Guest Editorial

Nanoneuropharmacology: A challenging concept in pharmaceutical investigations for the next decade

A rapid increase in the incidence of neurodegenerative disorders has been observed with the aging of the population. During the last decade, a large number of pharmacologic compounds with differing brain targets were investigated. Pharmacologic agents developed using classical strategies of pharmacologic development are frequently limited by pharmacodynamics and pharmacokinetics problems, such as low efficacy or lack of selectivity. In addition, many drugs have poor solubility and low bioavailability, and they can be quickly degraded or cleared. Furthermore, the efficacy of different drugs is often limited by dose-dependent side effects. The targeted drug delivery to the central nervous system (CNS), for the diagnosis and treatment of neurodegenerative disorders, is restricted due to the limitations posed by the blood–brain barrier (BBB), the opsonization by plasma proteins in the systemic circulation, and peripheral side effects.

The conventional approach to tackling brain disorders is to modify the availability of a functional transmitter or the class of transmitter. The main issue of neuropharmacology has been that the transmitter systems in the brain are widespread; hence, any drug modifying an abnormality in one part of the brain will inevitably induce an activity in another region of the brain where the transmission was previously functioning normally, thereby giving rise to side effects.

With the rapid development of nanotechnology, targeting drug molecules to the site of action could become a reality, reducing the effect of the drug on other sites while maximizing the therapeutic response. In addition, nanoparticles (NPs) can be prepared to entrap, encapsulate or bind molecules improving the solubility, stability, and absorption of several drugs, as well as avoiding the reticuloendothelial system, thus protecting the drug from premature inactivation during its transport. Apart from their therapeutic or pharmacologic use, NPs are developed for diagnostic purposes to monitor disease progression or pharmacologic targets. Advances in nanobiotechnology have already made an impact on neurosciences during the past few years with a tremendous increase in the number of scientific publications [Figure 1]. Further advances in nanoneurosciences are expected during the next decade, with focus on nanoneuroprotection and nanoneurotoxicology, for the improvement of the knowledge of physiopathologic mechanisms, of diagnosis, and of pharmacologic drug delivery for therapeutic applications. Different nanocarriers are being developed to diagnose, to treat, and to label biomarkers by delivering at a constant rate over time, extending up to days, weeks, or even months. Indeed, nanoneuropharmacology, that is, nanoparticle-mediated drug delivery, represents one promising strategy to successfully increase the CNS penetration of pharmacologic compounds.

The concept of neuroprotection denotes protection of neuronal cells. However, neuronal functions are tightly dependent on nonneuronal cells, that is, glial and endothelial cells. Therefore, the nanoneuroprotection might examine the possible effects on neurons as well as on glial and endothelial cells. This approach will certainly improve our approach of nanomedicine in relation to neuroprotection and neurodegeneration.

Although the applications of NPs are promising, their safety has to be considered at the level of the hopes they are arousing. Some recent observations suggest that NPs induce also neurotoxicity in certain conditions because of the high reactivity of these tiny particles related to their greater surface area per unit mass. The biological impacts of NPs depend on their size, chemical composition, surface structure, solubility, shape, and aggregation. These parameters can modify/affect the cellular uptake, protein binding, and the possibility of causing an injury. There is a potential for neurodegenerative consequences from NPs entry into the brain and more studies are required to establish the impact of NPs in the brain. The effects of NPs *per se* on neuronal cells should not be ignored while developing nanocarriers for pharmacologic drugs targeting the CNS. Changing one of the above characteristics will lead to a completely different type of NPs with modifications of properties, requiring a complete new risk assessment. However, the effects of NPs on neuronal dysfunction are poorly investigated [Figure 1]. Another critical issue for testing and reporting of effects of nanomaterials in biological systems is defining the behavior of the nanomaterial in the biological system. For instance, the distribution of NPs in different tissues or organs and at the subcellular levels is poorly studied. Only limited progress has been made to study the translocation of NPs across different membranes and their intracellular half-life. More effort is required to enable us to understand the intraneuronal targets of NPs and how NPs are cleared from neurons. Available *in vivo* data show that some NPs have the capacity to cross the BBB and modify drug delivery to the brain. Some NPs can induce oxidative stress and generate free radicals that could disrupt the endothelial cell membrane, causing BBB dysfunction. Therefore, further studies using dose- and size-related effects of structurally and biochemically well-characterized NPs are required to understand their *in vivo* neurotoxic effects. Thus, we suggest that investigation of nanoneuropharmacology should also deal with the effects of different types of NPs on the CNS and particularly on the BBB function.

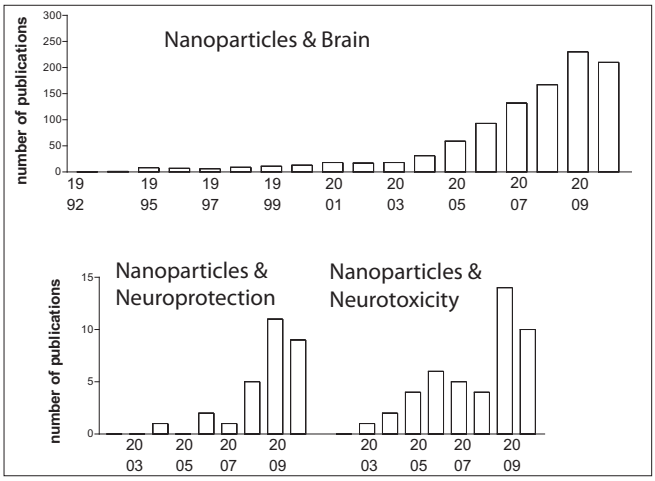

Figure 1: Number of publications per year with the indicated combination of keywords

Similar to most new technologies, there is a rising debate concerning the possible side effects derived from the use of NPs. The risk associated with exposure to NPs, the routes of entry, and the molecular level mechanisms of any cytotoxicity need to be well understood. The toxicity of NPs depends on whether they are persistent or whether the brain can raise an effective response to dispose them. Therefore, the risk/benefits ratio for the use of NPs has to be evaluated. Thus, the development of novel nanocarriers for neuropharmacology, therapeutics, and diagnostics must proceed in tandem with the assessment of toxicology and side effects of these particles.

Along with the rapid development of nanotechnology in neurosciences, it is essential to address the benefit and safety concerns surrounding nanomaterials. Most NPs are not characterized by a sufficient level of safety. Indeed, the process of synthesis, the impurities released during the synthesis and their toxicity should influence the nature of the polymer that will be used as a carrier in humans. The variability from batch to batch should be considered to get optimal and reproducible results and optimal applications. Finally, the effects of NPs in the environment after clearance from biological human fluids should also be analyzed.

NP-induced neuroprotection and neurotoxicity is still a new subject [Figure 1] that requires suitable attention among neuroscientists, in conjunction with other scientists. There is an urgent need for experts in the field of pharmacology, neurosciences, nanosciences, nanotechnology, nanotoxicology, nanomedicine, clinical scientist, physicochemistry, members of governmental regulatory agency to work together, thus endorsing the interdisciplinary nature of nanoneuropharmacology.

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