Understanding Intellectual Disability through Rasopathies

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Abstract

Intellectual disability, commonly known as mental retardation in the International Classification of Disease from World Health Organization, is the term that describes an intellectual and adaptive cognitive disability that begins in early life during the developmental period. Currently the term intellectual disability is the preferred one. Although our understanding of the physiological basis of learning and learning disability is poor, a general idea is that such condition is quite permanent. However, investigations in animal models suggest that learning disability can be functional in nature and as such reversible through pharmacology or appropriate learning paradigms. A fraction of the cases of intellectual disability is caused by point mutations or deletions in genes that encode for proteins of the RAS/MAP Kinase signaling pathway known as RASopathies. Here we examined the current understanding of the molecular mechanisms involved in this group of genetic disorders focusing in studies which provide evidence that intellectual disability is potentially treatable and curable. The evidence presented supports the idea that with the appropriate understanding of the molecular mechanisms involved, intellectual disability could be treated pharmacologically and perhaps through specific mechanistic-based teaching strategies.

Keywords

Learning deficit; RAS/MAP Kinase signaling pathway; phenotypic reversion

1. INTELLECTUAL DISABILITY

1.1. Introduction

According to the International Classification of Disease (ICD), mental retardation is a condition of arrested or incomplete development of the mind, especially characterized by impairment of skills manifested during the developmental period. Such skills are those that contribute to the overall level of intelligence, i.e. cognitive, language, motor, and social

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abilities. The disability originates in the individuals before 18 years of age, when the nervous system is affected or functionally altered. The disability can be observed for many everyday social and practical skills, as well as higher cognitive functions. For instance learning and memory, essential processes to acquire knowledge from the physical and social environment (Bolduc and Tully, 2009; Luckasson and Edwards, 2002).

Although the ICD and many other texts still use the term mental retardation, the preferred term currently is intellectual disability (ID). Degrees of ID are conventionally estimated by standardized intelligence tests, which are designed to measure the general intelligence quotient (IQ). A test score below 70 indicates a significant limitation in intellectual functioning. These can be supplemented by scales assessing social adaptation.

Intellectual abilities and social adaptation may change over time and more interesting, may improve moderately as a result of training (Harris, 2005). ID is a complex subject in many aspects; for a comprehensive revision, see Harris (2005).

1.2. Etiologies of Intellectual disability

As can be expected from a general term as ID, there is a large variety of etiologies, from single gene mutations to chromosomal abnormalities and a larger variety of environmental factors which can affect a normal development of the nervous system. The classification of causes of ID by the American Association on Intellectual and Developmental Disabilities (AAIDD) includes prenatal, perinatal and postnatal causes. Prenatal causes contain several general categories such as chromosomal disorders, syndrome disorders (including RASopathies), inborn errors of metabolism, developmental disorders of brain formation and environmental influences (including forms of malnutrition and the effects of certain drugs). Perinatal and postnatal causes mostly include a large variety of infections and traumatisms in these time periods; (For a complete classification of causes of ID see Luckasson and Edwards, 2002).

1.3. Treatment for Intellectual disability

There is no cure for ID and in general is considered to be a permanent condition, however, it can be treated through a number of strategies such as human development training, special education programs, life skills training and job coaching.

The idea that intellectual capacities and skills in individuals with ID could be improved by training is recent. The previous view considered ID as a static condition (Harris, 2005; Smith and Wehmeyer, 2012; Tassé et al., 2013). Nevertheless, it remains the concept that ID is caused by irreversible changes during development. Such long-standing view is supported by indirect evidence such as: (a) Presence of developmental defects by direct observation of morphological alterations in body features of diagnostic value (e.g. facial dysmorphia). (b) Presence of critical periods during development susceptible to environmental injuries (reviewed in Rice and Barone, 2000) and more recently, (c) genes involved in some cases of ID actually participate in embryonic development, as it is the case of a group of disorders discussed in the following section (Reviewed in Rauen, 2013).

Although the current view is quite straightforward and applicable to some cases, this seems not to be the case for all cases of ID (Ehninger et al., 2008; Haier et al., 1998). Investigations in animal models of genetic disorders indicate that learning disabilities and attention deficits can be caused by an alteration in mechanisms of molecular signaling. Such impairments were overcome by pharmacology and appropriate learning paradigms (Costa et al., 2002; Cui et al., 2008; Guo et al., 2000; Ho et al., 2007; Pagani et al., 2009) Thus, contrary to general belief, these deficits are not caused by a structural and irreversible alteration, but a functional one. Taken together, these studies support the idea that deficits in learning and attention could be treated in humans as well.

Still, an incomplete understanding of the mechanisms causing ID does not allow us to provide treatment, as we would do for many other health problems such as infections, hypertension or diabetes. To improve our understanding of ID it is essential to investigate specific cases, since different disorders have different etiologies and presumably different mechanistic basis.

A fraction of the cases of ID is caused by point mutations or deletions in genes that encode for proteins of the RAS/mitogen-activated protein kinase (MAPK) signaling pathway known as RASopathies. Here we examined the current understanding of the molecular mechanisms involved in this group of genetic disorders focusing in studies which provide evidence that ID is potentially treatable and curable.

2. RASOPATHIES

RASopathies are a group of neurodevelopmental disorders with overlyping clinical features and are characterized by germline mutations in genes that encode for proteins involved in the RAS/MAPK signaling (Reviewed in Rauen, 2013; Tartaglia and Gelb, 2005). Specifically, the member of the MAPK superfamily involved in RASopathies is the extracellular-regulated kinase 1/2 (ERK) (Figure 1). These mutations produced gain of function (GOF) alleles in positive regulators of the RAS/ERK signaling pathway (e.g. RAS) and loss of function (LOF) alleles in negative regulators (e.g. Neurofibromin 1; NF1). Therefore, both GOF and LOF mutations generate an enhanced signaling of this pathway. With the only exception of Noonan Syndrome with Multiple Lentigines (NSML) syndrome, all the observations related to the effect of mutations reported in RASopathies allow us to conclude that the main biochemical effect is an increase in the levels of activity in the molecular effector ERK. NSML can be caused by mutations in the gene Protein Tyrosine Phosphatase Non-receptor 11 (PTPN11) which encodes the protein SHP2. The analysis of two PTPN11 alleles-Y279C and T468M-only found in NSML, provide a more complex scenario (Kontaridis et al., 2006; Oishi et al., 2009). These alleles, encoding for the mammalian or *Drosophila* protein showed a reduced phosphatase activity in *in vitro* assays, however, the reported effect on ERK activity is opposite in those studies (discussed in Oishi et al., 2009).

There are unique phenotypical features in each RASopathy. Among them a variable degree of cognitive impairment is observed, ranging from a severe to null learning disability. They also share many other features, most probably because of an enhanced ERK activity during

development, including craniofacial dysmorphology; cardiac malformations; increased cancer risk; hypotonia, and cutaneous, musculoskeletal and ocular abnormalities. RASopathies are a group of disorders that affect approximately 1 in 1,000 live births, constituting one of the most common groups of syndromes (Rauen, 2013). For a comprehensive revision see (Rauen, 2013; Tartaglia and Gelb, 2005) and also see (Aoki et al., 2013), which describes the recently discovered gene RIT1 involved in Noonan syndrome (NS).

The phenotype - genotype correlation is poor in RASopathies. In other words, for each particular mutant allele a large variation in the phenotypes (e.g. facial dysmorphia, short stature, cardiac defects and skeletal malformations) can be observed (Castle et al., 2003; Tartaglia et al., 2002). The identification of the genes involved in different syndromes has shown that some of them can be allelic disorders (e.g. NS and Cardio-Facio-Cutaneous syndrome (CFC) are caused by different alleles of the gene KRAS) (Figure 1). A more interesting example is the case of the BRAF L597V allele, which is found in patients with NS and CFC (Sarkozy et al., 2009). Thus, the same allele produces phenotypes currently viewed as distinct disorders. Likewise, homozigotic twins with Neurofibromatosis type 1 (NF1) shows differences in phenotypic expression (Bauer et al., 1988). This variable phenotypic expression is classically attributed to interactions with other genes, environmental fluctuation and epigenetic variation in gene expression, as well as more specific mechanisms (Carey et al., 1979). In any case, RASopathies seem to be the spectrum of phenotypic expressivity resulting from altered RAS/ERK signaling. Studies in these disorders have described a variety of cognitive alterations (see next section).

2.1. Cognitive alterations in patients

Cognitive problems in patients with NF1 have been extensively studied (for a revision see North, 2000; Shilyansky et al., 2010). NF1 children do not show impairment in global cognitive abilities, however, they can show a lower score compared with unaffected siblings (Eldridge et al., 1989; Hofman et al., 1994; Kayl and Moore, 2000). Learning disability is found in 30 to 65 % of NF1 children (Rosser and Packer, 2003; Stine and Adams, 1989). Strikingly, up to 90% of NF1 patients can show a cognitive impairment when specific domains are examined (e.g. visuospatial functions, motor coordination, planning, organizational skills and reading/vocabulary) (Hofman et al., 1994; Hyman et al., 2005; Payne et al., 2011). This suggests a deficit in executive functions, which is consistent with more recent studies where a deficit in inhibitory control, working memory and cognitive flexibility as well as a global deficit in attention and executive functions were reported (Payne et al., 2011; Rowbotham et al., 2009; Roy et al., 2010).

The analysis of global cognitive abilities in patients with NS, **Costello syndrome (CS)** and CFC syndrome (see Figure 1) carrying mutations in most genes associated with RASopathies (i.e. PTPN11, SOS1, HRAS, KRAS, BRAF, RAF1 and MEK1) has been performed (Cesarini et al., 2009). These studies using different Wechsler intelligence scales according to age, found that all genes can be associated with a low IQ (<70), which is consistent with previous studies of NS of unknown genotype (Lee et al., 2005). However, the degree to which mutations in those genes affected the IQ was highly variable. While

mutations affecting proteins upstream of RAS (i.e. PTPN11, SOS1) (Figure 1) are less frequently associated with ID, mutations that affect components downstream of RAS (i.e. RAS, BRAF, MEK1) are generally associated with ID and a more severe cognitive impairment (Cesarini et al., 2009). A more recent analysis in a similar set of subjects also indicates autistic-like behavior in RASopathies (Alfieri et al., 2014).

In addition, adaptive behavior was analyzed in patients with NS or CFC (Pierpont et al., 2010). Adaptive behavior is defined as a collection of conceptual, social, and practical skills that all people learn in order to function in their daily lives (e.g. skills for self care and communication). Patients with NS and CFC showed a reduced adaptive behavior according to the Vineland adaptive behavior Scales (Sparrow et al., 2005), when compared with standardized scores in both groups, especially in daily living skills.

Again, the effects of mutations in genes encoding for components downstream of RAS produced a more pronounced phenotype. Both groups of patients showed the ability to learn and develop adaptive skills as they got older, since the scores increased with chronological age. However, differences in adaptive skills with standard peers became more apparent with age.

Although it is difficult to match and compare human behavior and mechanistic basis with any animal model, we have learned greatly from the latter. Noteworthy, the neuroanatomical organization in humans can differ substantially from that of animal models, especially of invertebrates. However, at the genetic and molecular level, where therapeutic drugs act, the degree of similarity is outstanding (Bolduc and Tully, 2009; Inlow and Restifo, 2004; Kandel, 2001). The study of the mechanisms underlying RASopathies allowed and will allow us to improve largely our understanding of ID.

3. RASOPATHIES AND ANIMAL MODELS

NF1 is caused by LOF mutations in the neurofibromin 1 gene (*NF1*), which encodes the GTPase activating protein, NF1, a negative regulator of RAS (Viskochil et al., 1990; Wallace et al., 1990; Xu et al., 1990). Since NF1 protein is a negative regulator, *NF1* LOF mutations produce an enhancement of RAS/ERK signaling.

Studies in mouse and *Drosophila* NF1 models have shown that a reduced NF1 function enhanced ERK activity and reduced learning and memory, in a development-independent manner (Costa et al., 2001, 2002; Guo et al., 2000; Ho et al., 2007; Silva et al., 1997).

In mice, the heterozygous deletion of *NF1* produces memory impairment in the Morris water maze, a hipocampus-dependent task (Silva et al., 1997). Interestingly, NF1 mice showed a normal learning curve in the training protocol used (10 days of training, twice a day) indicating that the acquisition or learning was normal. Nevertheless, with additional training (14 days) *NF1* +/− performed as good as wild type control mice, indicating that, as observed with NF1 patients, training produces improvement. The memory impairment seems to be associated with functional hipocampal alterations since *NF1* +/− mice showed a deficit in long-term potentiation (LTP) in CA1 pyramidal neurons with several protocols of stimulation (Costa et al., 2002). Strikingly, this LTP deficit was rescued with a higher

frequency of stimulation. Consistently, *NF1* +/− mice performed at a wild type level in a cued fear conditioning paradigm, an amygdala dependent task (Silva et al., 1997).

More interesting, both the LTP and behavioral deficit in *NF1* +/− mice can be rescued by reducing RAS activity through genetic or pharmacological manipulation (Costa et al., 2002). While heterozygous mice with either a single mutation in *NF1*+/− or in RAS +/−, showed LTP and spatial memory deficits, the double mutant *NF1*+/− /K-RAS +/− showed normal levels in both variables.

Additionally, in adult *NF1*+/− mice treated with lovastatin, an inhibitor of HMG-CoA reductase that inhibits RAS/ERK signaling, the deficit in LTP and spatial learning was rescued (Li et al., 2005). Furthermore, lovastatin administered to adult *NF1*+/− mice reversed the attentional deficit measured by lateralized reaction-time, a prefrontal cortex-dependent task which is believed to measure visuospatial attention (Li et al., 2005). Remarkably, lovastatin treatment appears to be effective in NF1 patients (Mainberger et al., 2013; and see section 5).

The *Drosophila* model of NF1 shows reduced immediate and long-term memory (LTM) in an associative olfactory paradigm (Guo et al., 2000; Ho et al., 2007). Although the *NF1* mutations affect both types of memory, the GTPase-activating domain that regulates RAS affects only LTM, while the C-terminal domain reduces the immediate memory through regulation of adenyl cyclase (Guo et al., 2000; Ho et al., 2007; Tong et al., 2002). Interestingly, the memory impairment detected in mutant fruit flies without the *NF1* gene could be rescued by expression of a human *NF1* transgene (Guo et al., 2000; Ho et al., 2007).

In the *Drosophila* model of NS, clinically relevant GOF mutations severely impaired olfactory LTM whereas learning was normal (Pagani et al., 2009). These investigations showed that the induction of LTM requires the activation of ERK as well as its inactivation by the presentation of the next trial of training. This resetting mechanisms acting on the ERK activity was disrupted by the GOF alleles. Thus, providing more time between the trials of training, the LTM impairment was reversed completely. Moreover, the LTM impairment was also rescued by a slight pharmacological inhibition of the phosphatase SHP2 (Pagani et al., 2009) (See section 3.1)

3.1. Enhanced ERK activity in Learning and Memory

Mutations in genes encoding for components of the RAS/ERK signaling pathways enhance ERK activity. Noteworthy, this evidence comes from studies in cell cultures and development. Therefore, in such experimental conditions, a higher activity of the RAS/ERK signaling can be expected to be involved in cell growth, proliferation, migration and survival (reviewed in Krens et al., 2006; Schlessinger, 2000), but not in cognitive processes such as learning and memory in adult organisms. This suggested that an enhanced RAS/ERK signaling during development generates abnormal neuronal organization and connectivity. However, since deficits in memory and attention were rescued in adult animals modeling NF1 and memory was rescued in NS models, a developmental defect is not a possible

explanation (Costa et al., 2001, 2002; Guo et al., 2000; Li et al., 2005; Ho et al., 2007; Silva et al., 1997; Cui et al., 2008; Pagani et al., 2009).

The effect of clinically relevant mutations was analyzed in a context of learning and memory, specifically after training in NF1 mice and NS *Drosophila* models (Cui et al., 2008; Pagani et al., 2009). These studies showed that basal ERK activity (before training) was normal in adult animals expressing different transgenes in specific neurons. However, an enhanced ERK activity was detected transiently after training in both models (Cui et al., 2008; Pagani et al., 2009). Despite differences in animal models (e.g. gene under investigation and behavioral paradigm), it is remarkable that in both model systems a similar effect was observed. These observations strongly support the concept that similar molecular mechanisms operates in different RASopathies. In addition, Cui et al., (2008) have provided exciting evidence on how a training-dependent enhanced ERK activity can affect LTP and learning. Consistent with previous studies (Costa et al., 2002), Cui and collages (2008) showed that a higher ERK activity increases synapsin I phosphorylation in GABAergic interneurons, which in turn reduces LTP and memory.

In *Drosophila*, ERK activity is increased after one session of training, peaking at 20 min, whereas a second session of training, (15 minutes after the first one), removed the remaining activation of ERK to basal levels (Pagani et al., 2009). This resetting effect of a second session of training on the activation of ERK seems to be a key feature in the memory deficit in the fly model of NS. Specifically, whereas a higher ERK activation can be detected after training in fruit flies expressing either a wild-type or mutant GOF allele, only the later had a deficit in both LTM and in the resetting effect of a second session of training. This observation suggests that the loss of the resetting mechanism involved in multiple training trials can affect LTM. However, those experiments cannot distinguish between a loss of the mechanisms of resetting of ERK activity and a condition in which the resetting mechanism is insufficient for such large ERK activation. Remarkably the mechanism of ERK resetting by successive training sessions provides the molecular basis to differentiate spaced and massed experiences (Pagani et al., 2009).

This evidence supports the idea that the studies of RAS/ERK signaling on neuronal plasticity and memory greatly contribute to our understanding of RASopathies and in turn of ID.

4. ERK SIGNALING IN NORMAL LEARNING AND MEMORY

Our understanding on the mechanistic basis of RASopathies is very incomplete; however, studies in animal models have provided exciting findings on the biological basis of normal learning and memory. These studies confirmed those findings from animal models of RASopathies, expanded our understanding on RAS/ERK signaling and provided testable hypothesis as well as potential molecular targets. Importantly, these investigations also arrived to the conclusion that ERK is an essential component for long-term behaviors. Therefore, examining the RAS/ERK functions in behavior will lead to a better understanding of mechanisms underlying RASopathies and ID as well. Figure 2 summarizes

mechanisms showing that RAS as well as ERK can be regulated through calcium and several different molecular inputs (i.e. glutamate receptors, growth factors and Dopamine).

ERK signaling has been identified as a key molecular component in long-lasting memory and the associated neuronal plasticity in both vertebrates and invertebrates (Alonso et al., 2002; Atkins et al., 1998; English and Sweatt, 1996; Feld et al., 2005; Impey et al., 1998; Kelleher et al., 2004; Martin et al., 1997; Pagani et al., 2009; Philips et al., 2013, 2007, 2011).

One of the first findings involving ERK in neuronal plasticity and memory was provided by studies of LTP, a model for the cellular basis of learning and memory. In rat CA1 pyramidal neurons, ERK was activated by LTP-inducing high-frequency electrical stimulation, as well as by stimulation of components necessary for LTP (i.e. PKC and *N*-metil-D-aspartate (NMDA) receptor) (English and Sweatt, 1996). Interestingly, as occurs with memory, LTP has a short-term form and a long-term form known as early-LTP and Late-LTP, respectively (Nguyen et al., 1994). As occurs with LTM, Late-LTP requires Ca2+ and cAMP-dependent signaling, new protein synthesis and CREB-dependent gene expression (Reviewed in Impey et al., 1999).

Additional studies showed that ERK is transiently activated after cue and contextual fear conditioning (Alonso et al., 2002; Atkins et al., 1998; Brambilla et al., 1997). Such ERK activation, as well as 24 hrs memory, is reduced by inhibition of NMDA receptor and MEK1/2 (Figure 2) (Atkins et al., 1998). In addition to blocking ERK activation, the MEK inhibitor also precludes LTP in hippocampal neurons. Similarly, ERK activation is detected after training in the Morris water maze, which is reduced together with LTM by infusion of a MEK inhibitor in the dorsal hippocampus, with no effect in short-term memory (Blum et al., 1999; reviewed in Xia and Storm, 2012).

Studies in long-term facilitation (LTF) in Aplysia supported and expanded these findings (Martin et al., 1997). By exposing a coculture of sensory-motor neurons to five pulses of serotonin, which mimics the training sessions to induce LTM in the intact animal, it was found that ERK is required for LTF, but not for short-term facilitation. Importantly, ERK had to translocate into the nucleus of the sensory neuron to contribute to LTF. Remarkably, a large body of studies in Aplysia contributed enormously with our understanding of the role of ERK signaling in learning and memory (for a review see, Sharma and Carew, 2004). In a detailed molecular dissection, Philips et al., (2007, 2011, 2013) showed transient ERK activation, in which the first training session recruits protein synthesis-dependent nuclear ERK activity. This activity recruits several molecules, including CREB kinase, providing an appropriate “molecular context” required for a second session in the induction of LTM (Philips et al., 2013).

ERK plays an important role in signaling not only in the stimulated spine, but also in neighboring spines (Harvey et al., 2008; Patterson et al., 2010; Zhu et al., 2002) and is needed for gene transcription during LTP (Impey et al., 1998). This makes it a good candidate to carry the signal from spines to the nucleus. However, it was proposed that the signal is carried to the nucleus by propagation of Ca2+ waves and somatic depolarization

(Dudek and Fields, 2002; Hardingham et al., 2001). Nevertheless, recent investigations shows ERK activation in the nucleus even after blocking voltage sensitive calcium channels (VSCCs) and with a very low somatic depolarization (Zhai et al., 2013). To be able to carry the signal, ERK would probably need a PKC-ERK positive feedback loop and physical protection (Tanaka and Augustine, 2008; Karpova et al., 2013; Zhai et al., 2013). In turn, RAS/ERK signaling also needs other signals, for example, PKA is needed to activate CREB in the nucleus (Impey et al., 1998). To activate these signaling multiple receptors and ion channels need to be activated (e.g. metabotropic AC-coupled receptors, NMDA and mGluR) (Figure 2) (Roberson et al., 1999; Zhai et al., 2013).

Recent studies in rat CA1 pyramidal neurons showed that sequentially stimulating three to seven spines lead to activation of ERK in the nucleus (Zhai et al., 2013). Interestingly, in this experimental condition the sequential stimulation of individual spines can be integrated during a 30 minutes interval. Additionally, the stimulation of spines which were spread on different branches was more effective to activate ERK than the same number of stimulated spines in the same branch. It would be interesting to determine whether the spatio-temporal requirements for ERK activation are affected in pyramidal neurons expressing clinically relevant mutations involved in RASopathies. Taken together, this evidence suggests that ERK is required for LTM induction during training or immediately after that (i.e. 15 to 30 min in fruit flies and mice, respectively).

Recent studies showed that training promotes a direct interaction of activated ERK with the nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ)(Jahrling et al., 2014). The degree of interaction between ERK and PPARγ correlates positively with the levels of memory in contextual fear conditioning of a mouse model of Alzheimer's disease (AD). Interestingly, such interaction also correlates with the score of dementia in patients with AD evaluated through the Mini-Mental State Examination test. This mechanism could be also affected in RASopathies due to its enhanced ERK activity. However, it is not clear whether such mechanism participates in a context different to AD since pharmacological agonist and antagonist of PPARγ did not showed any effect on memory in wild-type animals (Jahrling et al., 2014).

4.1. ERK in learning mechanisms required for LTM induction

In molecular studies, learning, or the acquisition of information from the environment by the nervous system, has been associated with memory induced by a single training session and immediate memory. Most likely, because the analysis of an immediate memory provides a more simplified condition in terms of cellular processes and a small time window where the mechanisms to be studied might occur. However, ERK activation seems to be required for protein synthesis-dependent long-term processes (i.e. late-LTP, LTF and LTM), but not for short-term forms of these processes (Atkins et al., 1998; Martin et al., 1997; Nguyen et al., 1994).

Of relevance to RASopathies, alterations in ERK signaling through several mutations in a *Drosophila* model of NS did not affect immediate memory but reduced most, if not all, LTM (Pagani et al., 2009). Since, in these studies, ERK signaling takes place during training (the time when information is acquired), this observation indicates that there are specific

mechanisms of information acquisition (or learning) required for LTM which are independent of short-term memory. This idea is consistent with previous observations (Cui et al., 2008; Philips et al., 2013). Thus, the mechanisms affected in RASopathies can be those associated with learning required for LTM induction.

5. CONCLUSIONS

Several animal models of RASopathies, including NF1 and NS, have been developed. As expected, those animals showed learning and memory impairment in different tasks and in the case of NF1 +/− mice, attentional deficits were also found. The proteins involved, NF and SHP2, and the signaling pathway in which they participate (Figure 1) are required for development. However, the behavioral deficit observed in these animals could be reversed to wild type levels genetically, pharmacologically and behaviorally. This is remarkable because in different models more than one general strategy was found to reverse the behavioral phenotypes. Yet, it is not clear whether the mechanisms underlying the behavioral deficits in those models are the same. Moreover, the pharmacological procedures used to rescue the behavioral phenotypes were completely different, but aimed at avoiding the enhanced RAS/ERK signaling. If the mechanisms involved in these models are the same, these investigations have provided multiple strategies to recover behavioral deficits. However, if different mechanisms are involved, this strengthens the idea that RASopathies, or at least NF1 and NS, can be reversible, given that even with distinct underlying mechanisms it was possible to reverse the behavioral alterations.

Of note, the reversion of learning and memory deficits in animal models is not an exclusive property of these related disorders. Pharmacological rescue of behavioral deficits in adult animals was achieved in very different disorders, such as X fragile syndrome, Rett syndrome, Down syndrome, Angelman syndrome, among others, reviewed in (Ehninger et al., 2008).

More interesting, administration of lovastatin to NF1 patients, as it was done in NF1 +/− mice, improved the synaptic plasticity and attention deficit showed before treatment (Mainberger et al., 2013). These studies also support that in NF1 patients, as in NF1 mice, an enhanced RAS signaling affects excitability and plasticity. It is tempting to speculate that lovastatin, or similar drugs, could be useful in the treatment of different RASopathies, not only in attention deficits but in other cognitive impairments and developmental alterations as well.

Thus, the evidence available supports the idea that ID could be treated pharmacologically. Noteworthy, the revised evidence on RASopathies constitute just an example of how cognitive impairment could be understood. However, we believe that our current understanding on mental health and treatment is severely and positively affected by this kind of findings.

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Highlights

- Rasopathies are used to understand Intellectual disability.
- Molecular Mechanisms involved in Rasopathies are analyzed.
- Enhancement of training-induced ERK activity is a key factor.
- Cognitive deficits are reversed by different strategies.

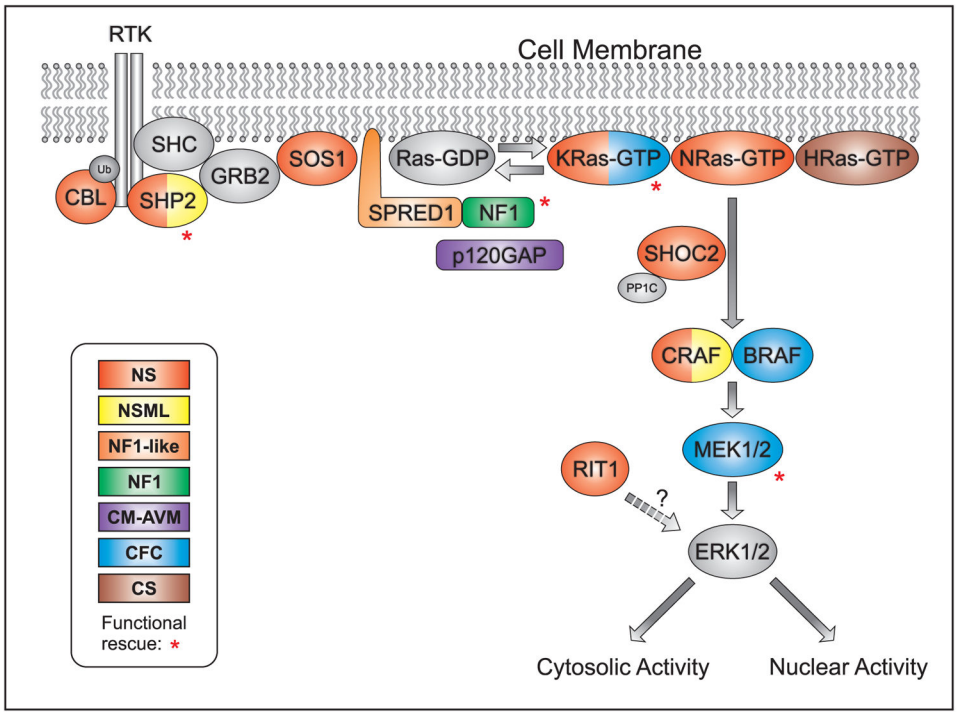

Figure 1. Schematic representation of Ras/ERK signal transduction pathway

RASopathies are a group of neurodevelopmental disorders with overlaping clinical features and characterized by germline mutations in genes that encodes for proteins involved in this pathway (illustrated in color code). This group includes the following disorders: Noonan syndrome (NS), Noonan syndrome with multiple lentigines (NSML), NF1-Like syndrome (NF1-like), neurofibromatosis type 1 (NF1), capillary malformation–arteriovenous malformation syndrome (CM-AVM), cardio-facio-cutaneous syndrome (CFC), and Costello syndrome (CS). Red asterisk indicates molecular components where functional rescued was achieved.

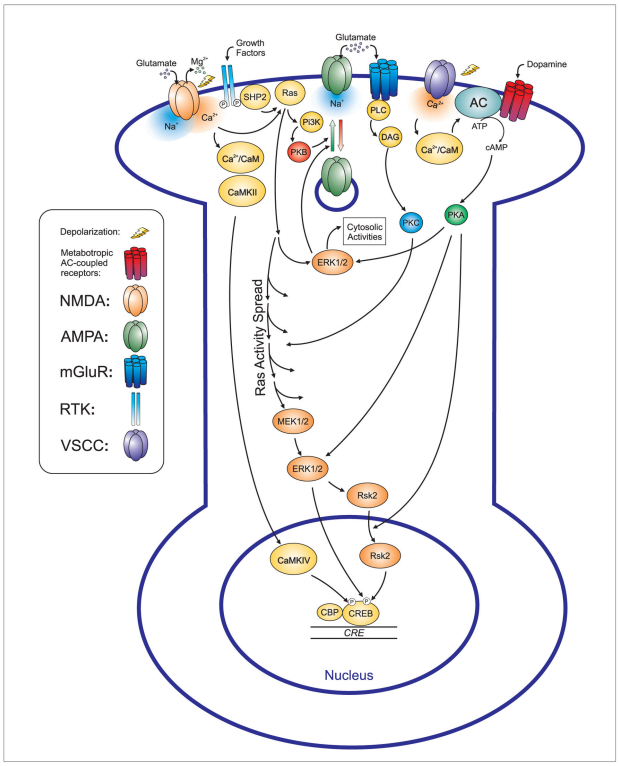

Figure 2. Activity-dependent ERK activation model and signal carried from spines to the nucleus by ERK

The activation of multiple receptors and complementary pathways are needed. The excitatory neurotransmitter glutamate over spines produces receptor activation, which in turn generates neuron depolarization and Ca2+ influx, through NMDA receptor and VSCC. Ca2+ activates many process, among them, Ca2+/Calmodulin (Ca2+/CaM) complex and RAS activation. Ca2+/CaM together with dopamine activate AC, increasing cAMP levels, which recruits and activates PKA. Activation of RAS, by Ca2+-dependent and growth factor-dependent mechanisms, can activates ERK through MEK1/2 and PKB through PI3K. mGluRs are able to activate PKC through PLC/DAG pathway. All these signaling pathways seem to be important for Erk activity, including nuclear and cytosolic activities (represented by a box) like AMPAR exocytosis regulation and Rsk2 phosphorylation. In the nucleus ERK and other kinases (Rsk2 and CaMKIV) phosphorylate and activate the cAMP response element-binding (CREB).