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Original article

Solving the crisis in psychopharmacological research: Cellular-membrane(s) pharmacology to the rescue?

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ABSTRACT

There is an urgent need for the introduction of novel and better (i.e., improved risk-benefit profile) compounds for the treatment of major psychiatric disorders, in particular mood and psychotic disorders. However, despite increased societal awareness and a rising public and professional demand for such agents from patients and physicians, the pharmaceutical industry continues to close down its psychopharmacology research facilities in reaction to the lack of success with the search for new psychotropics. It is high time to stop this untoward trend and explore "new" lines of investigation to solve the current crisis in psychopharmacological research. In line with the prevailing molecular view in drug research in general, also in psychopharmacology mechanistic explanations for drug effects are "traditionally" looked for at the level of molecular targets, like receptors and transporters. Also, more recent approaches, although using so-called systems- and function-based approaches to model the multidimensional characteristics of psychiatric disorders and psychotropic drug action, still emphasize this search strategy for new therapeutic leads by identification of single molecules or molecular pathways. This "psychomolecular gaze" overlooks and disregards the fact that psychotropic agents usually are highly hydrophobic and amphipathic/amphiphilic agents that, in addition to their interaction with membrane-bound proteins in the form of e.g. receptors or transporters, also interact strongly with the lipid component of cellular membranes. Here we suggest to develop a program of systematic, whole-cell level based, investigation into the role of these physical-chemical cellular membrane interactions in the therapeutic action of known psychotherapeutics. This complementary yet conceptually different approach, in our opinion, will complement drug development in psychopharmacology and thereby assist in overcoming the current crisis. In this way the "old" physical theory of drug action, which antedates the current, primary molecular, paradigm may offer "new" options for lead discovery in psychopharmacological research.

1. Introducing the problem

In his book "Explaining the brain: mechanisms and the mosaic unity of neuroscience", the philosopher of science Carl Craver proposes the metaphor of a mosaic to present a new conceptual model of the unity of neuroscience. In discussing his approach, which is aimed to reflect neuroscientific practice, Craver asserts that neuroscientific research serves two major goals 1) to explain the brain and brain function, and 2) how to control the brain with the aim to manipulate it, for instance for the purpose(s) of diagnosis and/or treatment of disease [1]. According to Craver's view, both goals are complementary in that manipulating is a way to discover and explain whilst explaining is a way to discover how to manipulate. The historic development of psychopharmacology as a separate area of investigation in neuroscience fits very well within the above described framework presented by Craver for neuroscience in general. Thus, especially in its formative years as a scientific (sub)discipline, when it was perhaps more properly known as pharmaco(logical)-psychology (for review see [2–4],), psychopharmacology first focused its inquiries on describing the effects of psychoactive drugs (i.e., a manipulation) on human behavior. At first, the main goal of this was to provide a better understanding of human brain function in health and disease by elucidating the molecular mechanisms underlying the therapeutic action of these psychotropic drugs. Later on, with the successful but largely serendipity-driven introduction of antipsychotics, anxiolytics and anti-depressants for the treatment of clinically defined psychiatric syndromes [5], psychopharmacology

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made a switch in its research approach and aspired not only to elucidate the molecular mechanisms underlying the therapeutic action of these psychotropic drugs, but also to also provide novel mechanistic explanations identifying specific, neurochemical, deficits as causative of the psychiatric disorders these drugs were intended to treat [6]. The outcome of such efforts, which had far reaching consequences for both pharmacotherapeutic and clinical psychiatric research and practice, unto this day are well-known and widely recognized as the so-called "dopamine hypothesis of schizophrenia" and the "(mono)amine theory of depression" (for historical reviews see [7–9]).

The drastic change in the focus of psychopharmacological experimentation and theorizing during the second part of the twentieth century was stimulated by societal developments following the end of the second world war accompanied by what has been called "a molecular turn" in the brain sciences [10]. Together, these paved the way for a high appreciation of efforts to speed up scientific and technological progress culminating in the development of novel theories, models and instrumentation by (molecular) biologists, geneticists and biochemists. At the same time, clinical psychiatrists contributed to the building and maintenance of a "psychomolecular gaze" by adopting a categorical, phenomenological model of disease based on the assumption that there are fundamentally different types of psychiatric illnesses which each have a different specific (neurochemical) cause [11]. Although undoubtedly successful as a heuristic tool in the development of current psychopharmacotherapeutics [12], in recent years the long-standing inclination to identify (single) molecular targets and neurochemical deficits as a guiding principle for novel lead finding in psychopharmacology and therapeutics for phenomenology-based psychiatric disorders is increasingly being criticized.

One line of criticism, drawing primarily from concerns voiced by clinical psychiatrists, asserts that rather than specifically correcting abnormal brain states associated with psychiatric disorders, psychiatric drugs non-specifically alter brain function. This then happens to be accompanied by relief of certain psychiatric symptoms, although usually only in clinical subgroups of treated patients. According to this view, such effects are not the result of a psychotropic-mediated "normalization" of chemical brain defects, but are the outcome of drug-induced changes in brain function which suppress or replace the original manifestations of psychiatric disorders [13]. Thus, one might say that one "abnormal" brain state is exchanged for another which differs enough in a positive sense "(i.e., relief of certain psychiatric symptoms) for it to be classified as clinically beneficial [14]. However, as this "drug-centered" model denies a direct link between the alleged molecular targets of psychotropics and disease-specific efficacy it also undermines the rationale of taking these targets to look for new and promising psychotherapeutics to treat clinically-defined psychiatric illnesses. This skeptical approach to interpretation of the curative powers of psychopharmacological compounds is supported by the continuing failure to unequivocally demonstrate the neurochemical deficits and/or derangements previously claimed to underlie psychiatric diseases in humans. It may, moreover, be compounded by the limited molecular target selectivity of most central nervous system (CNS) active drugs.

Another objection against the "specific drugs for specific disorders" approach from psychopharmacology and biological psychiatry alike, is that it is increasingly recognized that a single drug may be useful in the treatment of more than one psychiatric disease. However, at the same time, combinations of psychoactive compounds with different molecular targets and different effects on signaling in the brain have been approved for treating single clinical entities [15]. Adding to this is the well-known but still only partially explained time lag between initiation of therapy and clinical efficacy of antipsychotics and antidepressants. Following up on an earlier attempt to promote a so-called "dimensional" instead of the mainstream "categorical" approach in clinical psychopharmacology and therapy [16], accumulation of the evidence supporting the validity of the above arguments more recently led various initiatives. One aims to replace the current indication-based nomenclature of psychotropic drugs (e.g., antipsychotics, antidepressants, anxiolytics etc.) with a so-called "neuroscience-based" system, in which the pharmacological profile of the different groups of agents is used to classify them in order to provide a rationale for prescription of (combinations of) selected psychotropic drugs for treatment of individual patients [17]. Another, the Research Domain Criteria (RDoC) concept introduced by the United States National Institute of Mental Health (NIMH), involves the transdiagnostic quantification of relevant CNS dimensions on different levels of brain function, from genetics through pharmacology and neurocircuitry, to ultimately subjective experience and objective behavior. By doing that, RDoC attempts to elucidate the neurobiological substrate of psychopathology independent of categorical disorders [18]. For instance, RDoC domains relevant to depression are the so-called positive and negative valence systems, which govern how individuals respond to rewarding and aversive situations respectively, arousal systems that regulate circadian rhythm and sensorimotor systems dictating physical activity. Since RDoC is intended to complement current diagnostic categories it is, at least for the foreseeable future, not anticipated to replace current psychiatric classification systems. Irrespective of these and also other related initiatives (e.g. [19],) to bolster neurobiology informed psychopharmacological research, however, the concerns presented here do serve to illustrate the fact that the relation between the behavioral effects of psychotropic drugs and their proposed molecular mechanism of action in phenomenology-defined psychiatric disease states still remains unclear [20]. Consequently, for the time being a scientifically-validated and generally accepted explanatory framework spanning the different domains and levels of psychotropic drug action to provide guidance in pharmacotherapeutic decision making in psychiatry is lacking. More important for the discussion here, it is likely that (also) because of this so-called "explanatory gap" recent efforts to introduce new compounds with improved efficacy and/or a better side-effect profile have largely failed. Moreover, these conceptual issues have been compounded by an ongoing discussion concerning the translational validity of animal models used in preclinical psychopharmacological research [21]. Altogether, as a result of this failure to deliver on their promises and despite an enormous rise in societal demand, the number of psychiatric research programs in large pharmaceutical companies has dropped dramatically from the start of this century [22,23]. It appears that industrial and, albeit to a lesser extent, academic experimental psychopharmacology is "in crisis" and serious measures are urgently required to revitalize this once vibrant and productive branch of interdisciplinary work linking clinical psychiatry, neuroscience and pharmacology.

2. Defining the case

In a move to overcome the looming crisis, the pharmaceutical industry recently decided to implement a radical switch in its research strategy. This strategy change entails a transformation from what may be termed an "inverse-translational model", in which the search for novel compounds is largely guided by previously identified molecular targets of well-known and (partly) effective pharmacotherapeutics, to one of "forward-directed translation". Different from the original approach, this latter strategy aims at rational new target selection based on detailed knowledge and understanding of disease pathogenesis and pathophysiology (for recent review see, [24]). Thus far, unfortunately, this time- and money consuming reprogramming of research method has only led to limited tangible success. This is primarily the result of a persistent failure to solidly identify genetic and/or molecular disturbances causally linked to major psychiatric diseases and the consequent inability to develop adequate animal models for preclinical drug testing that are of any relevance to mental disorders in man associated with unique human symptomatology and social contextual factors (van der [25]). Also, other factors complicating the successful

development and implementation of the forward translation approach in psychopharmacology have been identified, such as a focus on safety and pharmacokinetics to the detriment of thorough pharmacodynamic characterization and relating it to novel compounds' pharmacokinetics over time in early phase trials in humans [26,27]. Therefore, different measures seem to be called for to deal with the current crisis. The question, however, is, which one(s) to consider?

Despite its insufficiency to provide a scientifically-proven explanatory framework for causally linking behavioral/clinical effects to specific molecular mechanism(s) of action in psychiatric disease states, it cannot be denied that the inverse-translational research strategy, at least until now, has been the most successful approach to the development of clinically useful psychopharmacotherapeutics (e.g., dopamine receptor antagonists, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors). Therefore, accepting that drugs act by influencing cell function and signaling and that this is causally linked to their physiological effects, we believe that it is rational to start the search for "solution(s)" to the crisis in psychopharmacology by (re) considering research strategies based, at least initially, on the "old", well-established (groups of) psychotropics whilst asking "new" questions concerning their level(s) and mechanism(s) of cellular action. As argued hereunder, in our opinion, this will inevitably require a critical (re)analysis and investigation of at least some of the pharmacological concepts on which current preclinical psychopharmacological research is built and consideration of alternative theoretical as well as experimental approaches to supplement the present methods of cellular target identification and lead finding in experimental psychopharmacology. As a (potential) consequence of such a "re-invention" of psychopharmacology, the definition of the term (molecular) drug target might have to be redefined to include "non-molecular" structures, in particular (cellular) membranes. We do not claim to be the first to voice this view (for examples see, [28–30,31,32]), but do feel that it deserves wider attention from (psycho)pharmacologists then it has been paid until now. More important, our ideas follow the recently rekindled interest in the physical nature of (psychotropic) drug action [32,33]. Moreover, they fit nicely into the mosaic, multi-model, approach to (mechanistic) explanation in neuroscience(s) propagated by Craver and others [1,34,35], and recently proposed by us as a conceptual tool to guide the further development of a comprehensive framework for modeling of nerve impulse propagation [36]. As a contribution to hypothesis and theory development but above all as an opinion statement, however, our article is first and foremost meant to provoke thought and stimulate discussion rather than provide an exhaustive review of the topic under discussion or detailed conclusions and recommendations.

3. Towards a solution: a hint from the past?

As a biomedical science, modern pharmacology, including psychopharmacology, not only strives for a complete and accurate description of what drugs do but also of how they do it. This second goal requires investigation into and formulation of a mechanistic explanation of drug action, in order to understand and make predictions about structure-activity relationships and thereby facilitate new drug development for the treatment of diseases. Drug action, as a complex phenomenon, can be described at different levels, including the organismal-, organ-system (s), tissue, cellular- and/or molecular level. The term "mechanism of action" therefore takes on a different meaning according to this hierarchy of complexity (Fig. 1).

Despite the long-standing and still unresolved debate in philosophy of science on the requirements for mechanistic explanation in neuroscience in general (for instance see, [1,37]), alike other areas in basic pharmacological research, in psychopharmacology for a long time many experimentalists agreed that proper mechanistic explanations of drug action should be looked for at the molecular level. According to this arguably reductionist view, true understanding of drug action can only be reached by a molecular-level description. As a result of this concept and line of reasoning ingrained in (psycho)pharmacological research and teaching, virtually all psychotropics in clinical use for treatment of major psychiatric disorders today were (and still largely are) accepted to specifically act, at least initially, by direct and exclusive interaction with one or more types of (cell) membrane-embedded or -associated molecules, in particular receptor, transporter and/or ion channel proteins [38]. Also, in the search for novel targets and better compounds emphasis was put on a "molecular level first" approach which was driven by historical developments in pharmacological theory and experimentation leading to the wide availability in (psycho)pharmacological research of molecular-(in essence protein)-target focused models and technology [6]. More recent additions to the psychopharmacological research toolkit from (epi)genetics and molecular science, like gene cloning and DNA/RNA engineering, and from information technology-driven bioinformatics, enabling large scale so-called "systems/network pharmacology" or "omics" approaches, have, as yet, not fundamentally altered the "classical", molecular level-directed, conceptual framework within which both academic and industrial experimental psychopharmacological research is pursued [39]. In fact, although seemingly redirecting attention from molecular level to multi-scale, "higher" level investigation and explanation of drug action [40,41], one might conclude that they have, thus far, only served to strengthen the older, dominant model of drug research in which alternative (i.e., not primarily molecular-level) explanations of drug action are largely ignored. Indeed, it is striking to note that in discussing new strategies to psychiatric drug development, overt consideration of cellular level effects is often skipped (see below for further discussion) whilst jumping directly from the molecular level to the network level. Furthermore, although promising as an innovative strategy in the search for new drug targets in disease types for which clear links have been established between molecular targets and pathways and disease pathogenesis and/or pathophysiology (e.g., infectious diseases, certain tumors and immunological disorders), for psychopharmacotherapeutics and psychiatric disorders in which such associations have not been firmly established this same strategy can be expected to be far less successful than suggested (for recent examples of this "precision medicine" approach but, in essence, continued molecular-level reasoning in addressing the future of psychopharmacology see e.g., [26]; van der [25]).

In considering how to overcome the apparent "explanatory gap" in psychopharmacology it is, therefore, interesting to note that this "fixation" on molecular-level explanation(s) has not always dominated the scientific discussion about the nature of cellular-level drug action. Initiating the modern era in pharmacology, from the middle of the nineteenth century onwards early pharmacologists like Buchheim and Schmiedeberg, as part of their mechanistic approach to explanation of organismal drug action, started to study the relation between the chemical characteristics of biologically active compounds and their physiological effects [42]. Later on, in various steps and using the law of mass action and derived equations as its physical and mathematical building block [43], this led to formulation of what is presently known as the receptor theory, i.e. the leading (and molecular) paradigm in current pharmacological research. However, as discussed comprehensively by historians like Maehle [44] and Parascandola [45], during the first decades after its original introduction in the early years of the twentieth century the receptor (protein) concept was highly controversial and met with very strong opposition from investigators who propagated the idea that the physiological action of drugs was primarily determined by their physical properties. In the view of this latter group of researchers, which included renowned scientists like Cushny and Straub and for a long time also counted the later Nobel laureate Henry Dale amongst its members, drug action was not explained by chemical combination with specific cellular constituents like receptor molecules but depended primarily on the ability of biologically active compounds to alter the surface tension, electrolytic balance, osmotic pressure and/or other physicochemical properties of cells. In this "physical theory of

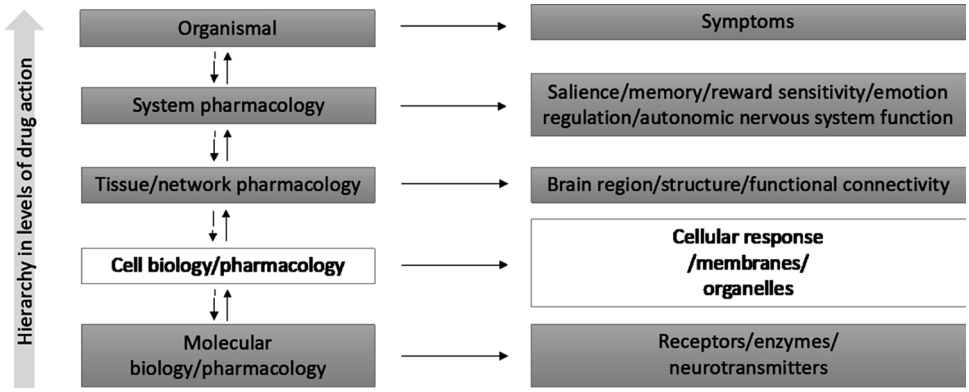

Fig. 1. Dimensional aspects of drug action in psychopharmacology with special attention for the role of cell-level mechanisms in the understanding of this complex phenomenon.

drug action" an important role was foreseen for a direct interaction of the drug with cellular membranes causing a deformation or other physical disturbance(s) thereof. Later developments in pharmacological research referred to above, but more detailed discussion of which is outside the scope of this opinion statement (for comprehensive historical overviews, however, see e.g. [46,47],), caused this latter line of inquiry to be rejected as a viable and independent approach to formulate the sought for unified and generally applicable mechanistic explanation of drug action in favor of the current paradigm. Nevertheless, upon closer scrutiny it appears that over the years a number of its fundamental tenets has been incorporated into the larger body of principles of pharmacology where it arguably forms the conceptual basis of the processes covered under absorption, distribution and excretion of drugs in living organisms [48,49], and as such contributes significantly to pharmacokinetic modeling of drug action. More important in light of the discussion here and in contrast to the receptor theory, however, the physical theory of drug action appears to favor a cellular (membranes) level description to explain and provide correct understanding of drug action.

As a consequence of the accumulating evidence supporting the concept(s) of the predominantly molecular, protein-oriented receptor theory, cellular membranes as such and in particular the lipid bilayers which form their structural backbone, were no longer seriously considered as potential loci of drug action. Rather the opposite occurred, in which attention was drawn almost exclusively to the importance of lipid membranes as physical diffusion barriers, serving for protection and compartmentalization of cells and cellular organelles, and as scaffolds, i.e., practically inert structural elements meant to provide a stable platform for the highly dynamic membrane-embedded or -associated proteins to perform their all important function in drug action as part of localized biochemical reactions and/or signal transduction cascades [50]. Indeed, in comparison to these drug-binding proteins which, similar to DNA, are vital to life itself and whose highly dynamic molecular structure, according to the reigning dogma of molecular biology, was thought to control function, the lipid component of membranes was considered as a rather dull, structure-poor fatty layer which, in line with dogma, was not expected to play a specific role in biological systems [51]. In other words, and using more conceptual terminology, the lipid component and with it the general physicochemical characteristics of cellular membranes were supposed to be causally irrelevant to the mechanistic understanding of drug action. The virtual absence of attention for anything but protein (and DNA/RNA) molecules as the primary targets of interest for finding a solution to problems plaguing modern (psycho)pharmacological research, in particular the lack of innovative, better and/or safer drugs, is therefore not surprising [39,52], if perhaps uncalled for (see e,g. [53,54],). Indeed, as so elegantly formulated by Lucio et al. [50] it is safe to conclude that "the protein component of the membrane has cast a long shadow for quite some time over the lipid membrane content". More important, as a result of this rather one-sided view of drug action, opportunities at innovation in psychopharmacological drug research (may) have been overlooked.

4. Leads for a cellular-membrane(s) level approach

Although understandable in light of the prevailing scientific atmosphere in molecular- and cellular biology and the vital contribution of the conceptual and experimental framework provided by the receptor- and other molecular-level oriented theories to the "blockbuster" success (es) of psychopharmacological research in the (recent) past, in hindsight this lack of attention from large parts of mainstream psychopharmacology for the role of the lipid component of membranes in the mechanism(s) of action of psychotherapeutics appears somewhat surprising. First of all, as noted above the large majority of established molecular targets of frequently used psychopharmacotherapeutics consists of integral and membrane-linked proteins. Considering this (sub)cellular location, activity of these molecular drug targets completely independent of the state of their immediate, primarily lipid, surroundings appears highly unlikely if not impossible. In fact, starting with the famous but already more than a century old Meyer-Overton rule for volatile anesthetics (for historical reconstruction see, [55]), and continuing into the present decade, membrane lipids as an organized entity have featured repeatedly as (direct or indirect) surfaces of action in physicochemical models meant to provide a (more) comprehensive view of the mechanism of action of both a good number of well-established psychoactive drugs, including antipsychotics, antidepressants, anxiolytics and lithium salts [55–59] as well as some novel "atypical" brain-active agents and neurotransmitters like nitric oxide, endocannabinoids, omega-3 fatty acids and inositol [60,61]. Many of these drugs are cationic hydrophobic or amphiphilic/amphipathic compounds which are well-known to accumulate spontaneously in both natural and reconstituted membranes even in the absence of their alleged protein targets [32]. As a result, important physicochemical features of the lipid bilayer may change, including fluidity, structure, surface charge, lateral pressure/organization and composition (Fig. 2A, B) [50,56]. Such changes not only have an immediate or long(er) lasting impact on the lipid component of membranes themselves [55,56], but also shape membrane protein function directly and/or indirectly, for instance by altering the organization and compartmentalization of proteins in membrane domains and modulation of cell signaling and gene expression ([62]; [63–67]; van [68,31]). In its turn, the physicochemical properties of the lipid bilayer affect the location of drugs and their distribution coefficient, which has considerable impact on the kinetics of the interaction between these drugs and their alleged molecular target(s) (Fig. 2A, B) ([32] and references therein).

This phenomenon may, for instance, underlie the often-noted

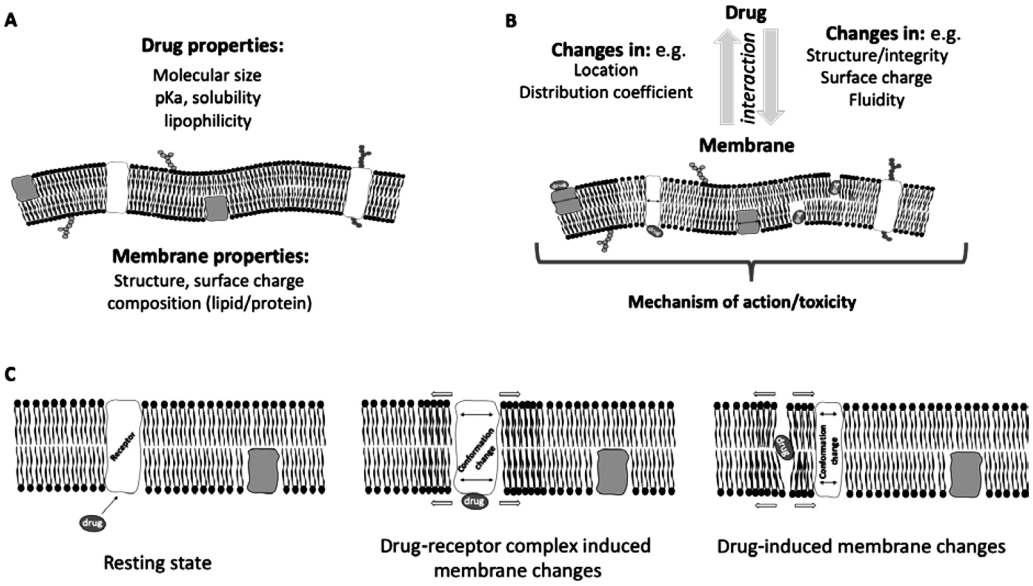

Fig. 2. Schematic representation of psychotropic drug-membrane interaction. Panel A represents the drug-physical chemical properties and membrane properties influencing drug-membrane interactions (A). Panel B illustrates possible consequences of the interplay between these drug and membrane properties following binding of the drug to the cellular membrane contributing to its mechanism of action/toxicity. Panel C provides a simplified graphical illustration of our proposed scheme of the mechanism of action of psychotropic drugs at the cellular membrane(s) level as a result of both direct 'specific' interaction of the drug with its molecular (protein) target and indirect 'off target' conformational changes in these molecular targets induced by the 'non-specific' physical-chemical interaction of these drugs with lipid (double layer) membrane components.

apparent discrepancy in experimental studies between the (clinically) effective plasma concentration of certain drugs and the concentration at which they are active on lipid membranes. An interesting example of the potential consequences for cellular physiology and homeostasis of this "non-specific" binding of psychotropic agents to the lipid component of membranes has recently attracted some public attention [69]. Using various strains of the (budding) yeast Saccharomyces cerevisiae as an eukaryotic in vitro model system lacking the primary protein drug target, exposure to the antidepressant sertraline, which is usually thought to act by binding to and blocking of the serotonin (re)uptake transporter, was shown to trigger an (adaptive) autophagic response to a potentially lethal disturbance of membrane curvature in a transporter-independent manner but at clinically relevant drug concentrations [70]. This protective cellular adaptation to sertraline administration was explained to be the final outcome of an interaction between drug molecules and membrane lipids initiated by a multi-stage, physicochemical cascade of reactions not directly targeting proteins. Interestingly, in their discussion of the results the authors of this study speculate on the relationship between this "trophic", cellular fitness promoting but time-dependent effect of sertraline in their model and the well-known but still largely unexplained time lag between start of administration and therapeutic efficacy of antidepressants in humans, which has also been linked to a slowly evolving neurotrophic effect. They put forward, that in specific contexts amphipathic/amphiphilic drugs such as sertraline and, perhaps, other antidepressants may similarly induce such a neurotrophic signal by altering the physical properties of cellular membranes. A similar "lipid theory", based on "non-specific" physicochemical interactions between membranes and psychoactive drugs, was invoked recently to (at least partly) explain the effect of antipsychotic phenothiazines and local anesthetics on glucose transport and metabolism in yeast [71]. Besides shedding new light on their level(s) and mechanism(s) of action and thereby providing possible leads to novel target and drug identification in psychopharmacology, studies such as these may also offer links to a better understanding of some of the troubling side effects accompanying the use of many psychotropic agents, for instance the relation between administration of antipsychotics and metabolic disturbances [72,73]. Moreover, from these and comparable studies (for review see [33], and references therein), a picture emerges in which cationic hydrophobic or amphiphilic/amphipathic drugs, which includes a large number of the currently used antidepressants and antipsychotics, are responsible for modifying membrane protein- and/or cellular function in (at least) two ways, 1) directly, i.e. via specific protein binding, and 2) indirectly, via "non-specific" physicochemical interactions with membrane lipids (Fig. 2C). The first, not surprisingly, has been studied extensively and forms the backbone of ongoing psychopharmacological discovery; the second still requires systematic investigation in order to get a better estimation of its contribution to the cellular-level mechanism(s) of action of different groups of psychoactive agents at different temporal scales and concentrations [74], and the way in which this "non-specific" part of psychotropic drug action relates to its far more extensively characterized specific part [32]. To start with, as part of a preclinical research and development program for this latter purpose large compound libraries containing both experimental and clinically used psychotropic drugs are to be tested systematically using, at least initially, relatively simple, optimally controlled in vitro models, including artificial and natural membrane preparations and well characterized unicellular eukaryotes and cultures of mammalian brain cells. As read outs biophysical and computational approaches, such as X-ray scattering, nuclear magnetic resonance and *in silico* molecular dynamics, may be considered as promising tools to provide a more detailed answer to the overarching question as to how these drugs interact with their molecular (protein) target(s) to modify cellular (patho)physiology and the important role of cellular membranes therein. Taking good note of the chemical complexity of biological membranes, as part of such a preclinical effort to bridge the "explanatory gap" and extend scientific understanding of psychotropic drug action at the molecular- and cellular level into a more complete and accurate view at higher levels of description, it will be essential to also pay proper attention to the highly variable lipid composition of membrane bilayers between and within different brain regions and specific cell types. This hitherto only scantly studied factor is increasingly recognized to play a vital role in the pathophysiology of major psychiatric syndromes, including schizophrenia, depression and anxiety disorders [64,75,76], and may therefore prove to be crucial in guiding the future development of more disease specific and/or safer (i.e., better side effect profile) compounds [77–79]. The urgency to start such a line of systematic experimental research into the physical nature and cellular (and ultimately, organ systems and organismal) consequences of the interaction of psychotropic drugs with membrane bilayers of different consistency is further illustrated by the (re)opened discussion on the role of chirality of membrane lipids in the enantioselectivity of many drugs belonging to this category [80,81]. Considering that many relevant data on the basic physicochemical characteristics, molecular target binding profiles and

cellular genomics and proteomics profiles of the currently used psychotherapeutics is already available from literature or other (academic and industrial) sources, in order to answer its primary goal(s), the above outlined experimental approach should be accompanied by a large-scale computational effort in which databases are built to store this information and probe them using dedicated, custom-made algorithms to search for novel, causal links between the cellular-level action of different psychotropic drugs and their physicochemical characteristics. Such a preclinical research program, requiring and combining experimental, computational and theoretical/modeling expertise, is expected to result in a new, cellular (membrane(s)) level explanation-based, grouping of established psychotherapeutics and/or testable predictions concerning the therapeutic potential of other compounds which have not been considered before to hold promise as psychotropic agents (for an extended outline of this approach see, [33]).

Finally and to emphasize its scientific potential, it is relevant to note that the impact of such research may extend beyond the borders of psychopharmacology to include renewed investigation of the neurochemical foundations of neurotransmission as, alike many psychotropics, also polar neurotransmitters, including GABA and dopamine, have been reported to bind to the lipid matrix of membranes via electrostatic attraction in a lipid specific manner [82–84]. Such a mechanism may also be of importance in the action of gaseous neurotransmitters like nitric oxide and the highly lipid soluble endocannabinoids [60]. Although thus far based primarily on preliminary work, using artificial membranes and computer simulations, these results do hint at the exciting possibility that, in addition to direct interaction with their respective protein receptor molecules, at least some neurotransmitters may also modulate neurotransmission by an indirect, lipid bilayer-mediated mechanism [85].

5. Some conceptual considerations

Notwithstanding its disappointing results so far and apparently waning interest from industry, albeit (re)sculptured into the contemporary shape of a large-scale informational effort, the forward-directed translational research strategy referred to above is still alive and kicking in psychopharmacology. Indeed, successful roads to identification of new drug targets for development of innovative psychotherapeutic drugs are often advised to run along the line of building large databases containing “big data” about pathogenesis and pathophysiology of the relevant psychiatric diseases, (epi)genetics, brain imaging, proteomics, behavioral- and pharmacological data. In a rather undefined manner, exploration of these amassed data using computational and statistical tools will then offer solutions to the current “crisis” and again open up a bright future for psychopharmacology (for broad examples of this kind of reasoning see, [24,26]). From the historic and scientific considerations described above, it will be clear that our above-outlined proposal to start filling in the “explanatory gap” between basic and clinical psychopharmacology and therapeutics for major psychiatric disease states differs considerably from this, and relates more to the “old school” inverse translational approach. In fact, our proposal draws on two main ideas: 1)(re)use and investigation of the current set of psychotherapeutics, and 2) cellular level description (s) of drug action, with special emphasis on the role of cellular membranes therein. Both are necessary steps to come to a more complete and accurate understanding of psychotropic drug action and identification of “new” types of drug targets amenable to development of innovative drugs. The first idea follows from purely pragmatic considerations. As investigators, we do have an enormous amount of data on this large group of compounds, ranging from the molecular- right up to the organismal (i.e., animal)- and clinical level. However, these data have always been gathered, analyzed and interpreted within the framework(s) provided by the ruling paradigm(s), theories, hypotheses and models (e.g., the receptor theory, the monoamine theory of depression and the dopamine hypothesis of schizophrenia). In its turn, the apparent success of these frameworks for a longtime legitimized continuation of experimentation along the same lines driven on by what has sometimes been called “the herd mentality in the biomedical sciences” which describes the important role of non-epistemic factors in directing areas of investigation [86]. However, now that stagnation has occurred and these fundaments of psychopharmacological research fail to guide identification of novel targets and innovative drug development any further, it may prove worthwhile to again probe these invaluable data but with an open mind and keen eye for alternative interpretations and/or categorization. The second idea underlying our approach follows from this and borrows for a number of its conceptual considerations from the elegant paper by Perouansky [87] about “the quest for a unified model of anesthetic action” and insightful comments thereon by, respectively, Ginosar and Binshtok [88] and Forman [89]. Whilst musing over the role of paradigms in our scientific way of thinking, our awareness of their influence and asking questions about their positive or negative impact on scientific progress, in the epilogue to his paper Perouansky [87] puts forward that scientific paradigms (in his case Claude Bernard’s notion of one anesthetized state) are a two-edged sword. On one hand, they may assist in solving identified problems in a more efficient manner by steering the research effort of a community of scientists into a specific direction but, on the other hand they suppress alternative, unconventional approaches. Continuing with a discussion of the characteristics of a complex system (in his case the brain), the role of bottom-up emergence of phenomena in a complex system as the result of interactions between “collections of diverse, interconnected, interdependent and adaptable elements (…….) on each hierarchical level of organization”, Perouansky [87] then notes that recognition of the importance of biological complexity to the correct understanding of a phenomenon of interest should help against making extrapolation errors by too easily “jumping from microscale to macroscale”. Moreover, “freed from the dictate of universality”, the various features of the phenomenon might then be investigated individually in the best possible way and at the correct level. This has immediate importance for the way we propose to address the “explanatory gap” in psychopharmacology. Without a shadow of a doubt the leading paradigms, theories, hypothesis and models of psychopharmacology have been of instrumental value for the development of drug treatments in psychiatry as they stand today. However, because of this success not only were other areas of exploration largely ignored, but also “weak links” in theorizing and/or experimental evidence for a long time were left unaddressed or not deemed to be of sufficient importance to overcome. Of the criticisms on this point already referred to in our introduction, within the context of drug action as a complex biological phenomenon with various levels of description and the risk of jumping to conclusions, the unexplained time lag between start of therapy and clinical efficacy of antipsychotics and antidepressants stands out as a prime example. As the studies from literature chosen by us intend to illustrate, in our view, in experimentation and discussions about the (possible) mechanism(s) underlying this important but still poorly understood phenomenon the cellular level perspective, and in particular the role of cellular membranes therein, has been lacking. Indeed, investigation of the cell as an organized entity and logical “nexus” of action, i.e., a natural connection point at the intersection between molecular and organ(ismal) level descriptions and mechanistic explanations of complex biological phenomena, is again recognized after having been neglected for a large part of the second half of the twentieth century [90,91].

At the same time, it is not to be advised that this recognition of the regained importance of cellular (membranes)level descriptions to scientific understanding of psychotropic drug action will be accompanied by a well-known scientific, and perhaps even general human, “intuition”, that Butler [92], in discussing theories of anesthetics action, referred to as the “metaphysical desire for unification”. Although more than 50 years old, Butler’s paper, and in particular its conceptual parts, is still relevant today when considering the formulation of (partly) new

theories and building of (partly) new models to accommodate cellular (membrane) level description(s) into a general framework for mechanistic explanation of psychotropic drug action. Indeed, as remarked by Perouansky [87], complexity in biological phenomena (such as drug action) "does not preclude the possibility that, on some levels of organization (…….) shared mechanisms for the different endpoints may emerge". However, one should be careful with interpreting such outcomes within the confines of a unitary theory as these are usually embedded within a dominant, but not always consciously identified or sometimes even forgotten, paradigm or dogma. For the case at hand this means that, in order to ensure maximal explanatory potential, novel cellular (membrane(s)) level description(s) of psychotropic drug action should try to evade this pitfall and not opt "up front" to be included as part of a "classical" effort to develop a general unifying theory and/or model of psychotropic drug action. As it stands, until proven otherwise, cellular (membrane(s)) level description(s) might do better in using the conceptual framework recently outlined by us for the comprehensive modeling of the nerve impulse [36]. In that paper, following up on the ideas of the philosopher of science Hochstein (2016, 2017) who believes that mechanistic explanation of neuroscientific phenomena is impossible by using only a single model we argue that the chances for constructing a comprehensive framework for understanding a complex cellular (membrane(s)) level phenomena like the nerve impulse (and in the current paper, psychotropic drug action at the cellular (membrane (s)) level) are higher if the different existent theories and models, which often focus on single aspects of the phenomenon of interest and therefore serve different purposes and may even hold conflicting assumptions to achieve those purposes, are allowed to exist alongside each other and not put together into an overarching theory or model to conform to a misinformed notion of (neuro)scientific unity. Rather the theories and/or models should become part of a dynamic, evolving, explanatory mosaic as suggested by Craver [1], in which, over time and dependent on their explanatory success, pieces may be added or taken away. Interestingly, although worded in a different way and specifically discussing bronchodilators as an example, at least in our opinion this is what Vauquelin (2017) is referring to in mentioning that "In accordance with Occam's razor principle, we are often tempted to explain all experimental data in terms of a single, all-encompassing model. (……)However, the statement by Box and Draper (..) that 'all models are wrong but some are useful' should remind us that all models are merely coarse/incomplete descriptions, and, (…….)Thus, it is conceivable that all three mechanisms play significant roles (….) and that it is only the prevalence of each mechanism that varies amongst the bronchodilators".

Of course, we recognize that our general approach and discussion thereof in this paragraph is rather unidirectional, i.e., it considers only "bottom-up" causation, and does not address a (large) number of other conceptual issues related to the "explanatory gap" in psychopharmacology, such as part-whole relationships and top-down causation in complex biological systems. However, we feel that doing so would unnecessarily complicate arguing our case and making our main points intelligible.

6. Conclusion

After reaching astounding heights during the second part of the 20th century, currently, whilst approaching the end of the first two decades of the next century, psychopharmacology finds itself in what may well be called "a scientific crisis". If perhaps not exactly in the sense defined for his notion of paradigms by the famous philosopher of science Thomas Kuhn in his seminal work 'The structure of scientific revolutions' [93], this crisis is nevertheless real and of a more existential nature. Indeed, the apparent failure of its leading paradigm(s), theories, hypotheses and models to guide successful identification and development of innovative and/or safer compounds for treatment of major psychiatric disorders, poses an imminent threat to the survival of psychopharmacology as a viable scientific (sub)discipline. In his attempt to use the philosophical framework provided by Kuhn to historically analyze the manner in which the ruling paradigms found their way into psychopharmacological research and practice, the well-known clinical psychiatrists and researcher David Healy observed that, at least for psychopharmacological investigation into the bioneural substrates of affective disorders, "despite a lack of convincing supporting evidence and disproof of their original premises" their status is maintained which suggests that "the core of this paradigm (in his case the amine hypothesis) is psychological in nature rather than neurobiological" [94]. Irrespective of whether the developments described by Healy and others are correctly referred to as the "psychopharmacology revolution" (for a critique of this interpretation see, [95]), Healy importantly notes that Kuhn also pointed to the fact that one of the consequences of working within the confines of a paradigm is a neglect of issues which may later seem relevant. Thus, according to Healy "revisions of paradigms frequently come from these areas of neglect rather than from the results of experiments being conducted in areas of interest to the paradigm" [94]. Similar to what was recently discussed by us within the context of the both conceptually and scientifically related debate on the physical nature of the nerve impulse [96] identifying and actively (re) visiting such apparent "areas of neglect" in psychopharmacology may open up new avenues for fruitful exploration of "new" mechanisms of action and targets for development of novel psychotropics. Here we have attempted to defend the position that, by doing so, integration into mainstream theorizing and experimenting of the "orphaned" physical theory of drug action, will be essential for bridging the "explanatory gap" and ensuring the revival of psychopharmacology as a once again vibrant area of neuroscientific investigation and new drug development. Furthermore, in addition to considering previously relinquished models of drug action, to solve the crisis in psychopharmacology it will also be inevitable to revisit the currently applied categorical classification of psychiatric disorders based on phenomenology and, if necessary, to complement or even replace it with a neurobiology based, transdiagnostic understanding of brain dysfunction in psychopathology. Of course, there are limitations and risks to this approach as it will again require substantial investments in both time and money for the development and implementation of appropriate and (partly) new theoretical and experimental models and readouts with no absolute guarantee of success. However, in light of the large unmet need and potential benefit for the ever-growing number of patients, the effort appears worthwhile.

Declaration of Competing Interest

All authors of the manuscript entitled: "Solving the crisis in psychopharmacological research: cellular-membrane(s) pharmacology to the rescue?" hereby declare to have no conflict of interest whatsoever.

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References

[1] C.F. Craver, Explaining the Brain. Mechanisms and the Mosaic Unity of Neuroscience, Oxford University Press, Oxford, 2007.
[2] A. Badiani, History of psychopharmacology, Encyclopedia of Psychopharmacology, Springer, Berlin, Heidelberg, 2014.
[3] D. Healy, 100 Years of psychopharmacology, J. Psychopharmacol. (Oxford) 7 (2) (1993) 207–214.
[4] U. Mueller, P.C. Fletcher, H. Steinberg, The origin of pharmacopsychology: emil Kraepelin's experiments in Leipzig, Dorpat and Heidelberg (1882-1892), Psychopharmacol. 184 (2006) 131–138.
[5] T.A. Ban, The role of serendipity in drug discovery, Dialogues Clin. Neurosci. 8 (3) (2006) 335–344.
[6] C.E. Dean, Psychopharmacology: a house divided, Progr. Neuro-Psychopharmacol. & Biol. Psychiatr. 35 (2011) 1–10.

[7] A.A. Baumeister, J.L. Francis, Historical development of the dopamine hypothesis of schizophrenia, J. Hist. Neurosci. 11 (3) (2002) 265–277.
[8] J. Moncrieff, Magic bullets for mental disorders: the emergence of the concept of an "antipsychotic" drug, J. Hist. Neurosci. 22 (2013) 30–46.
[9] S. Mulinari, Monoamine theories of depression: historical impact on biomedical research, J. Hist. Neurosci. 21 (2012) 366–392.
[10] J.M. Abi-Rached, N. Rose, The birth of the neuromolecular gaze, Hist. Human Sci. 23 (1) (2010) 11–36.
[11] A. Rudnick, The molecular turn in psychiatry: a philosophical analysis, J. Med. Philos. 27 (3) (2002) 287–296.
[12] A.A. Baumeister, M.F. Hawkins, The serotonin hypothesis of schizophrenia: a historical case study on the heuristic value of theory in clinical neuroscience, J. Hist. Neurosci. 13 (3) (2004) 277–291.
[13] J. Moncrieff, D. Cohen, Rethinking models of psychotropic drug action, Psychother. Psychosom. 74 (2005) 145–153.
[14] J. Moncrieff, D. Cohen, Do antidepressants cure or create abnormal brain states? PLoS Med. 3 (7) (2006) e240.
[15] P.J. Conn, B.L. Roth, Opportunities and challenges of psychiatric drug discovery: roles for scientists in academic, industry, and government settings, Neuropsychopharmacol. 33 (2008) 2048–2060.
[16] P. Baruch, M.-J. Filteau, R.H. Bouchard, E. Pourcher, P. Vincent, R. Jouvent, The dimensional approach to clinical psychopharmacology: a polysemous concept, J. Psychiatry Neurosci. 17 (2) (1992) 55–60.
[17] J. Zohar, S. Stahl, H.-J. Moller, P. Blier, D. Kupfer, S. Yamawaki, H. Uchida, M. Spedding, G.M. Goodwin, D. Nutt, A review of the current nomemclature for psychotropic agents and an introduction to the neuroscience-based nomenclature, Eur. Neuropsychopharmacol. 25 (2015) 2318-232.
[18] S.O. Lilienfeld, M.T. Treadway, Clashing diagnostic approaches: DSM-ICD versus RDoC, Annu. Rev. Clin. Psychol. 12 (2016) 435–463.
[19] H. Szechtman, B.H. Harvey, E.Z. Woody, K.L. Hoffman, The psychopharmacology of Obsessive-Compulsive disorder: a preclinical roadmap, Pharmacol. Rev. 72 (2020) 80–151.
[20] H. Uchida, W. Fleischhacker, G. Juckel, G. Gruender, M. Bauer, Naming for psychotropic drugs: dilemma and challenge, Pharmacopsychiatr. 50 (2017) 1–2.
[21] C.P. Mueller, Animal models of psychoactive drug use and addiction-present problems and future needs for translational approaches, Behavior. Brain Res. 352 (2018) 109–115.
[22] A. Abbott, Novartis to shut brain research facility, Nature 480 (2011) 161–162.
[23] J. Arrowsmith, P. Miller, Trial watch: phase II and phase III attrition rates 2011-2012, Nat. Rev. Drug Discov. 12 (569) (2013).
[24] P.H. Hutson, J.A. Clark, A.J. Cross, CNS target identification and validation: avoiding the valley of death or naïve optimism? Annu. Rev. Pharmacol. Toxicol. 57 (2017) 171–187.
[25] vander T.F. Doef, S. Zaragoza Domingo, G.E. Jacobs, W.C. Drevets, H.M. Marston, P.J. Nathan, M.B. Tome, C.A. Tamminga, J.M.A. van Gerven, M.J.H. Kas, New approaches in psychiatric drug development, Eur. Neuropsychopharmacol. 28 (2018) 983–993.
[26] R. Ciccocioppo, Grand challenge in psychopharmacology: setting priorities to shape a bright future, Front. Psychiatr. 8 (2017) 15.
[27] J. Van Gerven, A. Cohen, Vanishing clinical psychopharmacology, Br J Clin Pharmacol 72 (1 July) (2011) 1–5.
[28] A. Jutila, T. Soderlund, A.L. Pakkanen, M. Huttunen, P.K.J. Kinnunen, Comparison, of the effects of clozapine, chlorpromazine, and haloperidol on membrane lateral heterogeneity, Chem. Phys. Lipids 112 (2001) 151–163.
[29] J.Y. Chen, L.S. Brunauer, F.C. Chu, C.M. Helsel, M.M. Gedde, W.H. Huestis, Selective amphipathic nature of chlorpromazine binding to plasma membrane bilayers, Biochim. Biophys. Acta 1616 (2003) 95–105.
[30] I. Alves, G. Staneva, C. Tessier, G.F. Salgado, P. Nuss, The interaction of antipsychotic drugs with lipids and subsequent lipid reorganization investigated using biophysical methods, Biochim. Biophys. Acta 1808 (2011) 2009–2018.
[31] van A.B. Spriel, G. van den Bogaart, A. Cambi, Editorial: membrane domains as new drug targets, Front. Physiol. 6 (2015) 172.
[32] G. Vauquelin, Cell membranes … and how long drugs may exert beneficial pharmacological activity *in vivo*, Br. J. Clin. Pharmacol. 82 (2016) 673–682.
[33] J.M. Sonner, R.S. Cantor, Molecular mechanisms of drug action: an emerging view, Annu. Rev. Biophys. 42 (2013) 143–167.
[34] E. Hochstein, One mechanism, many models: a distributed theory of mechanistic explanation, Synthese 193 (2016) 1387–1407.
[35] E. Hochstein, Why one model is never enough: a defense of explanatory holism, Biol. Philos. 32 (6) (2017) 1105–1125.
[36] L. Holland, H.W. de Regt, B. Drukarch, Thinking about the nerve impulse: the prospects for the development of a comprehensive account of nerve impulse propagation, Front. Cell. Neurosci. 13 (208) (2019).
[37] J. Bickle, Philosophy of Neuroscience: a Ruthlessly Reductive Approach, Holland: Kluwer Academic Publishers, Dordrecht, 2003.
[38] S.M. Stahl, Essential Psychopharmacology. Neuroscientific Basis and Practical Applications, Cambridge University Press (second edition), Cambridge (UK), 2000.
[39] R.J. Winquist, K. Mullane, M. Williams, The fall and rise of pharmacology-(Re-) defining the discipline? Biochem. Pharmacol. 87 (2014) 4–24.
[40] A.L. Hopkins, Network pharmacology: the next paradigm in drug discovery, Nature Chem. Biol. 4 (11) (2008) 682–690.
[41] S. Zhao, R. Iyengar, Systems pharmacology: network analysis to identify multiscale mechanisms of drug action, Annu. Rev. Pharmacol. Toxicol. 52 (2012) 505–521.
[42] M.P. Earles, Early theories of the mode of action of drugs and poisons, Ann. Sci. 17 (2) (1961) 97–110.
[43] T. Kenakin, The mass action equation in pharmacology, Br. J. Clin. Pharmacol. 81 (2015) 41–51.
[44] A.-H. Maehle, A binding question: the evolution of the receptor concept, Endeavour 33 (4) (2009).
[45] J. Parascandola, To bond or not to bond: chemical versus physical theories of drug action, Bull. Hist. Chem. 28 (1) (2003) 1–8.
[46] M.R. Bennett, The concept of transmitter receptors: 100 years on, Neuropharmacol. 39 (2000) 523–546.
[47] A.-H. Maehle, The quantification and differentiation of the drug receptor theory, c. 1910-1960, Ann. Sci. 62 (4) (2005) 479–500.
[48] C. Peetla, A. Stine, V. Labhasetwar, Biophysical interactions with model lipid membranes: applications in drug discovery and drug delivery, Mol. Pharm. 6 (5) (2009) 1264–1276.
[49] S. Nagar, K. Korzekwa, Nonspecific protein binding versus membrane partitioning: it is not just semantics, Drug Metab. Dispos. 40 (2012) 1649–1652.
[50] M. Lucio, J.L.F.C. Lima, S. Reis, Drug-membrane interactions: significance for medicinal chemistry, Curr. Medic. Chem. 17 (2010) 1795–1809.
[51] L.A. Bagatolli, J.H. Ipsen, A.C. Simonsen, O.G. Mouritsen, An outlook on organization of lipids in membranes: searching for a realistic connection with the organization of biological membranes, Progr. Lipid Res. 49 (2010) 378–389.
[52] T. Kenakin, M. Williams, Defining and characterizing drug/compound function, Biochem. Pharmacol. 87 (2014) 40–63.
[53] A. Gulbins, F. Schumacher, K.A. Becker, B. Wilker, M. Soddemann, F. Boldrin, C.P. Mueller, M.J. Edwards, M. Goodman, C.C. Caldwell, B. Kleuser, J. Kornhuber, I. Szabo, E. Gulbins, Antidepressants act by inducing autophagy controlled by sphingomyelin-ceramide, Mol. Psychiatr. 23 (2018) 2324–2346.
[54] J.P. Huston, J. Kornhuber, C. Muehle, L. Japtok, M. Komorowski, C. Mattern, M. Reichel, E. Gulbins, B. Kleuser, B. Topic, M.A. de Souza Silva, C.P. Mueller, A sphingolipid mechanism for behavioral extinction, J. Neurochem. 137 (2016) 589–603.
[55] P. Seeman, The membrane actions of anesthetics and tranquilizers, Pharmacol. Rev. 24 (4) (1972) 583–655.
[56] D.B. Goldstein, The effects of drugs on membrane fluidity, Ann. Rev. Pharmacol. Toxicol. 24 (1984) 43–64.
[57] S. Schreier, S.V.P. Malheiros, E. de Paula, Surface active drugs: self-association and interaction with membranes and surfactants. Physicochemical and biological aspects, Biochim. Biophys. Acta 1508 (2000) 210–234.
[58] R. Oruch, A. Lund, I.F. Pryme, An intercalation mechanism as a mode of action exerted by psychotropic drugs: results of altered phospholipid substrate availabilities in membranes, J. Chem. Biol. 3 (2010) 67–88.
[59] E. Jakobsson, O. Arguello-Miranda, S.W. Chiu, Z. Fazal, J. Kruczek, S. Nunez-Corrales, S. Pandit, L. Pritchet, Towards a unified understanding of lithium action in basic biology and its significance for applied biology, J. Membr. Biol. 250 (2017) 587–604.
[60] S.R. Joca, F.A. Moreira, G. Wegener, Atypical neurotransmitters and the neurobiology of depression, CNS Neurol. Disord. Drug Targets 14 (2015) 1001–1011.
[61] J. Sarris, J. Murphy, D. Mischoulon, G.I. Papakostas, M. Fava, M. Berk, C.H. Ng, Adjunctive nutraceuticals for depression: a systematic review and meta-analyses, Am. J. Psychiatr. 173 (2016) 575–587.
[62] L. De Fililippi, M. Fournier, E. Cameroni, P. Linder, C. De Virgilio, M. Foti, O. Deloche, Membrane stress is coupled to a rapid translational control of gene expression in chlorpromazine-treated cells, Curr. Genet. 52 (2007) 171–185.
[63] P.V. Escriba, J.M. Gonzales-Ros, F.M. Goni, P.K.J. Kinnunen, L. Vigh, L. Sanchez-Magraner, A.M. Fernandez, X. Busquets, I. Horvath, G. Barcelo-Coblijn, Membranes: a meeting point for lipids, proteins and therapies, J. Cell. Mol. Med. 12 (3) (2008) 829–875.
[64] D.J. Luessen, R. Chen, Psychostimulants, brain membrane lipids and dopamine transmission, J. Biomol. Res. Ther. 5 (2) (2016) 143.
[65] T.K.M. Nyholm, Lipid-protein interplay and lateral organization in biomembranes, Chem. Phys. Lipids 189 (2015) 48–55.
[66] R. Phillips, T. Ursell, P. Wiggins, P. Sens, Emerging roles for lipids in shaping membrane-protein function, Nature 459 (7245) (2009) 379–385.
[67] Y. Uesono, Environmental stresses and clinical drugs paralyze a cell, Communicat. Integr. Biol. 2 (3) (2009) 275–278.
[68] van G. Meer, D.R. Voelker, G.W. Feigenson, Membrane lipids: where they are and how they behave, Nat. Rev. Mol. Cell Biol. 9 (2008) 112–124.
[69] D. Lowe, Antidepressants and Cell Membranes, (2012) https://blogs.sciencemag.org/pipeline/archives/2012/05/16/antidepressant_drugs_and_cell_membranes?r3f_986 = https://www.google.com/.
[70] J. Chen, D. Korostyshevsky, S. Lee, E.O. Perlstein, Accumulation of an antidepressant in vesiculogenic membranes of yeast cells triggers autophagy, PLoS One 7 (4) (2012) e34024.
[71] Y. Uesono, A. Toh-e, Y. Kikuchi, T. Araki, T. Hachiya, C.K. Watanabe, K. Noguchi, I. Terashima, Local anesthetics and antipsychotic phenothiazines interact non-specifically with membranes and inhibit hexose transporters in yeast, Genetics 202 (2016) 997–1012.
[72] D.S. Dwyer, H.B. Pinkofsky, Y. Liu, R.J. Bradley, Antipsychotic drugs affect glucose uptake and the expression of glucose transporters in PC12 cells, Prog. Neuropsychopharmacol. Biol. Psychiatry 23 (1999) 69–80.
[73] D.W. Haupt, J.W. Newcomer, Hyperglycemia and antipsychotic medications, J. Clin. Psychiatry 27 (2001) 15–26.
[74] B. Fichtl, I. Silman, M.F. Schneider, On the physical basis of biological signaling by interface pulses, Langmuir 34 (2018) 4914–4919.
[75] D.F. Horrobin, Schizophrenia as a membrane lipid disorder which is expressed throughout the body, Prostaglandins Leukot. Essent. Fatty Acids 55 (1996) 3–7.
[76] C.P. Mueller, M. Reichel, C. Muehle, C. Rhein, E. Gulbins, J. Kornhuber, Brain membrane lipids in major depression and anxiety disorders, Biochim. Biophys. Acta

1851 (2015) 1052–1065.
[77] E. Gulbins, M. Palmada, M. Reichel, A. Lueth, C. Buehmer, D. Amato, C. Mueller, C.H. Tischbirek, T.W. Groemer, G. Tabatabai, K.A. Becker, P. Tripal, S. Staedtler, T.F. Ackermann, J. van Brederode, C. Alzheimer, M. Weller, U.E. Lang, B. Kleuser, H. Grassme, J. Kornhuber, Acid sphingomyelinase-ceramide system mediates effects of antidepressant drugs, Nature Med. 19 (2013) 934–938.
[78] J. Kornhuber, C.P. Mueller, K.A. Becker, M. Reichel, E. Gulbins, The ceramide system as a novel antidepressant target, Trends Pharmacol. Sci. 35 (2014) 293–304.
[79] M. Schneider, B. Levant, M. Reichel, E. Gulbins, J. Kornhuber, C.P. Mueller, Lipids in psychiatric disorders and preventive medicine, Neurosci. Biobehav. Rev. 76 (2017) 336–362.
[80] H. Tsuchiya, M. Mizogami, The membrane interaction of drugs as one mechanism for their enantioselective effects, Therm. Med. 79 (2012) 65–67.
[81] H. Tsuchiya, M. Mizogami, Discrimination of stereoisomers by their enantioselective interaction with chiral cholesterol-containing membranes, Molecules 23 (1) (2018) E49.
[82] C. Wang, F. Ye, G.F. Velardez, G.H. Peters, P. Westh, Affinity of four polar neurotransmitters for lipid bilayer membranes, J. Phys. Chem. B 115 (1) (2011) 196–203.
[83] A. Orlowski, M. Grzybek, A. Bunker, M. Pasenkiewicz-Gierula, I. Vattulainen, P.T. Mannisto, T. Rog, Strong preferences of dopamine and l-dopa towards lipid head group: importance of lipid composition and implication for neurotransmitter metabolism, J. Neurochem. 122 (2012) 681-69.
[84] K. Jodko-Piorecka, G. Litwinienko, First experimental evidence of dopamine interactions with negatively charged model biomembranes, ACS Chem. Neurosci. 4 (2013) 1114–1122.
[85] R.S. Cantor, Receptor desensitization by neurotransmitters in membranes: are neurotransmitters the endogenous anesthetics? Biochemistry 42 (41) (2003) 11891–11897.
[86] J.R. Brody, S.E. Kern, Stagnation and herd mentality in the biomedical sciences, Cancer Biol. Ther. 3 (9) (2004) 903–910.
[87] M. Perouansky, The quest for a unified model of anesthetic action: a century in Claude Bernard's shadow, Anesthesiology 117 (2012) 465–474.
[88] Y. Ginosar, A.M. Binshtok, Mechanisms in anesthesia and analgesia: convention, crisis and the shoulders of giants, Anesthesiology 117 (2012) 451–453.
[89] S.A. Forman, A paradigm shift from biophysical to neurobiological: the fading influence of Claude Bernard's ideas about general anesthesia, Anesthesiology 118 (2013) 984–985.
[90] W. Bechtel, The cell: locus or object of inquiry? Stud. Hist. Philos. Biol. Biomed. Sci. 41 (2010) 172–182.
[91] M.A. O'Malley, S. Mueller-Wille, The cell as nexus: between the history, philosophy and science of cell biology, Stud. Hist. Philos. Biol. Biomed. Sci. 41 (2010) 169–171.
[92] T.C. Butler, Theories of general anesthesia, Pharmacol. Rev. 2 (1) (1950) 121–160.
[93] T. Kuhn, The Structure of Scientific Revolutions, University of Chicago Press, Chicago, 1962.
[94] D. Healy, The structure of psychopharmacological revolutions, Psychiatr. Dev. 4 (1987) 349–376.
[95] A.A. Baumeister, M.F. Hawkins, Continuity and discontinuity in the historical development of modern psychopharmacology, J. Hist. Neurosci. 14 (3) (2005) 199–209.
[96] B. Drukarch, H.A. Holland, M. Velichkov, J.J.G. Geurts, P. Voorn, G. Glas, H.W. de Regt, Thinking about the nerve impulse: a critical analysis of the electricity-centered conception of nerve excitability, Prog. Neurobiol. 169 (2018) 172–185.