Sensory impairment in mental retardation: a potential role for NGF

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Abstract

Sensory impairment is defined as the inability to interpret outside stimuli such as visual, auditory, verbal, sense of touch, taste or smell or feelings of pain. This leads to absence of sensation and neuronal coordination. The impairment may be caused by ageing and other physiological changes, accident or injuries or can be found in some cases of mental retardation (MR) also referred to as intellectual disability. Known cases of MR involving inability to accurately interpret an outside source or stimuli are: Fragile-X syndrome; Tuberous sclerosis complex (TSC) with associated autism spectrum disorder (ASD); Rett syndrome; Autism and ASD with or without MR; Chromosome 22q13.3 deletion syndrome; familial dysautonomia, Prader-Willi’s syndrome, Williams syndrome. In this review we will discuss in particular form of ASD and altered sensory sensitivity. The role of NGF in causing pro-nociceptive activity and its role in peripheral sensitisation is discussed under the light of its involvement in forms of MR where loss of pain perception is a main feature due to mutations to NGF receptors or NGF genes during development. Other forms of MR with altered sensory impairment will be considered as well as additional potential mechanisms involved.

Key words
Mental retardation • Autism spectrum disorder • Sensory impairment • Eph receptors • Pain • NGF • TrkA • Rett syndrome • Familial dysautonomia • Prader-Willi • Williams syndrome

Sensations of touch, pressure, vibration, limb position, heat, cold, and pain represent the somatic sensory system. Mechanoreceptors, proprioceptors and nociceptors relay the information from the periphery of the body to the central nervous system where sensory processing occurs. Briefly, primary afferent fibers of small diameter (A-delta and C fibers) mediate pain and temperature, while A-beta and A-delta mediate touch, vibration; A-alpha and A-beta mediate proprioception. These fibers innervate skin, muscles, viscera and their termination lies in laminae of dorsal horn of the spinal cord I to V conducting information of different modalities via ascending pathways to the brain areas devoted to sensory perception and integration.

Sensory impairment refers to a defect in sensing and passing on the impulse. This leads to absence of sensation and neuronal coordination. People with sensory impairment may not be able to hear or speak or view or smell or feel or react to the stimuli given to the respective sensory systems. Mental retardation (MR) or intellectual disability is a disorder appearing during childhood which entails impaired cognitive functions and different sets of deficits with at least two adaptive behaviours compromised (i.e. skills needed to live independently such as daily living skills communication and social skills). Intelligence Quotient (IQ) is generally set at lower than 70%. Intellectual disability is a broader term preferred to MR in recent literature but strictly
speaking it can appear at any age (e.g. dementia) or be acquired (e.g. following a stroke) so we will use the term MR in this review to define syndromes appearing before adulthood. Causes are unknown for up to half of the cases of MR but they can be genetic (Down syndrome, Prader-Willi, Fragile-X syndrome), due to problems during pregnancy (e.g. rubella) or during birth (e.g. anoxia), malnutrition and many others. One out of ten children who needs special education has some form of MR.

Altered sensory sensitivity in autistic spectrum disorders

Autism is a pervasive developmental disorder with an onset in early childhood and severe, often lifelong effects on communication, socialization, and tendencies toward restricted interests or repetitive behaviours (American Psychiatric Association definition). About 40% to 70% of children in the ASD have some abnormality in sensory sensitivity: ordinary sensations may be perceived as extremely intense or extremely dampened down (Biersdorff, 1994; Nader et al., 2004; Kern, 2006). Different reactions to different sensory modalities can occur at different times in the same individual (Baranek et al., 2006). For example sounds can be most unbearable when they are sudden or unexpected noises; high-pitched, continuous noises, complex or multiple sounds such as those in a supermarket. It has been reported a lack of reaction to pain and to high/low temperature apparently due to excessive opioid activity (Sahley et al., 1987; Sher, 1997); on the other hand it has also recently been claimed that reported reduced pain sensitivity in autism are related to a different mode of pain expression rather than to an insensitivity or endogenous analgesia failing to support an opioid theory of autism (Todjman et al., 2009). On the same note, Dubois reports the lack of concordant statements between a professional’s evaluations of facial expression of a child with autism following a noxious stimulus with parents’ report of their children’s pain (Dubois, 2010). Pain is not only expressed with facial expressions but also showing altered behavior that we need to learn to understand in order not to make the same mistakes done with babies and people with disabilities supposedly not able to feel any pain (Dubois, 2010). Another sensory modality affected in ASD is vision; in terms of visual sensitivity some levels of illumination may be too strong to be looked at; colours’ perception can be very vivid and intense as it is recognized in the paintings of people with Asperger’s syndrome (Mottron et al., 2001). Hypersensitivity to food textures that gradually diminishes with age but may persist in adulthood has also been reported. Moreover tactile sensitivity might be altered (Cascio et al., 2008); forms of touch used in social greetings or gestures of affection are overwhelming or too intense; scalp and palms are hypersensitive; a limited wardrobe is preferred according to the few textiles accepted (Defrin et al., 2004). Tactile hypersensitivity at the fingertip has been demonstrated in Asperger’s syndrome sufferers (Blakemore et al., 2006).

Molecular mechanisms underlying altered sensory sensitivity in autism spectrum disorders

Autism and mental disabilities have been associated with dysregulation of axon growth and guidance. In particular deficient axonal growth has been associated with cerebral dysgenesis and intellectual disability (Volpe, 2001). Increased white matter volume (Courchesne et al., 2001) and aberrant white matter adjacent to brain regions, implicated in social cognition in autistic individuals, has been shown in MRI studies (Barnea-Goraly et al., 2004). Recent data suggest that mis-wiring of connections in the developing brain, leading to improper information flow is involved in ASD (Catani, 2006). An exuberance of connections is shown in mouse models of ASD, consistent with the idea that autism may involve a sensory overload, and/or a lack of filtering of information.

Tuberous sclerosis complex (TSC) is a disease characterized by tumour predisposition, neurological abnormalities including epilepsy, MR and autism (Choi et al., 2008). Mutation in TSC2 (one of the genes involved in TSC) prevents axon growth cones from finding their proper destinations in the developing brain, not being able to respond to cues from Ephrin A4, which is responsible for correct axonal guidance, activating the molecular pathway mTOR (Nie et al., 2010). Rapamycin, a TOR inhibitor, could be used to prevent miswiring in the developing
brain (already used to prevent transplant rejection) (Jeste et al., 2008). Growth cones instead of collapsing continue to grow in the retinal projection to the brain. Eph receptors and ephrins, their ligands, have a wide variety of roles in the central nervous system, the most widely studied one being their involvement in nervous system development (Wilkinson, 2001). The Eph receptors represent the largest family of receptor tyrosine kinases in the mammalian genome and regulate various signaling pathways through a number of downstream effectors. Eph receptors and ephrins also persist in the adult brain, particularly in regions where neuronal circuits continue to be remodeled, such as the hippocampus (Grunwald et al., 2001; Filosa et al., 2009) and in the spinal cord where they contribute to pain modulation through phenomena of synaptic plasticity (Battaglia et al., 2003; Slack et al., 2008; Ruan et al., 2010).

Interestingly, elevated concentrations of NGF and other neurotrophins present at birth in the blood may be associated with the development of autism and MR later in childhood (Nelson et al., 2001; Miyazaki et al., 2004; Nelson et al., 2006). It has also been reported that NFG levels positively correlate with the customized centile and birth weight of infants, both of them lower in intrauterine growth restriction (IUGR), a failure of the fetus to reach his intrinsic growth potential, as NGF levels were higher in the appropriate for gestational age compared to the IUGR. Neurotrophins with their neuroprotective effect exert a critical effect during pre- and postnatal brain development (Malamitsi-Puchner et al., 2006).

NGF and pain

Nerve growth factor (NGF) is well known for its neurotrophic and survival activities (Levi-Montalcini, 1987). NGF signalling is mediated by the high affinity TrkA receptor and the low affinity p75NTR receptor. NGF, like other neurotrophins, is initially synthesized as a pro-form (pro-NGF), proteolytically processed and secreted as mature protein (Chao, 2003). Mature NGF promotes cell survival by binding to TrkA, while proNGF preferentially induces apoptosis through p75NTR (Lee et al., 2001). Interestingly NGF displays also a potent pro-nociceptive activity as release of NGF produces sensitization of the peripheral terminals of sensory neurons. NGF has been found in the synovial fluid of patients with chronic arthritis (Aloe et al., 1992). For a review see Pezet and McMahon (Pezet and McMahon, 2006). NGF is thus involved in pain transduction mechanism. Following tissue trauma, mast cells, macrophages, keratinocytes, and T cells all release NGF, which can then interact with its receptors, TrkA and p75NTR, on peripheral nerve endings. Once NGF binds to its receptors, intracellular signalling cascades are activated, which will then modulate the activity of ion channels in the nerve endings or enhance the release of the neuropeptides such as substance P (SP) and/or calcitonin gene-related peptide (CGRP) themselves responsible of peripheral sensitisation of nociceptors nerve endings (Pezet et al., 2001; Nicol and Vasko, 2007) (Fig. 1). Multiple action potentials are elicited at the nerve terminal following treatment with NGF or as a consequence of inflammation. Moreover gene expression can be modified upon NGF binding its receptor as the TrkA-NGF complex is retrogradely transported back to the cell. Upon treatment with NGF in vitro, expression of brain-derived neurotrophic factor (BDNF) is present in all DRG Trk-A expressing neurons (Salio et al., 2007). NGF affects also the gene regulation of voltage-gated sodium channels such as Nav. 1.3, 1.8 and 1.9. Post-translational modifications following NGF treatment are also responsible for increased sensitization of nociceptors (e.g. enhanced responsiveness of TRPV1 receptors) (Pezet and McMahon, 2006).

If NGF is administered in vivo to sensory neurons terminals or cell bodies, the same set of molecules (e.g. SP, CGRP, BDNF, TRPV1) is upregulated. NGF administered to humans it causes hypersensitivity and pain (Anand, 1995; Sah et al., 2003) while in animal models of pain it lowers pain threshold (McMahon et al., 1995; McMahon, 1996). In particular it has been shown an acute onset of thermal hyperalgesia (Della Seta et al., 1994) and a delayed onset for mechanical hyperalgesia (Molliver et al., 2005). Moreover, in animal models of inflammation such as carrageenan, Complete Freund’adjuvant, NGF levels increase into tissues and circulation (Woold et al., 1994). A summary of inflammatory conditions in which NGF has a demonstrated role as a mediator of pain is presented in Table 1 (Pezet and McMahon, 2006). Neutralization of NGF reduces sensory neurons expression of SP and CGRP (Pezet and McMahon, 2006); neutralization of endogenous
NGF prevents sensitization of nociceptors supplying inflamed skin (Koltzenburg M et al., 1999). On the other hand the pro-nociceptive activity of NGF has limited dramatically the therapeutical applications of NGF. Null mice for NGF and TrkA show lack of pain sensitivity and die shortly after birth due to sensory neurons requirement for NGF as a survival factor. In short, NGF plays an important role in pain processing in the postnatal period when the primary nociceptors lose their dependency on the growth factor (Pezet and McMahon, 2006).

Pain insensitivity in syndromes with mental retardation and NGF role

As NGF involvement in peripheral sensitization of sensory neurons has been demonstrated (for review see Pezet and McMahon, 2006; Nicol and Vasko, 2007) it has also been shown that mutations in both TrkA and NGF genes have a powerful effect on pain perception. Mutations in the TrkA/NGF receptor gene on chromosome 1 (1q21-q22) cause congenital insensitivity to pain with anhidrosis (CIPA) also known as Hereditary sensory and autonomic neuropathy type IV (HSANIV). The mutations abolish or reduce TrkA responsiveness to NGF. CIPA is an autosomal-recessive disorder characterized by recurrent episodes of unexplained fever, anhidrosis (absence of sweating) and absence of reaction to noxious stimuli, self-mutilating behaviour and MR (Indo et al., 1996; Auer-Grumbach et al., 2003). The mutations in particular induce frameshifts, nonsense, splice or missense variations which can be found either in the extracellular NGF-binding domain or in the intracellular signal-transduction domain (Indo, 2001). This neuropathy is related to environmental temperature and to the fact that the infant fails to cry when intramuscular injections are given. Parents or caregivers may notice the lack of perspiration on hot and humid days. Self-mutilation may be noticed as early as 6 months of age when the teeth start to erupt together with multiple bone fractures. Restlessness, temper tantrums, breath-holding spells, insomnia and almost no social communication are the early manifestations of moderate to severe MR. Patients affected by this neuropathy lack primary afferent fibers A-delta and C-fibers and sympathetic postganglionic neurons. Touch, vibration and proprioception are normal. Interestingly they also lack polymodal receptors that detect interoception. Overall, patients affected by CIPA lack the “fight or flight” reaction. It has also been noted a reduction of neurons in some brain in areas (e.g. basal forebrain cholinergic
The whole clinical presentation validates the interesting hypothesis proposed by Indo (2009) of an NGF-TrkA system essential for establishing a neural network devoted to interoception and homeostasis crucially affecting emotional behavior as well. It is well known that NGF mediate the cross-talk between the nervous system, the endocrine and immune systems as functional NGF receptors are present in the cell membranes of cells belonging to all three systems (Levi-Montalcini et al., 1996). Interestingly a mutation in the Trkb gene (coding for BDNF, NT-4 and NT-3 receptor) that impairs TrkB signalling results in obesity due to hyperphagia and impaired nociception, learning and memory (Yeo et al., 2004). A missense point mutation in the coding region of NGFB gene (R221W) (Einarsdottir et al., 2004), which disrupts the processing and secretion of mature NGF and causes intracellular accumulation of proNGF (Larsson et al., 2009) gives rise to loss of deep pain perception and temperature (in HSAN V patients) but sweating and intelligence are normal, thus indicating that mutations in the NGF TrkA receptor result in a more severe phenotype compared to mutation in the NGF gene itself. A similar mutation has been found in a population in Sweden in an 8.3-Mb region on chromosome 1 (1p11.2-p13.2). The homozygous patients lacked deep pain perception in bones and joints and had no protective reflexes, leading to gross bone and joint complications (Minde, 2006). It has been noted though that very few patients affected by HSAN V have been thoroughly assessed for their cognitive performance. For example it has been reported the display of bizarre behavior by patients affected by HSAN V, mostly men; insensitivity to pain is explicitly demonstrated in public places, often in exchange for money; a patient allowed other people to cause him injuries or causing himself injuries and laughing at this in front of everyone: cognitive performance being normal if tested (de Andrade et al., 2008). More research is sought to understand the coping strategies and the dysfunctional types of behaviors displayed by HSAN V patients.

Very recently is a humanized antibody against NGF called Tanezumab (Pfizer) has been shown to effectively block NGF interaction with its receptors, TrkA and p75NTR. Blocking NGF function peripherally is now considered to be a valid pain treatment and NGF-neutralizing antibodies are currently being assessed for their potential analgesic use in a clinical trial (see http://www.rinatneuro.com). Initial results of preclinical trials have shown that blocking NGF function later in life does not cause the same disabling effects caused by mutations of the Trk A/B genes during development (Lane et al., 2010).

Other forms of mental retardation and sensory abnormalities

Hemimegalencephaly (HME)

Paediatric HME is a congenital central nervous system disorder, characterized by monolateral cerebral hemisphere enlargement, intractable seizures starting in the post-neonatal period, and mental retardation. Moreover anomalies in the neuroanatomical structure of the brain have been found, such as altered cortical thickness and lack of lamination. Increased cerebral tissue levels of NGF and BDNF have been found in infants affected by HME in association with abnormal NGF receptor expression in subcortical blood vessels. It is also
reported a marked reduction of cortical choline acetyltransferase immunoreactivity which indicates alteration of NGF activity in the differentiation of this area potentially contributing to HME (Antonelli et al., 2004). The patients affected by HME usually have abnormal function of the involved hemisphere and can have sensory and motor dysfunction on the opposite side of the body.

**Phelan-McDermid syndrome (or chromosome 22q13.3 deletion syndrome)**

Another syndrome where affected children show MR and sensory abnormalities is the chromosome 22q13.3 deletion syndrome or Phelan-McDermid syndrome. Sensory processing abnormalities are present in all children with unusual responses to the environment and sensory stimuli: lack of responsiveness to verbal or pain stimuli (increased tolerance to pain is shown in almost 90% cases) but, hyper-responsiveness to tactile stimuli; poor thermoregulation is also shown in more than 50% of children affected by this syndrome. There is also an over-arousal to the environment (e.g. panic at sudden noises, telephone, or rapid movements in the visual field) quite common in forms of ASD. Interestingly patients affected tend to seek stimulation: oral (paper mouthing or licking glasses or iron objects), olfactory (smelling objects or people), or proprioceptive (lying on the floor or walking on the knees). All of these behaviors tend to decrease with developmental age (Phelan et al., 2001). On the other hand neither atypical visual exploratory behaviors (e.g. lateral glance orientated toward parts of objects or strange fascination with moving stimuli) nor auditory hypersensitivities have been reported (Philippe et al., 2008). Research aimed at finding neurobiological correlate for chromosome 22q13.3 deletion syndrome has shown that the deleted part codes for the Shank gene, which assemble glutamate receptors with their intracellular signalling apparatus and cytoskeleton at the postsynaptic density (Roussignol, 2005). Formation and stabilisation of synapses is thus affected: experimentally induced expression of Shank3 has been shown to be sufficient to induce functional dendritic spines in aspiny cerebellar neurons (Roussignol et al., 2005). Moreover also the WNT7B gene in the deleted part is also involved in the regulation of the dendritic development (van Bokhoven et al., 1997).

**Rett syndrome and altered pain sensitivity**

Rett syndrome (RT) is a severe neurodevelopmental disorder affecting mostly females and associated in most cases with a mutation in the X-linked MECP2 gene, a transcription factor. An apparent normal development is then followed by regression. RT syndrome is characterized by severe MR and physical disability. Unusual manifestations (e.g. hand stereotypies, such as frequent hand washes) accompany the syndrome and altered sensitivity to pain is one of those (Devarakonda et al., 2009), especially manifested in children with the age range of 6 to 10 years old (Downs, 2010). It has very recently suggested that the MeCP2 gene might be involved in setting pain sensitivity (Downs, 2010) via modulation of target genes. A recent study by Geranton (2008), points towards this direction linking serotonin, known to facilitate nociceptive transmission at the level of dorsal horn, and post-translational modifications of MeCP2 (e.g. phosphorylation), which regulate activity-dependent gene transcription. In a rat model of peripheral inflammation following injection in the hindpaw, chemical depletion of serotonin in the lumbar spinal cord reduced the phosphorylated levels of MeCP2, which usually accompany inflammation, and decreased mechanical pain sensitivity. It has been shown that brain levels of NGF, which also regulates the development and functioning of central cholinergic neurons, are decreased in girls affected by RT. In particular, NGF levels increase significantly with age in controls, but the opposite is observed in girls affected by RS, where a progressive age-dependent decrease of NGF is observed (Calamandrei et al., 2001).

In Rett syndrome there is a high risk of sudden death, which has been correlated with an alteration of ventricular repolarization. Interestingly it has been shown that NGF plasma levels were significantly lower in Rett patients with QTc interval prolongation in comparison with Rett patients with a normal QTc interval (Guidieri et al., 2004).

Very recently it has been reported that NGF levels are decreased in the hippocampus of a MeCP2 (1lox) null mice, considered to be a model for RT syndrome (Schaevitz et al., 2010).
Familial dysautonomia (hereditary sensory neuropathy type II), Prader-Willi syndrome and Williams syndrome

Other disorders entail insensitivity to pain such as a familial dysautonomia (hereditary sensory neuropathy II or HSN II) (Axelrod and Gold-von Simson, 2007) and Prader-Willi syndrome (Holm, 1993). In familial dysautonomia, an autosomal recessive disease where affected patients have chronic ulceration of the fingers and toes, autoamputation of the distal phalanges, and neuropathic joint degeneration associated with loss of pain sensation. For HSN II, which involves the developmental loss of neurons in sympathetic, sensory, and some parasympathetic ganglia, an inherited defect in the action of bNGF has been proposed (Breakfield, 1984). This and other studies (Davar et al., 1996) have not been able to demonstrate that the beta-NGF gene region could be considered the cause of this neurologic disease but on the other hand does not eliminate other genes involved in beta-NGF action, such as those coding for processing enzymes, receptors, or other subunits of the NGF complex. In the Prader-Willi syndrome, a human genomic imprinting-associated neurodevelopmental disorder, thermal and pain thresholds are significantly higher in adults affected by the syndrome than in controls. In particular the human necdn gene in chromosome 15q11-q12, which is a multifunctional signaling protein that stabilizes terminal differentiation of postmitotic neurons, maternally imprinted, paternally transcribed, is not expressed in Prader-Willi syndrome. It has been recently demonstrated that the paternally expressed necdn is required for physiological development of nerve growth factor (NGF)-dependent sensory neurons. Mutant mice for the necdn gene showed significantly high tolerance to thermal pain like seen in people affected by Prader-Willi syndrome (Kuwako et al., 2005). Interestingly, the absence of abnormalities on sensory nerve conduction studies, sympathetic skin responses and somatosensory evoked potentials has been shown in Prader-Willi syndrome (Priano, 2009).

Williams syndrome (WS) is a neurodevelopmental disorder caused by a 1.6 Mb deletion on chromosome 7 (7q11.23). It is characterized by severe impairments in visuospatial processing and oversensitivity to sounds (e.g., auditory fascination, hyperacusis- hypersensitivity to sounds- and pho-nophobia- extreme fear from sounds) (Zarchi et al., 2010). Mild to moderate retardation is also a prominent feature of WS (Alleva et al., 1999). It has been shown that NGF serum levels in people affected by W S are higher than in controls Interestingly, NGF serum levels stay constantly higher during childhood while in controls levels of serum NGF are higher only in early childhood and then decline later stages (Calamandrei et al., 2000). It has been proposed that some of WS features, such as hyperacusis and hypertension can be linked to higher NGF circulating levels.

Conclusion

Along the course of this review we have been able to appreciate that impaired sensation in MR may result from different causes, some of which still unknown. Children affected by different types of MR share a sensory integration deficit or sensory processing disorder. These children may have difficulty learning and performing everyday activities and have an inability to correctly interpret sensory information that our bodies receive through touch, taste, smell, seeing and hearing. A significant body of experimental evidence points to an important role for the NGF TrkA system in the impaired pain sensation in many neurodevelopmental disorders with MR. Mutations in the TrkA/NGF genes or excess levels of NGF do contribute to many of the abnormalities observed in syndromes where MR is a prominent feature together with alteration in sensitivity especially pain perception. Excess levels of circulating NGF might cause sympathetic hyperthrophy or hyperinnervation of target organs, which could underlie the hypersensitivity to external stimuli sometimes observed in neurodevelopmental syndromes. On the other hand the link between NGF and MR could be due to the important role of NGF in the development and survival of forebrain cholinergic neurons (Levi-Montalcini, 1987). If NGF levels are altered during critical early postnatal periods learning and memory can be dramatically affected leading to forms of mental disability. Very recently the so-called neuro-metabotrophic deficit has been recently proposed as having an important role in both neuropsychiatric diseases and neurodevelopmental syndromes and cardiometabol-
ic diseases (e.g., atherosclerosis, obesity, type 2 diabetes, metabolic syndrome) due to the role of NGF and other neurotrophic factor involved (Chandrakov et al., 2009).

Other mechanisms involved in dysfuntional sensory sensitivity in MR are altered wiring in the brain (e.g., impaired responses to guidance molecules such as the Eph/ephrins in the developing brain); altered neuronal morphology (e.g., dendritic tree abnormalities); cognitive difficulties in communicating and interpreting the meaning of an otherwise experienced sensations of pain, touch.

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