



RESEARCH ARTICLE

GLOBAL ONGOING TRENDS IN DRUG DESIGNING FOR THE TREATMENT OF TYPE 2 DIABETES AND NEURODEGENERATIVE DISEASES

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Abstract

T2D and neurodegenerative disorders are the diseases which increases with the age of people. T2D is described by hyperglycaemia, insulin opposition or relative absence of insulin take-up though NDs are described by the decrease in intellectual capacity, diffuse of the amyloid plaques & neurofibrillary tangles in AD and degeneration of dopaminergic neurons in the substantia nigra, prompting a decrease of striatal dopamine (DA) levels in Parkinson's sickness or disease. Knowing the neurodegenerative infections is critical in guaranteeing sound matured life. Although a few instances of familial neurodegenerative messes have been accounted for, yet the instrument for inconsistent neuronal degeneration remains generally in the shade [1]. Since traditional medications neglect to outperform the regular CNS defensive hindrances, along these lines, all together to conquer these obstacles, designated drug conveyance is of first importance for the treatment of Advertisement and Parkinson's disease. New age of medications has found through creative nanotechnology approaches, for example, polymeric nanoparticles are encouraging generators in the sighting of Promotion in light of the fact that nanoparticles are equipped for opening the tight intersections, crossing the BBB[2]. In this way, we can receive the updated things and fresher techniques, for example, nanotechnological, computational and quality treatment approaches for drug plan and conveyance.

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Introduction:-

Drug designing centers around all fields of including drug revelation, drug plan by normal methodology, target-based plan, drug union, drug digestion, structure-based medication plan, atomic demonstrating, ligand-based association, advancement of the nonexclusive medication, in silico chemo informatics and bioinformatics advances. Drug designing is a mind blowing creative cycle and are natural aspiration based on new medicines. This is otherwise called sane medication plan or normal plan[3]. This can be said as the advancement in medical history to yield critical helpful reaction. Actually drug is a natural molecule, when that is tied to objective site that can either control or set up the limit of a biomolecule which achieves the medicinal improvement. The medication planning incorporates the arrangement of such molecules that resemble the bio sub-nuclear target site perfectly healthy and charge to bind to it. Drug designing rely on the knowledge on the three dimensional design of bimolecular targets [4].

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T2D & neurodegenerative diseases they are generally connected with growing age. Diabetes is a sickness that makes it hard for the cells of the body to receive the glucose they need to produce energy. This develops when the sugar level in the blood is higher than the normal range. At the point when the level of glucose in the blood increments, example after a dinner, it triggers the arrival of the chemical insulin from the pancreas. Insulin animates muscle and fat cells to eliminate glucose from the blood and invigorates the liver to utilize glucose, causing the glucose level to diminish to typical levels. The human body is made up of tissues and are living things, and process food to remain alive. The food cells eat is a sort of sugar called glucose. Fixed set up as they are, the body's phones are totally subject to the circulation system in which they are washed to carry glucose to them. Without admittance to sufficient glucose, the body's cells have nothing to fuel themselves with and before long pass on[5]. People eat food, not glucose. Human food sources get changed over into glucose as a piece of the ordinary absorption measure. Once changed over, glucose enters the circulatory system, causing the degree of broke down glucose inside the blood to rise. The circulation system then, at that point conveys the broke down glucose to different cellular parts of the body.

There are 2 different types of diabetes and they are

1. Type 1
2. Type 2

Type 1 additionally called insulin-subordinate diabetes mellitus (IDDM) or adolescent beginning diabetes. Results when the body's resistant framework assaults and obliterates its own insulin-creating beta cells in our pancreas. Those who have kind 1 diabetes want every day injections of insulin to live. Most often it develops in kids or teenagers & money owed for about 8–10% of identified diabetes within the US. Although danger factors are not properly defined, autoimmune, genetic, and environmental factors are concerned within the ailment's improvement [6].

T2D is also referred to as noninsulin-based diabetes mellitus (NIDDM) or adult-onset diabetes. It generally takes place when the body produces enough insulin but can't use it efficaciously. Usually develops in adults over 40th aged. About 90–95% of human beings with diabetes have kind 2; about 80% are obese. More common among older; overweight humans who've a own family history of diabetes; have had gestational diabetes & are of African American, Hispanic American, Asian American, Pacific Islander, & Native American ethnicities.

Epidemiology

In 2017, approximately 462 million individuals were affected by type 2 diabetes corresponding to 6.28% of the world's population i.e. (4.4% of those aged between 15-49 years, 15% of those aged between 50-69, and 22% of those which are 70 and above). The major driving factors of Type 2 diabetes epidemic include overweight and obesity, sedentary lifestyle and increased consumption of unhealthy food containing high levels of red meat and processed meat, refined grained and sugar-sweetened beverages. Cardiovascular problems are one of the main reasons of morbidity, and kidney complications are highly prevalent in Asia among the patients experiencing Type 2 diabetes [7]

Prevalence

According to the information that was taken in 2017, we found a prevalence rate of 6059 per 100,000. Over 1 million deaths per year can be attributed to diabetes alone, making diabetes the ninth leading cause of mortality. Global pervasiveness of T2D is projected to increase to 7079 individuals per 100,000 by 2030.

Symptoms

Type 1 Symptoms

1. Usually expand over a quick time period, even though beta cell destruction can start months, even years, before symptoms arise.
2. Increased thirst and urination.
3. Constant starvation.
4. Weight loss.
5. Blurred vision.
6. Extreme fatigue.
7. If now not treated with insulin, someone with type 1 diabetes can lapse right into a life-threatening coma.

Type 2 Symptoms

1. Develop step by step and now not as important as type 1 symptoms.
2. Fatigue.
3. Frequent urination (specifically at night time).
4. Unusual thirst.
5. Weight loss.
6. Blurred vision.
7. Frequent infections.
8. Slow-recuperation wounds and sores.

Neurodegenerative Disorders

Neurodegeneration alludes to a reformist debilitation of the construction and capacity of nerve cells eventually prompting their deaths & damage. The outcomes of such neurodegenerative measures are generally seen as loss in engine neuron capacities, disabled sensory capacities, decrease in memory and intellectual capacities alongside hindrances in working of a few organs & organ systems. A portion of the normal neurodegenerative problems incorporate AD, PD, Huntington's disease (HD) & a nearly more uncommon situation names Amyotrophic Lateral Sclerosis. However, these include the most noticeable nervous illness among the rest. Huntington's illness is periodically experienced by adolescents, while most of these neurodegenerative problems are found in matured and old individuals with (familial) or without (inconsistent) a background marked by event in their family. Subsequently, the study of maturing depends altogether on tending to such maturing and senescence linked neurodegenerative problems. Nevertheless, better medical services furthermore, clinical offices have supported our concept of living a superior and better matured existence with higher future. Also, given the moderate beginning and reformist multiplication in the infection aggregate, a significant constraint in treatment of NDD problems has been the delayed analysis at the centers and careless mentality of patients & their closed ones towards starting signs and indications at home or work place[8].

Alzheimer's disease is that condition which influences the mind. The harmful effects are gentle from the outset and gotten more extreme over the long haul. It is named after Dr. Alois Alzheimer, who initially depicted the condition in 1906. Normal side effects of Alzheimer's infection incorporate cognitive decline, language issues, and incautious or flighty conduct. One of the primary highlights of the condition is the presence of plaques and tangles in the cerebrum. Another element is a deficiency of association between the nerve cells, or neurons, in the mind. These highlights imply that data can't pass effectively between various spaces of the cerebrum or in b/w the brain & muscles or organs. As the indications deteriorate, it gets more enthusiastically for individuals to recall late occasions, to reason, and to perceive individuals they know. In the end, an individual with Alzheimer's illness may require full-time help. As indicated by the National Institute On Aging, Alzheimer's illness is the 6th driving reason for death in the U.S. Nonetheless, other ongoing evaluations recommend that it could be the third driving reason for death, simply behind coronary illness and disease.

Different multi-disciplinary investigations (epidemiologic and clinical) were done with an end goal to recognizing the etiology, pathogenesis and hazard factors connected with AD. These contemplate uncovered solid proof - AD is connected with T2D and both these sicknesses share the equivalent patho-physiology theorizing that AD may be type-3 diabetes. Arising confirmations revealed numerous similitudes between both the sicknesses, for example, protein conformational messes, insulin opposition, irritation and endoplasmic reticulum stress, on the way commencement as well as stage exacerbation. Up until now, proof recommends that patients with hyperinsulinemia, insulin opposition and T2D are at an expanded danger of memory impedance and getting AD supporting the theory that T2D is connected with an expanded danger of AD and accordingly controlling diabetes could have a +ve effect in the avoidance of the AD Infection. As of now, a few medications are used for the treatment of both these illnesses however none of them orders complete reduction of the infection with the exception of, indicative help[9]. Also, these medications need viability because of their different constraints, for example, customary medication conveyance frameworks past the blood mind hindrance (BBB), absence of target explicitness and lessened strength. In this point of view, the arising field of nanotechnology has requested new procedures and devices to beat these difficulties. Essentially, Parkinson's sickness (PD) is additionally an ongoing reformist neurodegenerative issue and it is the 2nd normal neurodegenerative problem after AD. Patients display a scope of clinical manifestations, with the vastly recognized influencing; engine work incorporates resting quake, unbending nature, akinesia, bradykinesia and postural insecurity and non-engine side effects like dementia, melancholy, visual mind flight and autonomic brokenness. The principle neurochemical irregularity in PD is degeneration of neurons of dopaminergic at those

substantia nigra, prompting a decrease of striatal dopamine (DA) levels. Clinical decay resembles that of the reformist degeneration of that excess dopaminergic neurons. At present, utilization of Levodopa (L-dopa) as dopamine-substitution treatment is the main treatment of engine side effects in PD. In any case, this medication is endured with a significant constraint by creating dyskinesias if the L-dopa treatment is delayed. The pathophysiological instruments of L-dopa-initiated dyskinesia are inadequately seen, however non-physiological arrival of synaptic dopamine is probably going to assume a significant part in its turn of events. As of late, it has been recommended, in view of studies in rodents, that L-dopa incited dyskinesia might be related with a disturbed BBB and that this may thusly add to its pathophysiology, by additional fueling dyskinesia[10].

Recognizing new medications with restorative potential for the treatment of NDD is definitely not a straightforward errand utilizing regular methodologies. Old style treatments can't stop or back off the neurodegenerative movement. The presentation of another medication for the treatment of any sickness showing a far and wide frequency in the populace is a convoluted, hazardous, and expensive cycle, not just concerning cash yet additionally work, with a period of advancement between 10 to 14 years and an expense of around 1 trillion dollars. Also, the drug business faces the problem between lessening the effect of an infection, and working on the living nature of populace and, then again, the undeniable degrees of waste engaged with the medication creation at high scale, which may be significantly higher cycles than those of comparable mechanical cycles like petrochemicals, for instance. In this specific situation, green science strategies are harmless to the ecosystem, lessen cost and, in relationship with other "green" methods, for example, in silico approaches, contribute with high effectiveness to the achievement rate of medication advancement. In this audit, we feature the significance of utilizing both, trial and hypothetical methodologies like green science and sub-atomic demonstrating, expected to the levelheaded medication configuration focusing on NDD[11]. Our multidisciplinary research group is working in various organizations and nations, handling the absence of dynamic and powerful mixtures against NDD, by incorporating dynamic atoms, for example, tetrahydroquinolines, diN-subbed glycyl-phenylalanine subordinates, coumarin-quinoline half and halves, aryl-1, 2, 3-triazolyl benzylpiperidines, indolylpiperidines, also, glycogen synthase kinase-3 (GSK3) and tau-collection inhibitors, among all. These novel dynamic atoms have been acquired by utilizing a mix of green science conventions, prescient chemoinformatics devices, and sub-atomic demonstrating approaches[12].

Ongoing Trends In Drug Designing

Evidences collected so far points and sustain the hypothesis that T2D correlate with a prominent risk of AD and controlling diabetes could have a major impact in the avoidance of AD. AD patient's management is mostly dependent on the currently available treatments, which only offers symptomatic benefit. In situation like these, there is a need to develop a rectified plan that can take to disease modifying therapeutics. In this area, robust Diagnosis tool are essential for an early detection of AD. It is a very tough job in clinical trial setting to evaluate drug efficiency and for implementing finest patient management strategies [13]. As of now there are five FDA-approved Alzheimer's drugs that can administer symptomatic comfort by temporarily helping in memory retention and enhancing thinking ability. It's obvious that treatment strategies for AD are limited and can only provide a temporary relief from the drugs that modulate neurotransmitter disturbances. There are 5 drugs permitted for the treatment of AD, two are derived from plant alkaloids: galantamine, taken from *Galanthus woronowii*, and rivastigmine, which is based on physostigmine chemical structure extracted from *Physotigmavenenosum*[15]. These drugs inhibit acetylcholinesterase to improve cholinergic neural dysfunction and the cognitive symptoms associated with it that occurs in AD, the most common form of dementia. Many other alkaloids & their derivative have been studied for their capability to modulate cholinergic functions in AD and other dementias. These drugs do not cure the causes of Alzheimer's. Plenty of the new drugs in development process aim to transform the disease process itself, by targeting one or more of many wide-ranging brain changes that Alzheimer's causes. These variations generates potential "targets" for new drugs to completely stop or slow the progress of the disease[16]. Several alkaloids have been explored as potential treatment for PD motor symptoms that occur in the disease, via modulation of dopaminergic neurotransmission. Main compounds for drug discovery include ergot alkaloids from *Claviceps purpurea*, which gives templates for the advancement of synthetic drugs such as bromocriptine, used to alleviate PD symptoms[17]. Number of other alkaloids and their by-products has been proved for their capability to alleviate symptoms in neurodegenerative diseases, with some rising as disease-modifying agents. Alkaloids such as nicotine and caffeine have been said to provide protecting effects against development of neurodegenerative diseases and are conferred from an epidemiological side, with consideration of their mechanistic effects. There are number of drugs used today for treatment of many diseases with limitations like drug delivery, efficacy, cytotoxicity and most important drug resistance. Combined drug pathways have been tested since last few years in order to

improve the treatment, but the result is discouraging because of side effects and diminished potency in patients where drug develops resistance [18]

Drug designing & new trends

Nanotechnology is an arising multidisciplinary field that is changing therapeutic examination. It's anything but a massive potential in fundamentally propelling the treatment and counteraction of less number of sicknesses. Prominently, there have been now critical headways in utilization of different nanotechnology-based approaches towards the diagnostics and therapeutics of disease. Essentially, nanotechnology offers huge potential as far as medication conveyance and viability for NDD treatment [19].

Neurodegenerative issues are answerable for failing of cerebrum and fringe sensory system or peripheral nervous system(PNS). The remedial medication that are used generally for treatment of these issues can't go through the blood–cerebrum hindrance (BBB) as it grants entry of explicit supplements which are useful for development. Consequently, nanotechnology (NT) can be a ton of significant in taking care of this issue because there are various types of nanomaterials that can go about as proficient drug delivery system and help in intersection the BBB and giving compelling treatment to neurodegenerative problems like Alzheimer's infection (AD), Parkinson's sickness (PD) & some more. Hence, in this part, we attempted to aggregate every one of the new improvements identified with neurodegenerative problems and furthermore give a short outline about the significance of nanotechnology in changed biomedical applications[20]

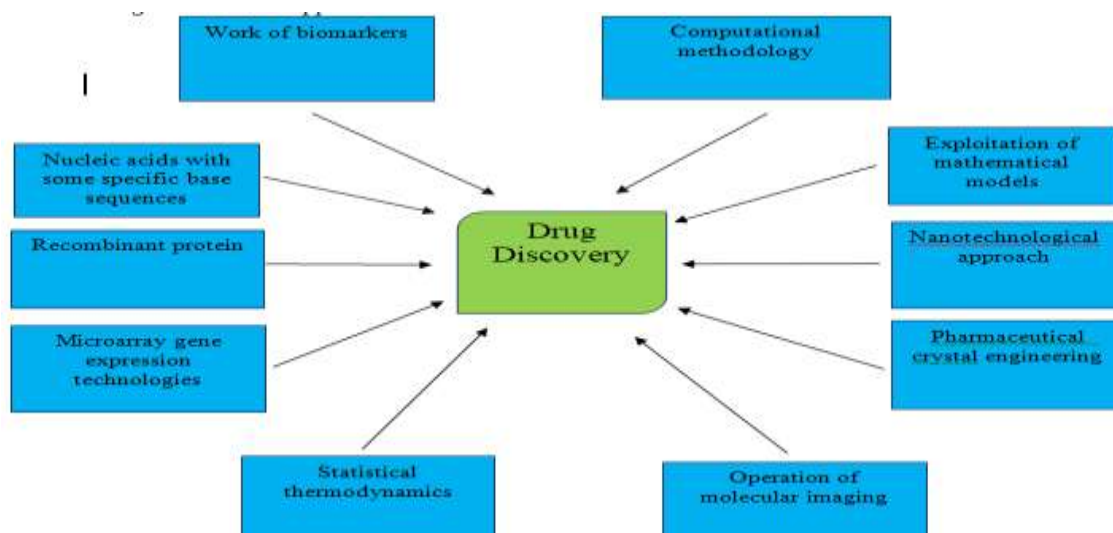


Figure-1:- Schematic diagram showing some of the new techniques used in drugs designing and discovery.

Recent studies tell of upsurge in the frequency of neurodegenerative issues like Alzheimer's illness, Parkinson's sickness, Huntington's infection, Prion illness, and amyotrophic parallel sclerosis. The treatment of a similar remaining part is an overwhelming test because of the restricted admittance of restorative moieties across the blood–cerebrum obstruction. Develop nanoparticles with a size under 100 nm gives multifunctional capacities to addressing these biomedical and pharmacological issues because of their remarkable physico-chemical properties alongside ability to cross the blood–cerebrum boundary[21]. Unnecessary to specify, there is a shortage of audit articles summing up late improvements of different nanomaterials including liposomes, polymeric nanoparticles, metal nanoparticles, and bio-nanoparticles toward the remedial and theranostics applications for different neurodegenerative issues[22]. Here, a wide range of nanomedicinal ways to deal with annihilate neurodegenerative issues is given, alongside a concise record of neuroprotection and neuronal tissue recovery, current clinical status, issues identified with wellbeing, harmfulness, difficulties, and future viewpoint. Polymeric nanoparticles are applicants in the examination of AD since those components are fit for opening tight intersections, crossing the BBB, high medication stacking limits, focusing towards the aberrant proteins of AD[23]. To fortify the pharmacological action of antiparkinsonian drugs, improving their infiltration of the BBB, various methodologies are conceivable. Among these, the prodrug approach gave off an impression of being the most encouraging, and numerous prodrugs have been arranged with an end goal to improve physicochemical attributes. Also, novel helpful systems dependent on plans connecting dopaminergic drugs with neuroprotective specialists, build LD striatal

levels. These methodologies offer supported arrival of the medication with no change of mind fixation, introducing promising roads for advancement of other successful new medicines for Parkinson's disease[24].

Ciphering or Bioinformatics approach in drug designing

The Human genome project has brought a revolution in the biomedical research and has a major effect on the biological researches mainly, in the area of proteomics and genomics lead to the discovery of new drugs. There is a lot of genomics & proteomics experimental data are compared in harmony to innovate untried drug discoveries and design with entrenched genomics & proteomics databases, with the guidance of computer software resulting in quick & accurate searches inside these databases [25]. Bioinformatics approach offers immense scope in drug discovery in order to seek an contemporary approach for aiding the design of clinical trials. A combinational pathway may lead to saving both time & cost. Computational neuropharmacology could observe the possible problem of add-on neuroleptics & antidepressant regimen for behavioral problems in the patient populations. Computational neuropharmacology grants a quantitative appraisal of effect of additional medication on disease-modifying therapeutic approaches and can be supportive in ameliorate clinical trial design [26].

Conclusion:-

As of now numerous medications are accessible to treat the neurodegenerative jumble particularly, AD and PD with various aim& systems of activity. Notwithstanding, none of these medications has demonstrated to be huge as far as adequacy inferable from their different impediments. The current drug for AD like those anticholinesterase inhibitors & the most recent NMDA receptor inhibitor, Namenda offer moderate indicative help at different phases of the illness, yet don't hold movement of this neurodegenerative turmoil[27]. Likewise, the most widely recognized medications used for the treatment of Parkinson's sickness are Sinemet & (Levodopa/Carbidopa). Levodopa is the most ordinarily recommended and viable medication for controlling the indications of PD, especially bradykinesia and unbending nature. Levodopa is shipped to the nerve cells in the mind that changed over into dopamine to be utilized as a synapse. Then once more, Sinemet is the best medicine & have the most un-transient incidental effects; it is related with high dangers of long haul incidental effects, for example, compulsory developments (dyskinesia)[28]. At the point when utilized on a drawn out premise, levodopa may likewise cause fretfulness, turmoil, or strange developments. Along these lines, thinking about multifactorial nature of the infection, various factors must be dealt with while handling such infection. Subsequently, it is important to introduce new methodologies, eg, nanotechnological and quality treatment approaches for designated drug conveyance just as pharmacological mixtures with various properties that might apply their impact heterogeneously on various components ensnared with PD & AD. In this undertaking, the developing significance of nanotechnology has become likely decision, because of its considerable notoriety in the field of nanomedicine. There are numerous biocompatible nanoparticles answered to be powerful to conquer these constraints & could fill in as a compelling medication conveyance framework with slight improvement of physical, compound and organic properties[29]. These fresher ages of medication conveyance frameworks enjoy significant upper hands over customary drug conveyance frameworks. To put it plainly, nanoparticles offer an extraordinary potential in drug conveyance across BBB because of their little sizes and simplicity of surface adjustments.

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