylserine, *PPI* polyphosphoinositide, *PLA₂* phospholipase A₂

^a Values for PCP, TFP, QTP, HPD, PMZ, and CLO were obtained from Table 1 [130] BBA biomembranes, and those for PRZ, CTM, DZP, ZIP, and RSP were taken from Table 1 [132] JOCB.

^b Values for QTP, CPZ, TFP, PCP, NTP, AMI, IMI, HPD, PMZ, CLO, and OLP were calculated from data presented in Fig. 3 [131] SMJ, and for PRZ, CTM, DZP, RSP, and ZIP from Fig. 2 [132] JOCB.

^c Values for NTP, AMI, IMI, OLP, CLO, PMZ, PCP, QTP, HPD, TFP, and CPZ were obtained from Table 1 [131] SMJ, and for PRZ, CTM, DZP, ZIP, and RSP from Table 2 [132] JOCB.

membrane following its activation, dissimilar to phospholipases [76]. It is important to mention that ZIP, PCP, CPZ, and NTP decreased the phosphorylation process significantly, while the remaining 12 drugs either decreased or increased it insignificantly.

The conclusion here is that phosphorylation of myosin light chain is not a committed process for psychotropic drugs to induce their therapeutic actions at the cellular level.

In the studies on surface pressure *mN/m*:(mma) [$\text{\AA}^2$] isotherms, using pure monolayer lipid species (neutral and acidic), it was shown that all amphiphilic psychotropic drugs increased the (mma) of acidic lipid monolayers using MilliQ H₂O as sub-phase at 37°C. The absolute lipophilic

drug DZP did not show this property, as this molecule has no cationic moiety to attach the negatively charged head groups of phospholipids (see Scheme 1).

Some lines of enquiry, as mentioned before, have indicated that schizophrenia may possibly be the result of an inflammatory process caused by a certain slow infective cerebral pathogenic virus, which induces encephalitis [8, 19, 23, 44, 67]. Considerable interest has been raised in this hypothesis and is strengthened by the finding that cerebral ventricular dilation has been shown by CAT and MRI scanning of the brain, as mentioned in “[Etiology of psychiatric disorders](#)”. The findings in [131] and [132] actually show that all psychotropic drugs (antipsychotic and antidepressant drugs) indeed inhibit the activity of cellular PLA₂ at different potencies, although they induce this action mainly on the cytosolic type. It is well known that increased PLA₂ is an important inflammatory parameter. Thus the action of psychotropics mimics the action of non-steroidal anti-inflammatory drugs (NSAID), which are the main line of treatment in almost all chronic inflammatory collagen diseases affecting human connective tissues like rheumatoid syndrome, Behçet’s disease etc. Therefore, by reduction of AA liberation via inhibition of PLA₂, psychoactive drugs (antidepressants and antipsychotics) oppose human platelet aggregation *in vitro* in a manner that might be similar to NSAIDs like ASA (acetyl salicylic acid), a cyclooxygenases inhibitor. Results of a recently published paper of a Polish group have shown that some psychoactive drugs actually do exhibit antiplatelet activity *in vitro* [48]. It has to be admitted, however, that there is no clear evidence up to the present day in the medical literature confirming that patients using psychotropic drugs are less prone to ischemic heart disease.

When psychotropic drugs intercalate in the cell membrane especially in between the molecules of the inner leaflet of the phospholipid bilayer, it changes the alignments of many receptors, including D₂ receptors (see Fig. 6), the proposed target for many psychotropic drugs. It should be emphasized here again that the intercalation theory does not exclude the role of receptor-mediated induction of the action of psychotropic drugs, but when the alignment of a receptor is disturbed or changed, then the signal transmitted by the first messenger (neurotransmitter for example) will be modified or altered [130–132, 180]. It is possible that this is the situation in neurons, and this could explain how psychotropic drugs induce their pharmacological action and/or their side effects. We say here side effects because disturbance of alignment does not only include D₂ receptors, but also others, which are nominally (theoretically) not responsible for causing a predisposition to psychiatric diseases.

It is important to discuss what is actually happening in the inner leaflet of the membrane.

All effects exerted by psychotropic drugs on the three metabolic processes, PPI cycle, PLA₂ metabolism, and MLC phosphorylation, were actually mainly through intercalation in the membrane lipid-bilayer in a receptor-independent mechanism. This observation was also confirmed by studying the effects of these drugs on pure lipid monolayer species (neutral and acidic) using the Langmuir technique. It has to be stressed here that intercalation does not exclude receptor-mediated action of psychotropic drugs. Diazepam (hypnotic/anxiolytic/anti-epileptic), for example, did not affect PPI cycle, PLA₂, and MLC phosphorylation in the same way as the antipsychotic and antidepressant drugs did [132]. The receptor-independent disturbance of these three metabolic phenomena can be explained by intercalation of these drugs mainly between molecules of membrane phospholipids especially in the inner leaflet of the phospholipid bilayer inducing a disturbance in membrane curvature and thus the substrate availability for the enzyme catalyzing these vital metabolic phenomena [22, 132] (see Fig. 5).

Conclusion and future perspectives

The work reviewed here contributes to an elucidation of the mechanism of action of psychotropic drugs at the cellular level. The data prove that the drugs studied affect the three above-mentioned metabolic phenomena (PPI cycle, PLA₂/arachidonate metabolism, and MLC phosphorylation) via intercalation into phospholipids of the inner leaflet of the cell membrane. Solid-state ¹³C- and ³¹P-NMR studies have disclosed the interaction between CPZ and PS liposomes at the atomic level where the positive charge in the CPZ tail amino group makes an ionic bond with the phosphate- and carboxyl groups of PS, while the tricyclic lipophilic phenothiazine moiety is embedded among the acyl groups [34, 127]. It has also been proposed that the therapeutic potentials of anesthetics (which are also cationic amphiphiles) are proportional to their solubility in the lipid/aqueous interface [139]. These two last mentioned facts/findings backed the intercalation theory. It is important to emphasize that this theory does not exclude the receptor theory but adds new knowledge concerning how these drugs affect the above-mentioned metabolic processes. These effects could represent the real pharmacological action of these drugs, or their side effects, or both. To prove the intercalation theory more profoundly, one should try these techniques (Langmuir monolayer) and methods (PPI cycle and PLA₂ metabolism) not only with psychotropic drugs but also with drugs affecting other systems of the human body, for example drugs used to treat cardiopulmonary, CNS, and digestive system diseases, also in later experiments, with different cell lines. As a future

complementary method, to strengthen the theory of intercalation of psychotropic drugs in-between membrane phospholipids, solid-state ¹³C- and ³¹P-NMR should be undertaken also with the remaining 16 psychotropic drugs used in the work discussed in this review, where the cationic amphiphilic drug (CPZ) has shown to interact with PS. Fluidity of cell membranes including neurons, is secured by PUFAs in sn-2 acyl positions of membrane phospholipids, this is needed for normal metabolism and cell functions besides PUFAs enhance efficacy of psychotropics [25, 160] via facilitating their intercalation in-between acidic glycerophospholipids [34]. Since many of these PUFAs are essential fatty acids, they must be taken into the human body through the diet, implicating the importance of nutritional habits in the society.

If this theory could be verified, then this could change the ways of our understanding about how drugs (not only psychotropic ones) operate at the cellular level and thus add the intercalation theory to the already accepted drug–receptor theory, which currently represents the mainstay, if not the only theory explaining the action of drugs on human subjects.

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