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A Review on Peptide-Mediated Strategies for the Treatment of Central Nervous System Disorders

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ABSTRACT:

the therapeutic potential of peptides in treating various central nervous system (CNS) disorders and their promising future clinical applications.Actually, peptides are considered the new generation of biologically active tools because they are key regulators in cellular and intercellular physiological responses, which possess enormous potential for the treatment of various diseases Despite their therapeutic potential, peptide drugs face challenges such as poor bioavailability, low stability, invasive administration, and limited blood–brain barrier penetration, driving the development of stable, controlled-release delivery systems.Considerable efforts have been made to design new drugs based on peptides and recent developments in technology and science have provided the means and opportunity to produce a stable as well as controlled-release form of peptide and protein drugs to combat poorly controlled diseases and to increase patients' quality of life. A major challenge in this regard, however, is the delivery of peptides over the blood–brain-barrier. This review gives an over view of some strategies used to improve both bioavailability and up take of peptide drugs for delivery into the brain .Indeed ,recent findings suggest that the use of peptides by conjugation to a poler such as nano particles can off ertremendoushope in the treatment of brain disorders. The polymer conjugation improves pharmacokinetics by increasing the molecular mass of proteins and peptides and shielding them from proteolytic enzymes. These new strategies will create new opportunities for the future development of neuro therapeutic drugs. In the present review we have focused our attention on the peptide controlled delivery, summarizing literature reports on the use of peptides and nanotechnology for the treatment and diagnosis of brain disorders. 2011 Elsevier Ltd. All rights reserved.

KEYWORDS:

Peptides Drug delivery Nanoparticles Nanotechnology Blood–brain barrier CNS diseases Activity-dependent neuro protective protein (ADNP), Alzheimer's disease, Davunetide, NAP, neurodegenerative diseases, neurological disorders.

1.INTRODUCTION :

1.1. DISCOVERY OF ADNP AND ITS DERIVATIVES

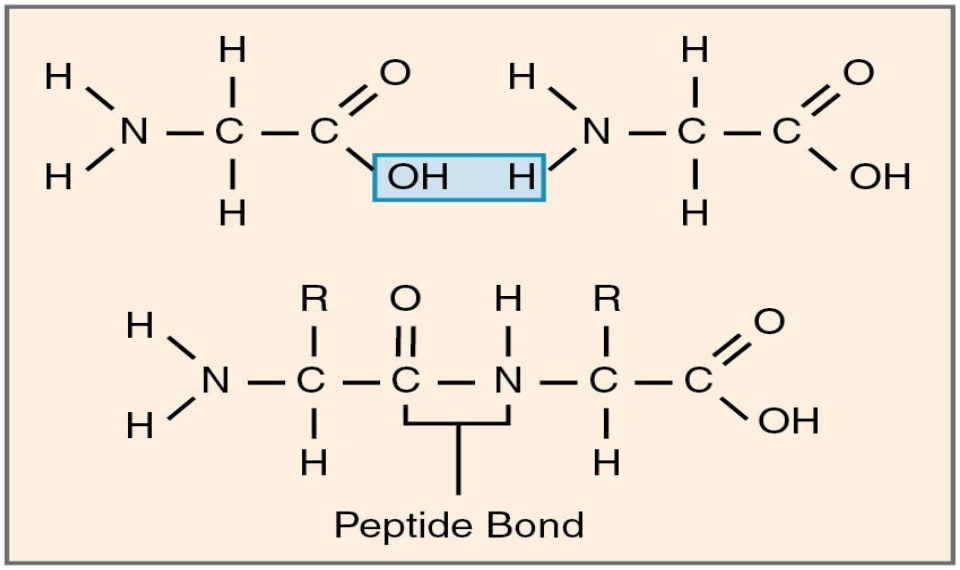
Activity dependent neuro protective protein (ADNP) was discovered in the lab of Prof. Illana Gozes [1]. Its production in glial cells is regulated by vasoactive intestinal peptide (VIP) [2, 3]. ADNP-deficient mouse embryos died on E8.5 9.0, in association with neural tube closure failure. The ex pression of Oct4, a gene associated with germ-line mainte nance was markedly augmented in the knockout embryos. In contrast, the expression of Pax6, a gene crucial for cerebral cortex formation, was abolished in the brain primordial tis sue of the knockout embryos [4]. These data suggested that ADNP is crucial for brain formation. Further experiments showed that ADNP regulates >400 genes during embryo genesis [5], including key developmental genes and encom passing an interaction with the chromatin remodeling com plex SWI/SNF [6]. The expression

of ADNP was further found to be present in both astrocytes and neurons and to be regulated by pituitary adenylate cyclase-activating polypep tide (PACAP) [7]. It was also detected in microglia [8] in blood circulating cells [9] and other organs [10]. ADNP was found to regulate its own expression [11]. Other regulatory mechanism associated with ADNP expression includes, hormonal regulation [12] as well as NO cGMP [13] and xenon associated with anesthesia [14]. Recently, ADNP was found to have a role in erythropoiesis in zebra fish [15],

Its down-regulation was seen in the lymphocytes of multiple sclerosis patients [16] and the serum of Alzheimer's disease patients [17]. In addition, schizophrenia patients showed an imbalance between transcripts of ADNP and its sister protein ADNP2 which may impact disease progression [18] In this respect, ADNP het erozygous mice develop Alzheimer's-like tau pathology, cognitive deficits and neuronal cell death [19] and ADNP expression is modulated in a mouse model of Alzheimer's disease [20]. At the gene level, deletion of the ADNP locus was found to be associated with mental retardation [21] and recent find ings discovered ADNP mutations in autism Recently, de novo mutations in the ADNP gene were found in individuals with autism [22,]. Moreover, ADNP interacts with many other proteins that are products of genes mutated in autism [22]. ADNP shares an epitope of activity, NAP (NAPVSIPQ, drug name, davunetide) with activity-dependent neurotrophic factor, ADNF [23] termed ADNF-9 (or SAL), SALLRSIPA [24]. . NAP was shown to have a brain bioavailability after intranasal administration [25]. As NAP and SAL are chiral molecules, their enantiomers D-NAP and D-SAL [26], were also tested and were shown to have therapeutic efficacy, as will be described below. This suggests that their action is not receptor-dependent. ADNP, NAP and ADNF-9/SAL have been reviewed be fore [27], the current review provides a 2013 perspective + update and future horizons.

Amino acids are joined together by peptide bonds to form polymers referred to as peptides or proteins .Peptides generally contain fewer than 40 amino acids, while proteins contain 50 or morePeptide drugs have great therapeutic potential but are limited by poor bioavailability, low stability, invasive delivery, and blood–brain barrier penetration. By this definition, insulin is the smallest protein available, having molecular weight of 5800 Da Many peptides have been used as drugs since the commercial introduction in the 1920s and 30s of insulin, thyroid hormone and factor VIII. Peptides play a vital role in regulating physiological functions and treating a wide range of diseases.Table1 lists some peptide and proteins currently under clinical development and those already marketed (DegimandCelebi,2007). Concomitant with these proceedings, research has made great progress in understanding the function of peptides and proteins (PashaandGupta,2010;Brasnjevicetal.,2009). Accordingly, peptides and proteins have become important targets in neuro pharmaceutical drug design for the treatment of a wide variety of central nervous system(CNS) disorders such as is chemia, inflammatory CNS diseases, neurodegenerative diseases, and acute and chronic pain syndromes (Pardridge,2001;Moghbelietal.,2010;Siposetal.,2010). Poor absorption and high enzymatic degradation of peptides and proteins are them a in barriers to their efficacy by the oral route .Never the less, delivery of these molecules through appropriate non-invasive routes has been studied(Soaresetal.,2007;Wuetal.,2008 Alternative routes of administration for peptide and protein pharmaceuticals, such as buccal (Veuillezetal.,2001), nasal (Pontiroli,1990),rectal(Mackayetal.,1997),vaginal(Acartürketal.,2002),andpulmonary(Smith,1997),have been under investigation and the results of many of these efforts have been reported in the literature. The need to find a non-injectable/non-invasive route of administration for peptides has focused attention on oral administration, the traditional method to ensure patient compliance (Soaresetal.,2007) With oral administration, there are several factors that will affect the pharmacodynamics and pharmacokinetics of the drugs. As a result, the delivery of therapeutic peptides and proteins remains a priority for many researchers an pharmaceutical companies (Banga,1995;DegimandCelebi,2007;AudieandBoyd,2010). Several advantages have been observed for controlled delivery of peptides: Conventional drug therapy requires periodic doses of therapeutic agents;–controlled delivery and the formulation can provide maximum stability, activity and bioavailability;–some solubility problems can be seen in conventional formulations;–controlled delivery of peptide and protein drugs provides improved efficiency,reduced toxicity and improved patient convenience

efficiency,reduced toxicity and improved patient convenience



1.2. THERAPEUTIC USAGE OF PEPTIDES :

Controlled drug delivery is delivery of drug at a rate or to a location determined by needs of the body or disease state over a specified or extended period of time during the therapy. Many other strategies have been used to improve both bioavailability and uptake of peptide drugs. These strategies can be as signed into three general methods: inhibition of enzymes, chemical modification to target an uptake mechanism, and conjugation with a transported substance (EgletonandDavis,1997;Gentiluccietal.,2006). Thus, advances in biotechnology and chemistry have led to the use of an class of bioactive molecules based on peptides and the industrial production of potentially therapeutic peptides is now possible(AudieandBoyd,2010). Peptide drug modification too can be broadly divided in to several categories: lipidization, structural modification (peptide mimetic), glycosylation, use of nutrient transporters, prodrugs, vector-based, cationization, and polymer conjugation(Wittetal.2001;Gentiluccietal.,2006). Post-translational structure modification of intact, naturally occurring peptides by chemical manipulation has provided several useful analogs showing improved performances as therapeutics. The first approaches were based on simple modifications of N-or C-terminus, N-and Ca-methylation, or single amino acid replacement with their D-amino acid equivalent (Sasubilli and Gutheil, 2004;Saganetal.,2004). With the introduction of iso steric groups, peptide bond modifications (Ahnetal.,2002)resulted in a variety of peptidomimetic classes, such as peptoids (Horwell,1995),retro in verso peptides(FletcherandCampbell,1998), aza peptides (Zega, 2005),urea-peptidomimetics (BakshiandWolfe,2004) and sulphonamide peptides/peptoids (BrouwerandLiskamp,2004 ever al examples of sugar amino acids caffolds have been used in biologically active peptide sequences, such as RGD-containing integrinant agonists, somatostatin, LHRH, and enkephalins (von Roedernetal.,1996).These hybrid molecules have properties arising largely from the combination of structural characteristics of carbohydrates with the functional group diversity of peptides. Specific modification of peptide structure has been developed to prolong and/or enhance the biological activity of the peptide drug at the target site(Spampinatoetal.,2003). For example, the peptide glycosylation has proven a useful methodology (Wittetal.,2001) for enhancing bio distribution to the brain and cyclization reactions proved useful in designing highly protease-resistant peptide mimetics (Tugyietal.,2005). In this manner, the design approach for peptide drugs can be best expressed as inter disciplinary, as it incorporates the efforts of organic, medicinal, and biological chemists with that of physicists, pharmacologists, physiologists, and pathologists (Stolnik and Shakesheff,2009). The use of conformational constraints, bond replacements, and other modifications must be weighed against stability, receptor affinity, membrane permeability, elimination, and various independent attributes of the human body (i.e., age, sex, pathology, etc.). This can be accomplished in several way

1.Increase bioavailability. For peptides that induce their effect within the CNS, membrane permeability is a significant obstacle. The gut-barrier can be circumvented via non-oral dosing routes.

2.Reduce elimination. Peptides within the systemic circulation are generally eliminated via both renal and hepato-biliary routes, based on size and lipophilicity of the respective peptide.

3. Alter biodegradation. Endogenous peptides are rapidly bio degraded by proteolytic enzymes

4. Increase the time in the 'receptor compartment'. Efflux mechanisms exist within the brain that greatly reduce the time it takes for the drug to bind to the receptor

5. Increase selectivity and/or affinity of the peptide for the receptor. Peptides may be adapted to enhance their ability to recognize and interact with specific receptor subtypes.

1.3. ADNP IN NEUROLOGICAL DISORDERS :

PROTECTIVE EFFECTS OF NAP AND OTHER ADNP-DERIVED PEPTIDES

Several mechanisms were demonstrated in the action of ADNP-derived peptides, among which are a protective effect on glia-depleted neurons in culture by NAP [28], inhibition of beta amyloid aggregation by NAP [29], promotion of neu rite outgrowth in a concentration-dependent manner in rat hippocampal and cortical cultures by ADNF-9 and NAP [30] and metal chelating and anti-oxidant properties by several analogs and derivatives of NAP.Anti-inflammatory properties were also demonstrated by NAP [31]A main mechanism of NAP action is stabilization/fortification of microtubules. The protein tubulin, constituting the microtubule backbone, was shown to be a target of NAP and its related peptides D-NAP, D-SAL and ADNF 9 [32]. Recently, NAP was shown to enhance interaction between microtubules and microtubule associated proteins, and to enhance microtubule polymerization under conditions of zinc intoxication [33]. . It was further shown to inhibit microtubule-severing and protect microtubule-dependent axonal transport [34]Other studies showing an effect of NAP and its related peptides on microtubules were reviewed previously [35]and therefore will not be described here in detail. Because of its microtubule stabilizing proper ties, NAP showed efficacy in disease models involving microtubule disruption (see below).

1.4. NAP AND LEARNING:

NAP showed neuro-protection and cognitive enhancement not only in disease models, but also in healthy animals. When administered by nasal application, NAP improved performance in the Morris water maze in middle-aged rats [36]. Offspring exposed prenatally to D-NAP + D-SAL per formed better than control animals in the Morris water maze, whereas exposure to either D-NAP or D-SAL alone showed only a trend for improvement, and aged animals receiving D NAP+D-SAL learned significantly faster than age-matched controls [37].

1.5. NAP IN NEURODEGENERATIVE AND NEURO LOGICAL DISEASE MODELS :

Because of ADNP's protective effects and its involvement in neurological disorders, its derivatives were tested in many disease models. NAP efficacy was described in previous reviews from our lab [38] and will not be reiterated here. We will mainly focus here on reviewing works that have not been recently reviewed.

1.6.PARKINSON'S DISEASE (PD):

Microtubule dysfunction was implicated in PD. NAP was protective in a cellular model of PD, increasing viability of human SH-SY5Y cells and rat PC12 cells exposed to dopamine, 6-OHDA and MPP+ [39]. In vivo,

intranasal NAP was beneficial in a mouse model of PD, ameliorating motor deficits and reducing aggregation of alpha-synuclein in the sub stantianigra of mice overexpressing human alpha-synculein · Both of these effects targeted major hallmarks of this model [40]. However, NAP did not improve olfactory function or alpha-synuclein pathology in the olfactory bulb, suggesting that its effects are regionally specific. On going studies aim at revealing the effects of longer duration, as well as a higher dose, of NAP administration, including the effects on tau pathology.

1.7. AMYOTROPHIC LATERAL SCLEROSIS (ALS):

In a model of ALS, T g N(SOD1-G93A)1Gur transgenic mice, daily treatment with D-NAP, starting from day 2 of age resulted in a prolonged life course, which was associated with a significant decrease in tau hyper phosphorylation [41].

1.8. HEAD INJURY AND ISCHEMIA:

In mice subjected to closed head injury (CHI), a well characterized model of head trauma, NAP injection after injury reduced mortality and facilitated neurobehavioral recovery, reduced edema and caused brain-tissue recovery. It also decreased tumor necrosis factor-alpha levels in the injured brain and was shown to protect PC12 cells against tumor necrosis factor-alpha-induced toxicity [42] Later, gene array analysis revealed that a major gene transcript that specifically increased after CHI and decreased after NAP treatment was the cell surface glycoprotein Mac-1 (CD11B anti gen, also known as the complement receptor 3). Thus, Mac-1 was suggested as a marker for the long-term outcome of head injury and as a potential target for NAP protective actions [43]. Accordingly, mice deficient in Mac-1 were tested for their susceptibility to head injury as compared to Mac-1 expressing mice. The former line was shown indeed to be more resistant to head injury, and NAP increased recovery in normal mice These finding were independently extended to show that microglia engulf presynaptic inputs during peak retinogeniculate pruning and that engulfment is dependent upon neural activity and the microglia-specific phagocytic signalling pathway, complement receptor 3(CR3)/C3 [44]. Together the results indicate similar operating mechanisms during development and injury, with a potential role for NAP treatment in cases of developmental impairments, see below.

1.9. HYPOXIA, ISCHEMIA AND EXCITOTOXICITY:

Following permanent middle cerebral artery occlusion, a model of stroke, NAP was more efficient than D-NAP in reducing motor disability and infarct volumes. These effects persisted 30 days after NAP administration, and NAP significantly reduced the number of apoptotic cells [45]. NAP treatment improved neurodevelopmental outcome in apolipoprotein E (ApoE)-deficient and control mouse pups ex posed to postnatal hypoxia compared to non-treated pups. ApoE-deficient mice showed a greater susceptibility to hy poxic damage and better response to NAP treatment [46]. In a model of hypoxic-ischemic brain injury in neonatal rats induced by common carotid artery ligation, ADNF-9 and NAP administered separately significantly preserved the number of neurons in CA1, CA2, CA3, and dentate gyrusregions of the hippocampus, compared with vehicle-treated group. Histopathological evaluation demonstrated that ADNF-9 and NAP significantly diminished number of "apoptotic cells" in these regions in both the ligated and non ligated hemispheres. The density of the neurons in these regions was significantly higher with a combination therapy of ADNF-9 and NAP. ADNF-9+NAP combination treatment also significantly decreased NO overproduction in the hypoxic-ischemic hemisphere [47]. Having anti-oxidant properties, NAP prevented oxidative damage to DNA and lipid membranes induced by hypoxia-ischemia (HI) and by hypoxia-induced seizures, in correlation with modulation of the glutathione system [48].

NAP was also able to prevent impairments in learning and long-term spatial memory and to significantly reduce brain damage up to 7 weeks following the neonatal HI injury [49] Thus, most of the beneficial outcomes

of NAP treatment in hypoxia and ischemia models result from anti-apoptotic and anti-oxidant activity. Similarly, NAP reduced the number of apoptotic neurons through activation of PI-3K/Akt pathway in the cortical plate or both PI-3K/Akt and MAPK/MEK1 kinases in the white matter in a model of excite toxic brain damage in the new born mice Excito toxic damage was also associated with an epilepsy model of kainic acid toxicity, and resultant cell death was protected in part by NAP treatment · Cell culture studies suggested that NAP protection against tau hyper phosphorylation was preceded by protection against caspase 3 activation as a results of ischemia and glucose deprivation [50]

2. NAP AND DIABETES:

In a rat model of diabetes induced by streptozotocin (STZ), impaired spatial memory in the water maze was improved by NAP. T2 magnetic resonance imaging revealed atrophy in the prefrontal cortex of the diabetes rat group, which was prevented by NAP treatment. Immunohistochemical analysis showed that NAP treatment protected against major loss of the synaptic marker synaptophysin and astrocytic apoptosis, resulting from STZ treatment [84].

2.1. RETINAL EFFECTS OF NAP AND ADNF-9:

Because of the developmental role of NAP and ADNP, and the fact that the retina develops from the brain, the effects of NAP and other VIP-associated peptides in the retina were investigated by several groups. Both ADNF-9 and NAP were neuroprotective in retinal ganglion cells (RGC) in vitro, increasing the percentage of surviving healthy cells purified from new born rat and enhancing axonal outgrowth and increasing survival after retinal ischemia and optic nerve crush In contrast, NMDA excitotoxicity reduced the levels of both VIP and ADNP, suggesting a neurprotective role for these proteins . In vivo, intravitreal NAP admini stration reduced the size of laser-induced retinal lesion Transfection of NAP into retinal Müller cells resulted in re duced hypoxia-induced retinal injuries and promoted retinal neurons growth

2.2. NAP AND NEURODEVELOPMENTAL DISORDERS:

Because NAP is derived from ADNP which is necessary for normal brain development, examining its effect in models of neurodevelopmental disorders was of high importance. Ischemic insults and a model of cerebral palsy (excitotoxic ity) were discussed above. We will review below animal models of other common developmental disorders

2.3. SCHIZOPHRENIA :

Schizophrenia is now widely recognized a neurodevel opmental disorder [90]. Therefore, it is not surprising that schizophrenia patients display abnormalities in ADNP ex pression Schizophrenia affects ~1.1% of the adult population in a given year The core treatment for schizophrenia is antipsychotic medication Haro and colleagues divided illness remission into two, including clinical remission and functional remission. The clinical re mission refers to current antipsychotics having an effect on psychotic symptoms but not effectively addressing functional remission (cognitive impairments) and generally showing only 25.5% remission worldwide, thus positioning schizophrenia as a global healthcare problem The ADNP regulating peptide, VIP, originally isolated from the intestine, but later found as a major brain neuropep tide, has been shown to improve cognitive function under compromised conditions in rodents Recent studies identified duplications of the VIP receptor gene VIPR2 (or VPAC2) as conferring significant risk for schizophreni· Furthermore, the VIP-related peptide, PACAP and its preferring receptor, PAC1 have been also linked to schizophrenia and to the gene disrupted in schizophrenia (DISC1). DISC1 has been associated with proper organization of microtubules. PACAP reduces the association between DISC1 and DISC1-binding zinc-finger protein to induceneurite outgrowth. On the other hand, expression of stathmin1 (amicrotubule destabilizing protein), which induces abnormal axonal arborizati on, is up regulated in PACAP-knockout mice and the brains of patients with

schizophrenia. Thus it is likely that, in the schizophrenic brain, neural development dependent on these two systems has been disturbed . The possibility that the regulation of these two systems could lead to new treatments for schizophrenia is of further interest and the use of DISC1-mutated mouse [97] with verification in another mouse model of microtubule-deficiency, the stable-tubule-only (STOP)- deficient mouse for drug testing is of translational interest. The effect of NAP, which is derived from ADNP, was tested in the STOP-deficient mouse model of schizophrenia. NAP treatment protected against hyperactivity and cognitive deficits associated with this model In humans, protective effects of NAP on function in schizophrenic patients were found, when looking at a composite score of activities of daily living, but not on composite cognitive score A follow up study explored, using magnetic resonance spectroscopy (MRS), the effects of NAP on N-acetylaspartate (NAA), a marker of neuronal in tegrity, and choline, a marker of cell membrane turnover and white matter integrity. Choline/Creatine (Cr) for the high NAP dose group showed a significant increase over placebo. Baseline NAA/Cr correlated with the composite cognitive score, as did individual cognitive domains of attention/vigilance, verbal learning, and social cognition; how ever, neither metabolite correlated with functional capacity In general NAP (davunetide) seemed to increase Cho line/Creatine (Cr) and NAA/Cr in the dorsolateral prefrontal cortex. These last data is indicative of neuro protection, raining a hope that NAP may be efficient as a treatment for schizophrenia.

2.4. FETAL ALCOHOL SYNDROME :

Neural tube defects (NTDs) are common following pre natal exposure to ethanol, and constitute a major problem in cases of alcohol consumption during the pregnancy, also termed “fetal alcohol syndrome”. Because ADNP is essential for neural tube closure NAP and related peptides were investigated for effects on neural tube formation in fetal alcohol syndrome Several neuroprotective proteins, including D-NAP, L-NAP and SALLRSIPA (SAL) were effective in preventing ethanol-induced NTDs The peptide P7A-NAP (NAPVSIAQ), though not neuroprotec tive, was also bene ficial probably because of inhibition of L1 mediated cell adhesion, which was also shown for NAP]. These data suggested that ethanol-induced teratogene sis is mediated at least in part by adhesion molecules. A combined treatment with NAP and SAL prior to ethanol exposure reduced ethanol-induced increase in pro inflammatory cytokines (tumor necrosis factor alpha, inter leukin 6 and keratinocyte chemoattractant cytokine (KC) and also ameliorated memory deficits NAP+SAL treatment prevented the ethanol-induced decrease in the expression of the gamma-aminobutyric acid A (GABA) receptor subunit GABAbeta3 in the embryo but not in the adult brain but their optic isomers D-NAP and D-SAL did not affect GABAA expression, while normalizing NR2A and NR2B expression NAP+SAL pre vented the decrease in GABAA5 receptor subunit and the upregulation of NR2A and NR2B in a model of fetal alcohol syndrome The latter effect was also observed with D NAP and D-SAL, and was associated with reversal of alco hol-induced learning deficits. Both peptides changed ADNP expression without affecting down-regulation of VIP in the cortex, probably because they act downstream to VIP Later, this effect was shown to be mediated by restoring C fos expression in the hippocampus in this model and NAP and SAL were also shown to reverse alcohol-induced increase in BDNF expression Regarding neuroprotection in a model of fetal alcohol syndrome, NAP reversed the decrease in neuronal growth, differentiation and synaptic connection caused by co culturing neurons with astrocytes from prenatal ethanol ex posed (PEE) fetuses. These beneficial effects may be attributed to activation of mitogen-activated protein kinase/ extracellular signal-regulated protein kinase (MAP/ERK), the phosphatidylinositol-3-kinase (PI-3K)/Akt pathways and the transcription factor cAMP response element-binding (CREB) protein, which were all observed following NAP administration If those mechanisms are relevant to other disease models as well, then they could explain NAP actions on tau phosphorylation, as activation of the PI3-Akt pathway results in reduced tau phosphorylation due to GSK inhibition Regarding neuro differentiation, sequential tyrosine phosphorylation of Fyn kinase and the scaffold protein Crk associated substrate (Cas) was involved in NAP activity [114] as well as activation of polyADP ribosylation and inhibition of the microtubule severing katanin activity under conditions of tau depletion NAP also prevented alcohol-induced apoptosis in fetal mouse brains, as reflected in a decrease in

cytochrome c and caspase levels as also seen in cell culture systems[]. Finally, dietary D-SAL prevented ocular defects resulting from alcohol-induced teratogenesis .

2.5. DOWN SYNDROME :

Down syndrome is a genetic disorder resulting from trisomy in chromosome 21. Incubation of normal human cortical neurons with 50μM H2O2 for 1 hour serves as an in vitro model of human Down syndrome and results in morphological and structural changes consistent with neuronal degeneration and loss of viability of more than 60% of the neurons present in the culture. Addition of ADNF-9 (SAL) or NAP resulted in significant increases in survival of normal neurons treated with H2O2, as well as increase in neuronal survival and reduction of degenerative morphological changes, similar results were found in Down syndrome neurons [119]. In an in vivo genetic model of Down syndrome (Ts65Dn mice), as in models of fetal alcohol syndrome (above), pre natal NAP+SAL prevented the changes in expression of NR2A, NR2B, and GABA(A)beta3 levels as well as learning deficits, hyperactivity and changes in expression of ADNP, VIP and NR2B associated with this model .

3. SUMMARY:

NAP and its derivatives have been increasingly shown in recent years to have beneficial effects in models of neurodegenerative and neurological disease. Over the last decade, administration of NAP gave promising results in animal models, raising a hope that NAP will also be efficient in human diseases. Although NAP was originally isolated from a protein necessary for neurodevelopment – ADNP - exploring the biochemical outcomes of NAP treatment reveals a wide range of effects which can contribute to its beneficial behavioural effects, that go beyond enhancing neurodevelopment and include anti-inflammatory, anti-oxidant, neuroprotective and microtubule stabilization, which are common to most if not all neurological disorders. The great advantage of NAP lies in its small size and ability to penetrate the blood brain barrier even with systemic administration, but high bioavail -ability was seen with other, less invasive routes of administration, such as intranasal application. In addition, NAP does not seem to have any detrimental effects. It remains to be determined whether NAP exerts its action through a receptor or other mechanisms, even though the fact that D NAP seems effective argues against the former possibility. Current studies are aiming at elucidating the precise cellular mechanisms of NAP actions using advanced microscopic and cellular and biochemical methods.

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5. LIST OF ABBREVIATIONS :

AD = Alzheimer's disease

ADNF = Activity-dependent neurotrophic factor

ADNP = Activity-dependent neuroprotective protein

CHI = Closed head injury

NTDs = Neural tube defects

NR2 = Nuclear receptor 2

PD = Parkinson's disease

PACAP = Pituitary adenylate cyclase-activating polypeptide

CONCLUSION :

Overall, the CNS is highly protected from the influence of exogenous substances and endogenous substances pass through many barrier structures, of which BBB is the most critical one. This makes it very difficult to effectively deliver drugs to the brain lesions. One of the most urgent problems to be solved is to find an effective, reliable and non-toxic method to cross or bypass the BBB. For this reason, minimally invasive or non-invasive methods should be explored to a greater extent. With the development of nanotechnology, it is a good strategy to use nano materials to treat CNS disease through intravenous administration and trans nasal administration. But what cannot be ignored is the neurotoxicity of nano materials, which is related to the size, shape, and surface modification of nanoparticles. Nanoparticles with good biocompatibility should be selected for treatment and the dosage of nano materials should be strictly controlled. CPPs can be used as drugs, vectors and ligands in the delivery system to treat CNS diseases. The combination of CPPs and nanomaterials has a good development prospect in the treatment of CNS diseases. However, there are still some limitations that need to be addressed to promote its use. The physicochemical properties changes and pharmacokinetic issues of nanoparticles after CPPs modification should be noted, and the density of CPPs on nanoparticles should also be studied. To achieve safer and more effective nano formulations.

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