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GOLD NANOMATERIALS IN CONTEMPORARY NEUROPHYSIOLOGY, NEUROLOGY AND PSYCHIATRY RESEARCH

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Abstract. Nanoneurology and nanopsychiatry are today promising, rapidly growing disciplines, and many research efforts have so far been focused in design of nanoparticle-based biosensors and drug delivery systems that would be an addition to conventional diagnostic methods and therapeutic strategies. Gold nanoparticles (AuNPs) are especially important in these research areas since it has been shown that they can successfully alter physical and chemical properties of many medications, as well as other substances applicable in neuroscience research. This concise article focuses on experiments and theoretical assumptions regarding application of AuNPs in neurosciences performed during the past 10 years in *in vitro* conditions and animal experimental models. Issues such as AuNP - mediated detection of brain neurotransmitters, and transport through blood brain barrier are also discussed, as well as association of AuNPs with medications commonly applied in modern neurological and psychiatric practice.

1. INTRODUCTION

Rapid development of nanotechnology at the beginning of the 21st century has caused profound changes in the field of fundamental biomedicine, as well as some clinical disciplines [1-6]. Various nanomaterials have been successfully designed and applied as efficient drug carriers, diagnostic bioassays and objects for cell biology research [7-17]. In clinical research, nanomaterial-based medications have been proposed as potential future addition to conventional therapy for many neurological diseases, especially cancers. It was estimated that inclusion of these medications in contemporary cancer treatment, could increase specificity of the drug for malignant cells while on the other hand minimizing the potential damage to the surrounding healthy tissue and other harmful side-effects [18,19].

In recent years, there has been limited data indicating that gold nanoparticles could be an important addition to diagnostic and treatment strategies for several psychiatric diseases. Nanopsychiatry as a novel and rapidly growing research area, has introduced several innovative concepts regarding conjugation and functionalization of nanoparticles with psychiatric medications. Gold nanoparticles (AuNPs) specifically, have been successfully associated with some antipsychotic medications [20]. It remains to be seen whether these drug-nanoparticle interactions will provide better distribution and bioavailability of therapeutics in affected areas of central nervous system.

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Unfortunately, research in these fields is often faced with numerous methodological and technical difficulties. Not all gold nanoparticles are the same, regarding their physical and chemical properties, such as diameter, shape, surface charge etc. Furthermore, although there have been significant discoveries in *in vitro* conditions, in living tissues and organisms, many aspects of AuNP distribution, accumulation, and elimination remain unknown. Finally, toxicity of many forms of AuNPs is not fully investigated, and very few research efforts have been made to evaluate their potential toxic effects in vertebrate laboratory animals.

This concise article focuses on experiments and theoretical assumptions regarding application of AuNPs in neurosciences performed during the past 10 years in cell cultures, animal models. Issues such as AuNP – based targeted drug delivery and AuNP biochemical properties are also discussed, as well as ideas and recommendations for further research in the emerging fields of nanoneurology and nanopsychiatry.

2. COLLOIDAL GOLD SUSPENSIONS

Colloidal gold suspensions have been used for centuries due to their supposed health benefits. In alternative medicine, AuNPs have been traditionally used as an addition to conventional treatment of joint pain relief, obesity, addictions, Parkinson's disease some types of cancers etc. The claims that AuNPs are effective in these diseases are not verified, and to our knowledge, so far, official evidence-based medicine did not find any substantial proof that ingestion of colloidal gold can be an efficient substitute for conventional therapy in neurologic and psychiatric diseases.

Nevertheless, in many countries colloidal gold solutions are often sold as nutritional supplements, and manufacturers state that they are beneficial both for neurological disease prevention and as potential therapeutics. These over-the-counter products are sold without prescription and are at relatively low prices available to general population which may carry certain public health risk. In recent years colloidal gold dietary supplements consisting of gold nanoparticles sized 10-30 nanometers, can even be bought online using popular internet shopping sites which further diminishes the control of these products by regulatory bodies and agencies.

The average diameter of colloidal gold nanoparticles used in experimental neurosciences usually ranges from 5 to 70 nanometers and it is one of the main factors influencing light absorption and reflection of the NP solution, and subsequently, its color. The peak surface plasmon resonance also partially depends on the AuNP diameter and it is usually between 520 nanometers for small NPs, and 570 nm for larger particles. Gold nanoparticles in general are usually sold in stabilized suspension forms in citrate buffer or phosphate buffered saline. Colloidal gold containing nanorods is often sold as water dispersion stabilized with Cetyltrimethylammonium bromide, which is a common surfactant. It has been suggested that Cetyltrimethylammonium bromide has several chemical properties that makes it cytotoxic in in vitro conditions which is potentially a big obstacle when performing experiments in cell cultures and isolates [21].

Several studies regarding bioavailability, biodistribution and protein interaction of colloidal gold nanoparticles have been done during the past decade. For example, Sonavane et al. (2008) demonstrated uneven distribution of AuNPs in various tissues and organs after intravenous administration in mice. This research demonstrated that colloidal AuNPs are mainly accumulated in liver, lung and spleen, although other organs such as brain were also affected [22]. This brain accumulation is of potential significance in design of colloidal AuNP – based medications. Interaction of colloidal gold nanoparticles with human blood has also been studied. Dobrovolskaia et al. (2009) investigated plasma protein binding profiles for surface of citrate-stabilized AuNPs, having in mind nanoparticle size (30 and 50 nanometers). Elements of coagulation, as well as the complement system were analyzed [23]. Since many pharmacokinetic features of colloidal gold particles sized from 5 to 50 nanometers are relatively known, these nano-systems are important candidates for functionalization as drug carriers or biosensors.

3. GOLD NANOPARTICLES AS BIOSENSORS IN CENTRAL NERVOUS SYSTEM

Functionalized gold nanoparticles have recently been applied as part of biosensors for detection and monitoring various processes both in central nervous system [24,25]. Many of these biosensors were design in order to quantify certain physiological properties of vertebrate brain. For example, glass capillary nanoelectrodes sheathed with AuNPs were developed to monitor the levels of dopamine in the rat striatum [26]. These sensors proved to be highly selective for dopamine which is an important neu-

rotransmitter affected in numerous neurological and psychiatric diseases. These findings are also important as a basis for creation of a future neurophysiological animal experimental model.

In another publication, ferrocene-capped gold nanoparticle/streptavidin conjugates were also shown to be useful in indirectly quantifying levels of dopamine [27]. The sandwich-type electrochemical biosensor was tested for dynamic range, detection level, selectivity, interference as well as the reproducibility.

Apart from dopamine, Au-based systems for other neurotransmitters were evaluated as well. In 2011, Chauhan et al. developed a gold electrode modified by gold-nanoparticle-CaCO*f* hybrid material and tested it on neurotransmitter acetylcholinesterase which was purified from rat brain. The principle of this biosystem was the detection of organophosphorous insecticides which inhibited brain acetylcholinesterase [7]. The authors claimed good reusability of the sensor, and if these results are confirmed in the future research, this method might be valuable in neurotoxicology studies.

A combination of gold and platinum (bimetallic) nanoparticle H_2O_2 biosensor was manufactured to test the levels of yet another neurotransmitter, glutamate [28]. $C_3(OH)_2mim][BF_4]$-Au/Pt biosensor was sensitive in detecting glutamate concentration variations in subcortical structures of the rat forebrain.

On the other hand, many AuNP- based biosensors were created specifically to detect pathological changes in brain tissue. Recently, Elshafey et al. (2013) described a label-free impedimetric immunosensor based on gold nanoparticles-protein G which was able to detect brain epidermal growth factor receptor (EGFR). The study, performed on brain homogenates and plasma, showed excellent reproducibility of the method, as well as good sensitivity and specificity [9]. Since EGFR is a potentially important marker of cancer tissue, there is a vast potential application of this sensor system in both the fields of oncology and fundamental cancer research.

Gold nanoparticle can in some circumstances be used for X-ray computed tomography tracking of cancer cells in malignant brain tumors. In 2013, Astolfo et al. presented this method and tested it on rat glioma cells. This technique was probably the first in vivo synchrotron computed tomography study, in which gold nanoparticles as CT signals were applied [29].

Finally, gold nanostructures as electric microdevices were reported to be applicable in neurophysiological research of action potential. Recently, Kim et al. (2013) described a microelectrode based on 500 nm nanograin structures with relatively low impedance and high electrical stimulation capability in comparison to conventional gold microelectrodes. The system proved capable of evoking action potentials in rat hippocampal neuronal culture [30]. Apart from application as the part of a cell biosensor, this method could be useful for creation of in vitro model suitable for research of axonal conductivity.

4. GOLD NANOPARTICLE AS DRUG DELIVERY SYSTEMS

Nanoparticles in general, when adequately functionalized can serve as efficient drug carriers to various cells, tissues, and organs [14,31-38]. It is assumed that this way, selectivity for pathological tissue such as cancer, can be increased while at the same time reducing negative side effects of the therapy. In fundamental research, in vitro and in laboratory animals, nanoparticles have so far been used as drug delivery platforms for a variety of neurological and psychiatric medications, including antipsychotics, antidepressives, antiepileptics, and chemotherapy for brain cancers. Research on AuNPs has mainly been focused of brain cancer medications, some anti- Alzheimer's therapeutics, while there is very limited data on AuNP-antipsychotics interactions.

In 2014, Cheng et al. described novel transactivator of transcription (TAT) peptide-modified gold nanoparticle platform which is able to effectively pass through blood-brain barrier and reach brain tumor tissue [39]. Blood-brain barrier in general is the main obstacle for many neurological and psychiatric medications, so any therapeutic system capable of crossing this histological boundary could prove useful in designing novel treatment strategies and improving therapy outcomes and disease survival. Furthermore, a medication capable of more efficiently crossing blood-brain barrier can be administered in much lower concentrations which results in fewer unwanted systemic adverse effects, such as nephrotoxicity and hepatotoxicity. In the above-mentioned study, gold nanoparticle – based system was used for delivering a chemotherapeutic agent (doxorubicin), as well as gadolinium contrast agent which is commonly applied for magnetic resonance imaging [39].

Apart from brain tumors, gold nanoparticles might be successfully used as drug delivery platforms for other neurological diseases. For example, recently, Gao et al. (2014) synthetized AuNPs@POMD-pep system (gold nanoparticles/polyoxometalate with Wells-Dawson structure /peptide) for targeted inhibition of Amyloid-β in central nervous system [40]. Amyloid-β –induced neurotoxicity is an important hallmark of Alzheimer's disease, and many research efforts have been focused on its reduction by applying various chemical compounds. This platform, as the one previously mentioned, was able to effectively cross blood-brain barrier which is one of its major advantages.

Certain antipsychotic medications can be prepared in a form of nanosystem with the help of gold nanoparticles, which might improve their biodistribution, bioavailability and therapeutic efficiency. Thioridazine, which belongs to phenothiazine typical antipsychotic class of drugs, sometimes used for treatment of schizophrenia, is one of such medications. It has been shown that using gold nanoparticles, it is possible to manufacture ethyl cellulose (EC) microcapsules containing thioridazine [20]. Nanoparticles substantially increased thioridazine encapsulation which may be useful for further psychopharmacology research.

Unfortunately there is a significant lack of scientific data regarding association of gold nanoparticles with psychiatric medications, as well as overall feasibility of this kind of drug delivery platforms. For example, to our knowledge, no study has ever been done to test the possibility of facilitating the delivery of antidepressants to central nervous system by gold nanoparticles. Biophysical and chemical interactions between AuNPs and sedatives, mood stabilizers and stimulants are also unclear.

5. CONCLUDING REMARKS

It should be noted that nanoneurology and nanopsychiatry are today promising, rapidly growing disciplines, and many research efforts have so far been focused on the design of nanoparticle based biosensors and drug delivery systems that would be an addition to conventional diagnostic methods and therapeutic strategies. Gold nanoparticles are especially important in these research areas since it has been shown that they can successfully alter physical and chemical properties of many medications, as well as other substances applicable in neuroscience research.

Most research studies covered in this article were done either in *in vitro* conditions or in experimental animal models. In the future, it remains to be seen whether any of these findings can be applied in clinical conditions. Before any of these nanosystems can be tested in human subjects, adequate tests need to be performed in order to evaluate potential toxicity in kidney, liver and other organs. Nevertheless, the potential for application of gold nanomaterials in neurology and psychiatry is immense, and it can be expected that in the next several decades these applications will become an important part of many clinical research protocols.

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