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The Nanotechnological Approach in Treatment of Drug Addiction

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Review Article

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ABSTRACT

Drug addiction is a major health concern worldwide in which addiction plays major role. Addiction is caused by activation of the dopaminergic pathway within the brain. Initially individuals will take drugs based upon their interest, however using continuously will result in changes that make a dependant person out of control and they will be addicted to the particular drugs. On the other hand Nanotechnology is a scientific endeavour, in which there is utilization and creation of materials on the nanometer scale. The sector of engineering is presently undergoing development in many areas. The technology is anticipated to make innovations and play an important role in numerous medical applications. Here this article tends to introduce an engineering science approach which makes utilization of gold nanorod-DARPP-32 siRNA (short interfering RNA) complexes called as nanoplexes that concentrate on this dopaminergic signal pathway within the brain. The shift within which there is an interaction between localized longitudinal plasmon resonance peak of gold nanorods (GNRs) and siRNA. There is uptake of those nanoplexes in dopaminergic neurons *in vitro* during plasmonic increased dark field imaging. There is no determined toxicity with cistron silencing of the nanoplexes within these cells was proven by the reduction in the expression of key proteins like DARPP-32, ERK, and PP-1. In vitro model of the blood–brain barrier (BBB) nanoplexes were shown to transmigrate. So, these nanoplexes utilizing brain-specific delivery of acceptable siRNA seems to be fitted for therapy of dependency and other brain diseases. Nanotechnology has associate increasing impact within the health care industry not only in diagnostic and therapeutic areas and also in the delivery targeted into specific sites and across some complicated biological barriers.

INTRODUCTION

Addiction is a chronic sickness which is characterized by use of drugs which is compulsive and troublesome to manage by the individual. Initially individuals will take drugs based upon their interest, however using continuously will result in changes that make a dependent person out of control and insist them to take medication. These brain changes may be persistent, that is why dependence comes under "relapsing" disease because people once got treated from drug addiction can become drug addicts at any time even after years.

Changes in the Brain When Someone Takes Drugs?

Most medication has an effect on the brain's "reward circuit" by flooding it with dopamine which is a chemical messenger. This system controls the body ability to experience pleasure and encourages individuals to repeat doing pleasurable things like taking favorite food and being with loved persons. The individuals will take drug again and again due to overstimulation of this reward circuit [1-5].

As someone keeps on using these medications, the brain will get adjusted to the increased dopamine levels by making cells in the reward circuit with no response. This leads to a state called as tolerance which make

individuals to take more drug than the amount they took for the first time as they won't have the same experience which was before. They may take a lot of the drug, attempting to attain equivalent dopamine high levels. It also can make them to experience less pleasure from things they once enjoyed.

Nanotechnology is a branch of engineering that deals with the design and manufacture of minute electronic circuits and mechanical devices designed at the molecular level [6-10]. Nanotechnology is commonly mentioned together with micro-electromechanical systems (MEMS); a theme that sometimes includes technologies beyond the molecular level.

Nanotechnology, a multidisciplinary scientific endeavour, involves creation and utilization of materials, devices on the nanometer scale. The sector of engineering is presently undergoing explosive development on several fronts. Nanotechnology plays an important role in many medicinal applications, not only in drug delivery and also in molecular imaging as well as in biomarkers and biosensors [11-15]. This also plays an important role in Target-specific drug therapy and also for early diagnosing of pathogenesis of the diseases.

Nanotechnology in Drugs

The use of nanotechnology in drugs offers some exciting possibilities. Some techniques are solely imaginary, whereas others are at varied stages of testing and really getting used these days.

Nanotechnology in drugs involves applications of nanoparticles presently under development, similarly as longer vary analysis that involves the utilization of manufactured nano-robots to create repairs at the cellular level (sometimes named as nanomedicine). Whatever you call it, the utilization of nanotechnology within the field of medication may revolutionize the way we observe and treat damage to the human body and disease in the future, and lots of techniques solely imagined a few years past are creating remarkable progress towards turning into realities [16-25].

Drug Delivery

One of the major application of technology in drugs presently being developed involves using nanoparticles to deliver drugs, heat, light or other substances to specific forms of cells (such as cancer cells) [26-32]. Particles are built in such an order that they are attracted to diseased cells to permit direct treatment of these cells. This system reduces harm to healthy cells within the body and permits for earlier detection of disease.

Therapy Techniques

Researchers have developed "nanosponges" that absorb toxins and take them away from the blood. The nanosponges are compound nanoparticles coated with a red blood cell membrane. This will allow the nanosponges to travel freely within the blood and attract the toxins [33-40].

Diagnostic Techniques

Researchers have developed a new sensor technique by using carbon nanotubes which were embedded in a gel; that may be injected underneath the skin to watch the extent of nitric oxide within the blood. Inflammation is indicated by nitric oxide so the extent of it is important which gives direct monitoring of inflammatory diseases. There are tests conducted in laboratory mice with this sensor technique in which it remained functional for a year.

Nanotechnology in Drug Addiction

Drug addiction is a major health concern worldwide in which addiction undergoes activation of the dopaminergic pathway within the brain. Adela C. Bonoiu et al, tend to introduce an engineering science approach that utilizes gold nanorod-DARPP-32 siRNA (short interfering RNA) complexes (nanoplexes) that concentrate on this dopaminergic signal pathway within the brain [41-49]. The shift within the localized longitudinal plasmon resonance peak of gold nanorods (GNRs) was accustomed to show their interaction with siRNA. Plasmonic increased dark field imaging was accustomed to visualize the uptake of those nanoplexes in dopaminergic neurons *in vitro* [50-57]. Cistron silencing of the nanoplexes within these cells was proven by the reduction in the expression of key proteins (DARPP-32, ERK, and PP-1) of the present pathway, without causing toxicity. These nanoplexes were shown to transmigrate across associate degree *in vitro* model of the blood–brain barrier (BBB). So, these nanoplexes utilizing brain-specific delivery of acceptable siRNA seems to be fitted for therapy of dependency and other brain diseases [58-63].

Nanotechnology has associate increasing impact within the health care industry not only in diagnostic and therapeutic areas and also in the delivery targeted into specific sites and across some complicated biological barriers [64-69].

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DISCUSSION

In Narcotic addiction there is activation of the dopaminergic pathway in the brain, within which adenosine 3′, 5′-monophosphate-regulated phosphoprotein (DARPP-32) has an important role. Recently, each dopamine and salt receptors are involved in causing alteration of DARPP-32, leading to signal-regulated enzyme (ERK) mitogen-activated protein (MAP) kinase cascades activation. ERK has major role in altering the properties of some medication of abuse [70-76]. The observations indicate that the central molecular triggering the alterations associated with substance abuse is DARPP-32. Therefore, they tend to hypothesise that the concealment of DARPP-32 quality expression utilizing siRNA antagonism in dopaminergic neuronal cells can result in drug addiction inhibition.

However, a serious limitation for the employment of this gene silencing method is that the lack of strategies and with efficient delivery of siRNA molecules to focus on specific cells/tissues. The siRNA really have a short half-life particularly in physiological conditions, because they are vulnerable to endogeneous nucleases degradation. Therefore, they have vectors which will not solely defend them from the process of degradation within the biological environment, however additionally bring them to cells/tissues and facilitate their entry into the cells. Furthermore, the brain, which is the organ for drug addiction therapy is inaccessible organ for siRNA delivery because of the presence of the blood–brain barrier (BBB), which is responsible for brain-specific delivery of 100% of large-molecule medicine and ninety eight of all small-molecule neurotherapeutics [77-80].

Recently both nanorods (GNRs) and gold nanoparticles (GNPs) have gained more interest as site-specific carriers of some therapeutic and diagnostic agents, initially because of their biocompatibility. Their surface can be changed easily to include cationic charges, which will have constant static complexation with siRNA which is an anionic genetic material, aiming for targeted delivery or silencing [81-86].

Adela C. Bonoiu introduced a nanotechnology-based different approach for factor silencing-mediated drug addiction therapy. They tend to explain that GNRs electrostatic complexation with nanoplexes which is used for modulating dopaminergic communication pathway. Moreover, they tend to determine that the delivery of the nanoplex involving siRNA against the DARPP-32 factor in DAN cells resulted not only DARPP-32 silencing, but also other downstream effector molecules of this pathway, like ERK and macromolecule phosphatase-1 (PP-1). Finally these nanoplexes showed considerably higher transmigration potency across a BBB model *in vitro* that of free siRNA. Therefore, these nanoplexes seem to be ideally fitted to brain-specific delivery of applicable siRNA for treatment of not only addiction and also different brain diseases.

The GNR nanoplex-mediated modulation of dopaminergic communication pathway, alongside the observation of its transport across the BBB *in vitro* model is predicted to guide the new nanotechnological treatment choices for drug abuse by modulating each transcriptional and translational event within the brain which is concerned with the addictive behavior.

The main goal of the treatment is to reduce the withdrawal symptoms of drug addiction. In this area this gene silencing will have major role and a new approach.

In this study, they are many results which were encouraging and suggest the *in vivo* approach. Firstly, the nanoplexes will have negative charge causing interaction with different biomolecules and physiological proteins non-specifically. Next, they have an effect on very high potency of sequence silencing in an exceedingly sustained manner. Finally, their ability to cross the BBB *in vitro* and maintain their practicality influences the *in vivo* success.

Other study has been evolved developing quantum rod (QR) for the delivery of tiny interfering RNAs (siRNAs) to human neuronal cells. For down-regulating the dopaminergic pathway, PEGlyated QRs with different functional groups (amine and maleimide) was designed which is related to the substance abuse behaviour selectively [87-91]. The method has more compatibilities and very limited cytotoxicities.

Many other method invoving Lipofectamine, siPORT and polyethylenimine (PEI) polymer are developed. But toxicity and high reactivity in physiological surroundings of those materials have restricted for more studies (e.g. *in vivo*).

Nanotechnology approach which utilizes siRNA-nanoparticle complexes has to be developed into a strong tool for treatment of many pathological or behavioral conditions at the genetic level within the human brain. This could have the application of siRNA-based therapeutics against not only in drug addiction, but also against many different chronic diseases [92-94]. Within the current report, they tend to present 2 kinds of anisotropic nanocrystal quantum rod (QR)-siRNA nanoplex styles, which are supported phospholipid micellar system, for gene silencing-mediated drug addiction therapy.

As this DARPP-32 plays a major role in abuse behavior which involves activation of the dopaminergic signaling pathway in the brain, the addiction behavior is controlled by modulating the gene expression of DARPP-32. For carrying biomolecules quantum rod has become an attractive tool because of its distinctive properties over the organic dye, like tunable emission wavelength, single excitation supply for wide selection of emission, less tendency to photobleaching and longer period of time. And the limitation for this is the toxicity issue with the heavy-metal nature. The phospholipids employed in our study (DSPE-PEG-Amine and DSPE-PEG-Maleimide) can be divided into 3

moieties: (i) DSPE, the hydrophobic part to form the QR into aggregates, (ii) PEG, the spacer to overcome the steric barrier and (iii) amine or maleimide-functional groups for siRNA conjugations by electrostatic force or covalent bond. Phospholipids were chosen during this study as a result of wonderful *in vivo* biocompatibility, drug load capacity and tumor targeting capability of QD-phospholipid complex are demonstrated by our group. Thus, the designs given here are often quickly adopted and may provide us an extra "layer" that permits targeted treatment to some diseases along with employment of drug [95-97].

In another study Mahajan demonstrated that the dopamine- and cAMP-regulated phosphoprotein of DARPP-32 is responsible for pathogenesis of drug addiction by changing both transcriptional and post-translational events in dopaminergic neurons of the brain. DARPP-32 is a central mediator of the extracellular signal-regulated kinase (ERK) signaling cascade activity, the activation of which results in mechanism that propagates the cycle of addictive behaviors. Mahajan hypothesized that inhibition of the gene expression of DARPP-32 by dopaminergic neurons *in vivo* using specific short interfering RNA (siRNA) will get rid of the behaviors associated with drug addiction. An innovative gene therapy for drug addiction was discovered by silencing of DARPP-32 utilizing an innovative, nanoparticle-based delivery system using gold nanorods (GNR) complexed with siRNA specific for DARPP-32 plus tranferrin to specifically cross the blood-brain barrier (BBB) and neurons which were targetted. In this proposal, they chemically characterized the GNR (nanorods) and develop stable nanoplexes containing siRNA and transferrin, which can effectively silence DARPP-32 gene expression *in vivo* conducted in the brains of an animal model of opiate addiction, thereby suppressing addictive behavior. Additionally, they generated mechanism-based pharmacodynamics (PD) models for evaluating DARPP-32 signaling and its implications in drug dynamics.

Based on the above hypothesis, the subsequent specific aims are planned.

1) To optimize the conditions for the efficient delivery of gold nanoplexes across the BBB, *in vivo*, in an established rat model of chronic opiate abuse employing a GNR-DARPP- 32siRNA nanoplex and to judge its result on gene silencing and therefore the protein expression of DARPP-32.

2) To analyze the effects of delivery of GNR-DARPP-32 siRNA nanoplexes *in vivo* on opiate withdrawal behavior in an established rat model of chronic opiate abuse.

3) To develop predictive models of DARPP-32 signaling employing a novel multi-scale analytical approach to work out the complex interrelationships between cell systems and drug factors that will influence drug addiction and its treatment.

Further the pharmacodynamics models can emerge from this study will facilitate describe, understand, and predict the complicated interactions between neurotransmitters with their receptors and complicated mechanisms of action that underlie the method of drug addiction. Medicines of abuse act on the dopaminergic system of the brain and perturb the function of dopamine and cAMP-regulated protein of thirty two kDa (DARPP-32), that is vital to the pathological process of dependency. This project involves silencing of DARPP-32 gene expression using innovative nanotechnology based siRNA therapeutics delivered to the brain *in vivo* as a new approach in the drug addiction treatment [98-100]. In addition, they are going to generate pharmacodynamics (PD) models for evaluating DARPP-32 signal and its implications in dependency.

CONCLUSION

Nanotherapy, combined with ancient psychological and scientific methods, might yield a more practical therapeutic approach. However, there are many limitations for effective siRNA delivery and activity *in vivo* that should be overcome for achieving therapeutically effective sequence silencing. Though the study demonstrates the effectiveness of this use of GNRs as a good transport platform for siRNA, *in vitro*, their effectiveness *in vivo* has to be determined.

The ability of the GNR-siRNA nanoplex to cross the blood-brain barrier recommends that they can be administered by a peripheral i.v. route also. Lastly, this is not only sole therapy for the treatment of addiction. Rather, DARPP-32 sequence silencing may be used initially to interrupt the cycle of addiction. Moreover, this nanotechnology-based sequence silencing approach additionally might have a task in broader applications for the treatment of various different brain specific diseases/disorders.

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