Mini-Review of Neural Regeneration Peptides in Brain Development

Abstract
During mammalian and especially human ontogenetic brain development, cues of chemotactractive and chemorepulsive character are interacting in a spatial-temporal manner to direct neuroblasts to the dedicated locations in the neocortex. Finally, neuroblasts differentiate to fulfill their respective function in the neural circuit. Most if not all of these important molecules, that direct neuronal migration, display activity profiles in the nanomolar range. In contrast, the novel gene family of Neural Regeneration Peptides (NRPs) has a neuronal survival and chemotactic activity profile in the subpicomolar range which makes the NRPs interesting candidates to represent the main constituents for neuronal chemoattraction during ontogenesis as well as injury or disease states of the brain. This review is focusing on early gene expression of the mouse nrp gene within the cortex as well as on the potential for the drug candidate NRP2945 to provide breakthrough treatment options for chronic disease states of the brain in the future.

Keywords: Human ontogenetic brain development; Spatial-temporal manner; Neural regeneration peptide; Chemokine receptor subunit

Abbreviations: CAPS-2: Calcium dependent Activator Protein for Secretion 2; BDNF: Brain Derived Neurotrophic Factor; CXCR4: Chemokine Receptor with CXC Motif 4; GABA: Gamma Amino-Butyric Acid; GABA A receptor: Gamma Amino-Butyric Acid Receptor A; GAERS: Genetic Absence Epilepsy Rats from Strasbourg; LGS: Lennxø-Gastaut Syndrome; MAP-2: Microtubule Associated Protein-2; MOG-EAE: Myelin Oligodendrocyte Glycoprotein Induced Experimental Autoimmune Encephalitis; NRP: Neural Regeneration Peptides; NRP2945: Neural Regeneration Peptide 2945; NT-3: Neurotrophin-3; PTZ: Pentylenetretrazol; RefSeq: Reference Sequence; SVZa: Anterior Subventricular Zone

The Neural Regeneration Peptide (NRP) molecule entity belongs to a family of gene encoded proteins which are inherent to all mammals. These NRPs are ultra-potent when used in vitro neuronal survival, chemotraction as well as neuronal differentiation assays [1]. NRPs are binding as agonists to a novel plasma membrane receptor complex at subpicomolar concentrations. This NRP receptor complex is currently under investigation and consists of CXCR4 and another undisclosed chemokine receptor subunit. CXCR4 activation by NRP leads to increase of GABA A receptor subunit (alpha and beta) protein expression and upregulation of GABA [2,3]. In this mini-review the company CuroNZ has investigated the ontogenetic gene expression patterns of the mouse nrp gene coding for Neural Regeneration Protein (nrp gene with GenBank identification RefSeq: NM_001013372.2) in the developing pre- and postnatal mouse brain.

The mouse nrp gene has been found expressed in the embryonic cortical anlage specifically in neocortical layers that are coinciding with the day of emergence of the respective cortical layer during embryonic ontogenetic development. When looking for co-expressing factors for the nrp expressing cells, it becomes obvious that vimentin is the dominant molecule. This intermediate filament is expressed in the embryonic cortex solely in radial glial cells that are providing the scaffold for radial neural migration of excitatory neurons during neocortical development. A subgroup of mouse nrp expressing cells is co-localized with the neuronal specific protein MAP-2. This aforementioned immunocytochemical analysis provides indirect evidence that the NRP gene family is directly involved in “building” embryonic brain architecture by exerting a chemotactractive effect on migrating and developing neuroblasts. This process is followed by final neural differentiation by establishing a functional neuronal network. At day of birth (P0 mouse), nrp gene expression is ceasing in the cortical plate and emerges in the CA1/CA3 and sub granular zone of the hippocampal formation (active neuronal proliferation zone for neural precursor cells) as well as in the mitral/granular layer of the Bulbus olfactorius (Figure 1). The latter near “nasal” zone expression location could indicate that the nrp gene could well be the elusive “driver” of the rostral neural migration stream which originates from the anterior subventricular zone (SVZa) sending neuroblasts towards the B. olfactorius and replenishing and simultaneously renewing olfactory neurons during the lifetime of a mammal. It also has been recently established that the rostral migration stream is controlled by CXCR4 activation [4].

Because of the extreme potency of the NRP peptides (characterized 24-mer mouse nrp-derived peptide shows efficacy with EC-50 values in the low femtomolar range within in vitro assay testing of neuronal survival and chemotraction), this
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Citation: NRP2945 and is now ready for testing in healthy adult volunteers. This strategy provides improved physico-chemical shelf life stability for the compound. This drug candidate is named NRP2945 and is now ready for testing in healthy adult volunteers.

NRP2945 has shown a range of pharmacodynamic activities within different animal models of neurodegeneration including optic nerve ligation, MOG-EAE (Myelin Oligodendrocyte Glycoprotein induced Experimental autoimmune Encephalitis), hemi-section spinal cord injury and preclinical relevant models of epilepsy. NRP2945 completely suppressed pentylenetetrazol (PTZ) induced convulsive seizures in male adult Wistar rats [2]. NRP2945 is also capable of suppressing typical absence seizures that are common to the rat strain GAERS when administered as a single subcutaneous bolus. We are currently testing chronic administration paradigms for seizure control in these rats. For the planned clinical phase I/II trial, children with severe refractory epilepsy being categorized as Lennox-Gastaut Syndrome (LGS) will be enrolled to monitor whether NRP2945 will succeed in significantly reducing the seizure load within these young patients who are experiencing a multitude of different types of seizures that are currently only partially controlled by approved adjunctive treatments.

In conclusion, in the future NRPs could provide a viable option for chronic treatment of neuro degenerative diseases by providing a high level of safety with no known off-target effects as well as long-lasting inhibitory network stimulating effects. NRP2945 is diminishing seizure activity during pathological states of global brain circuits. For example it is known that during Status Epilepticus, GABA A receptors are internalized into the cell cytoplasm and therefore are unavailable for extracellular administered and normally effective drugs like benzodiazepines. In contrast, NRP2945 can quickly upregulate protein expression of the synaptic GABA A receptor system as well as GABA and can therefore provide a meaningful inhibitory stimulus during severe states of epilepsy.

References