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APPLICATION OF NANOPARTICLES IN PSYCHOPHYSIOLOGY AND PSYCHIATRY RESEARCH

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Abstract. During the past two decades, rapid development of nanomedicine has offered new opportunities in designing and evaluating novel treatment strategies for several neurological and psychiatric diseases. Application of nanomaterials as drug carriers in psychiatry has potentially numerous advantages, primarily in terms of the increased therapeutic efficiency of the medicament, and reduction of toxicity. Several research efforts have already been focused on the synthesis of antipsychotic and antidepressant nano-based drug delivery systems. Many of these nanoparticle systems have been successfully tested both in in vitro conditions and on animal experimental models. This short review presents and discusses recent discoveries in the emerging field of nanopsychiatry.

1. INTRODUCTION

During the past two decades, rapid development of nanomedicine has offered new opportunities in designing and evaluating novel treatment strategies for several neurological and psychiatric diseases. Nanoparticles, sized approximately between 1 and 100 nanometers, have in some circumstances the ability to pass through many biological obstacles, such as blood-brain barrier. That ability makes them applicable as potentially very effective markers of pathological brain tissue, as well as drug carriers. Many nanoparticles have a large surface area which enables them to be an integral part of effective drug delivery systems. Many experimental studies have so far been focused on applications of these nanomaterials in treatment of certain brain tumors, although many other neurological conditions may also have great potential when designing nano-based therapy [1-6].

Recently, some researchers have suggested that nanoparticles could be used in various psychiatric diseases. Schizophrenia, endogenous depression, bipolar disorder, and essentially, most of the disorders today treated with antipsychotic and/or antidepressive medications are potential candidates for nanotherapy. This is mainly because of the small size of nanoparticles, and also numerous possibilities regarding their conjugation with various medications, markers as other biologically active compounds. Today, certain authors often use the term “nanopsychiatry” to emphasize the importance of combining psychiatry with this emerging research area [7,8].

Nanomaterials also are applicable in experimental neurophysiology for identification and evaluation of certain physiological mechanisms related to normal brain function. Similarly as nanoparticles loaded with medications can be applied in clinical research for design of therapy strategies, they can also be used in fundamental medical sciences, such as behavioral physiology. The novel methods based on combining nanoformulations and medications that

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act as receptor agonists/antagonists may enable researchers to detect and asses physiological signaling pathways in various parts of the brain during normal mental responses to external or internal stimuli [8-11].

2. NANOPARTICLES AND BLOOD-BRAIN BARRIER

In neurology and psychiatry practice, one of the major challenges that physicians have so far been faced with, was inability of many medications to pass through blood-brain barrier [12-17]. This is the reason why in the past, many otherwise potentially efficient and non-toxic medicaments, were not included as possible solutions for brain disorders. Development of new nanomaterials as drug carriers has offered new opportunities both for researchers in fundamental medical areas and pharmaceutical industry.

Blood-brain barrier (BBB) is a complex system consisting of endothelial cells, astrocyte end-feet, and pericytes. BBB endothelial cells are connected with tight junctions (zonula occludens) which can prevent the diffusion of large hydrophilic molecules and microorganisms, such as bacteria, from plasma to the brain extracellular fluid. The probability that the compound will successfully pass through BBB depends on the diameter of the molecule, its surface charge and liposolubility. Some proteins expressed on capillary endothelial cells may also modulate BBB permeability. Typical example is P-glycoprotein (permeability glycoprotein, in some literature also called “ATP-binding cassette sub-family B member 1”) which can significantly impact bioavailability of many medicaments [18].

Of all nanomaterials able to penetrate BBB, nanoparticles made of biodegradable polymers might have the biggest applicability [17-20]. These biomaterials are relatively stable and may not interact with the reticuloendothelial system, which gives them enough time to reach the target area. The toxicity of these nano-systems is also relatively low, although further research is needed to make the definite conclusion.

3. ANTIPSYCHOTIC MEDICATIONS IN NANO-SYSTEMS: POTENTIAL VALUE OF POLYMERIC BIOMATERIALS

Recently there have been several research efforts to associate frequently applied antipsychotic medications with polymeric biomaterials. The main goals have been either to increase bioavailability / therapeutic effect of the drug or to reduce negative side effects of chronic antipsychotic administration, such as the extrapyramidal symptoms.

In psychiatry, one of the most commonly used antipsychotics is haloperidol. It represents an integral part of the treatment for schizophrenia and acute psychosis during delirium. In the past, biomaterials Polylactic acid (PLA) and Polylactic-co-glycolic acid (PLGA) in nanoparticle form loaded with haloperidol were successfully produced using homogenization and sonication methods [21]. According to the authors, the methodology described in this study is applicable to other hydrophobic-drug-polymers, and can be used for production of nano-based systems of different size and drug content [21]. This might further allow development of specific nanoparticle carriers loaded with an antipsychotic medication that would produce the biggest therapeutical effect with minimal side-effects. If these observations are confirmed in future experiments, it could open numerous possibilities regarding future clinical trials of nanoparticle-associated antipsychotic drugs.

Another frequently used antipsychotic, risperidone was also successfully developed in Polylactic-co-glycolic acid nanoparticle formulation [Table 1] [22]. In this study, Muthu et al. used nanoprecipitation method synthetize PLGA nanoparticles of risperidone using Poloxamer 407 (polymeric stabilizer). It has been demonstrated that when risperidone is administrated to laboratory animals in this form, its antipsychotic effects are more prolonged, possibly because of the accumulation of the active metabolite 9-hydroxy risperidone [22]. Also very important observation of these experiments was the reduction of extrapyramidal side effects in Swiss albino mice following the intravenous administration of risperidone-loaded nanoparticles, when compared to controls.

Manjunath and Venkateswarlu have performed a study on a yet another atypical antipsychotic, clozapine, which is today also routinely used for schizophrenia treatment [23]. The research investigated pharmacological properties of clozapine solid lipid nanoparticles in animal experimental model after intravenous and intraduodenal administration. It was found that the bioavailability of this clozapine drug delivery system is much higher compared with conventional administration [23]. Indeed, solid lipid nanoparticles may in the future prove to be very applicable not only as drug carriers for antipsychotics, but also for many other lipophilic medications, enabling them to effectively pass the blood-brain barrier.

Table 1. Major psychiatric medications as the possible part of drug delivery nano-systems.

Generic name of the medication	Nanoparticle-based system	Reference
Haloperidol	PLA / PLGA	Budhian et al. International journal of pharmaceutics, 2007;336:367-375.
Risperidone	PLGA	Muthu et al. Nanomedicine: nanotechnology, biology, and medicine, 2009;5:323-33.
Clozapine	Solid lipid nanoparticles	Manjunath & Venkateswarlu. Journal of controlled release. 2005;107:215-28
Valproic acid	Dextran-stabilized and polysorbate 85-coated nanoparticles	Darius, et al. The Journal of pharmacy and pharmacology. 2000;52:1043-7.
Duloxetine	Solid lipid nanoparticles	Patel et al. AAPS PharmSciTech. 2012;13:125-33.
Venlafaxine	Chitosan nanoparticles	Shah, et al. J Appl Polym Sci. 2009;112:2876–87.
Mirtazapine	Ethyl cellulose-based system	Choudhary et al. J Adv Pharm Sci. 2013;3:511-20

4. ANTIDEPRESSANTS AND NANOPARTICLES: APPLICATION OF BIOMATERIALS AND SOLID LIPID NANOPARTICLE FORMULATIONS

Apart from the mentioned research efforts regarding antipsychotic medications, during the past decade, several studies have been focused on investigating the possibility of synthesis of a nano-based system for targeted drug delivery that would include antidepressant drug as its integral part. Similarly as with antipsychotics, the main goal would be to increase effectiveness, and to reduce toxicity of such complex compound.

In 2000, Darius et al. published a study on mouse brain tissue kinetics of valproic acid associated with dextran-stabilized and polysorbate 85-coated nanoparticles. It was concluded that nanoparticles may help in reduction of potentially toxic metabolites of valproate [12]. This study is one of the first in which nanoparticles were loaded with a drug commonly used as mood-stabilizer. Indeed, apart from its applications in the treatment of epilepsy, valproic acid, at different dosages is also applied in psychiatry as occasional therapy for bipolar disorder, and other conditions in which severe depression symptomatology may be present. If in the future a nanoparticle-based valproate medicament is proven efficient for human treatment, it could open the possibility of increasing the valproate doses in neurological and psychiatric diseases without the fear of toxic side-effects.

Recently, another major antidepressant medicament, duloxetine was designed and produced in solid lipid nanoparticle formulation [24]. Duloxetine (in the pharmaceutical market known as Cymbalta) is a serotonin-norepinephrine reuptake inhibitor (SNRI), in some countries occasionally applied for the therapy of moderate/major depression and generalized anxiety disorder. The potential problems in clinical duloxetine application is chemical instability and inefficiency due to the inactivation (first-pass metabolism). Patel et al. suggested that solid lipid nanoparticles of duloxetine have higher stability in *in vivo* conditions [24]. This form could greatly improve the therapeutic effectiveness of the drug after the oral administration.

It was also shown that various biopolymers, until today relatively rarely applied in neuroscience research, can also be associated with antidepressant drugs [25]. For example, chitosan biomaterial, in nanoparticle form was successfully loaded with venlafaxine hydrochloride [25]. Chitosan is today one of the most frequently researched biomaterials, whereas venlafaxine is a potent serotonin–norepinephrine reuptake inhibitors with many similarities to duloxetine. The study in question tested the nanosystem using conventional microscopy and spectroscopy methods (transmission electron microscopy, dynamic light scattering, X-ray photoelectron spectroscopy, etc.). It goes without saying that it is expected that in the future, the same formulation will be tested on laboratory animals in terms of establishing drug efficiency and toxicity.

Choudhary et al. have recently demonstrated that it is possible to design and produce a nanoparticle drug delivery system for water soluble antidepressant mirtazapine which belongs to the class of mixed serotonin/nor adrenaline reuptake inhibitors [26]. For synthesis of mirtazapine nanoparticles, the authors used ethyl cellulose, a common biomaterial with some unique physical and chemical properities [26]. The study also investigated drug release rates in different in vitro conditions.

5. CHALLENGES IN NANOPSYCHIATRY RESEARCH

As mentioned previously, it is obvious that application of nanoparticles as drug carriers in psychiatry has potentially numerous advantages, primarily regarding the increased therapeutic efficiency of the medicament. However, despite this initial rapid development of the nanopsychiatry field, today there are hardly any clinical applications of these nanosystems regarding their potential addition to the conventional treatment. So far, virtually all studies are carried out either on experimental animal models, or in in vitro conditions. Unfortunately, there are several issues that need to be addressed before eventually a clinical trial is designed and implemented.

First of all, the potential toxicity of many nanoparticle systems has not yet been properly evaluated [27-29]. There is a significant lack of data regarding neuro, neprhro and hepatotoxicity for many commonly used biomaterials. Although in some cases there have been numerous research efforts in this direction, the results are often inconclusive or conflicting. Many nanomaterials are sometimes proclaimed safe by studies testing acute toxicity, however this does not necessarily mean that they have no detrimental health effects on the long run. This is particularly important when assessing immuno and genotoxicity of nanoparticles [30-35].

The situation is further complicated by the lack of established gold standard tests for toxicity evaluation of nanoparticles [36]. For example, although it is known that some nanomaterials may have some immunomodulatory effects, different tests (i.e. ELISA and Plaque forming cell assay for assessment of humoral immune response) may in some cases produce different results. Similar problems exist when it is needed to evaluate genotoxicity and cancer potential of nanosystems. Since nanotechnology in general is relatively new research area, so far, for most nanomaterials, not enough time has passed in order to conduct a valid research, and to come to a definite conclusion regarding cancerogenicity. In psychiatry research, it is imperative that all these issues are resolved before decision is made for any potential clinical trials, especially because the treatment for most of the diseases mentioned in this text often lasts for long time periods during which any toxicity effects, however minor, can manifest in its severe forms.

6. FUTURE OF NANOPSYCHIATRY

It can be expected that in the future many more psychiatric drug nanoparticle formulations will be designed and tested in *in vitro* conditions and on laboratory animals. Most of the research so far has been focused on polymeric biomaterials, mostly because of their biodegradability and the ease of synthesis. On the other hand, there is a significant lack of data regarding the possibility of producing conjugates between psychiatric medicaments and inorganic nanomaterials. Gold and iron nanoparticles are today widely used in clinical research, and numerous studies have emphasized their potential as drug carriers in cancer therapy [37-42]. Perhaps, these nanomaterials, when associated with psychotherapeutics, could have similar physical and chemical properties as the case with cytostatic drugs.

The majority of the nanopsychiatry studies mentioned in this article has been focused on the development and assessment of nanoformulations consisting of antipsychotics and antidepressants. In many countries, however, most commonly prescribed medications in psychiatric practice are anxiolytics such as benzodiazepines (typical examples include Diazepam, Lorazepam and Midazolam), which are commonly used for treatment of anxiety, panic disorder, insomnia, convulsions etc. It remains to be seen whether successful conjugation of these drugs with nanoparticles would have positive impact on their biodistribution and bioavailability.

Finally, apart from new opportunities in therapy of psychiatric disorders, another major benefit of nanomaterials in the past decade has been the possibility of their application in fundamental neurosciences. Nanoparticles may in the future be useful as markers of specific regions of the central nervous system which could be of great importance in psychophysiology research. Unique physical and chemical properties of some nanosystems could be helpful in determining the connection between morphological aspects of brain tissue and normal psychic functions. The development nanomaterisls as contrasting agents for novel imaging techniques

such as nuclear magnetic resonance and positron emission tomography may help us understand the physiological basis of many normal and pathological mental conditions.

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