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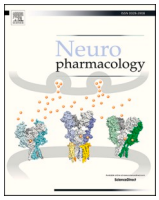

Neurobiology, molecular pathways, and environmental influences in antisocial traits and personality disorders

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ABSTRACT

Personality disorders (PDs) are psychiatric conditions characterized by enduring patterns of cognition, emotion, and behaviour that deviate significantly from cultural norms, causing distress or impairment. The aetiology of PDs is complex, involving both genetic and environmental factors. Genetic studies estimate the heritability of PDs at 30%–60%, implicating genes involved in neurotransmitter regulation, such as those for serotonin transporters and dopamine receptors. Environmental factors, including childhood trauma and chronic stress, interact with genetic predispositions to induce epigenetic modifications like DNA methylation and histone modifications, contributing to PD development.

Neurobiological research has identified structural and functional abnormalities in brain regions related to emotional regulation and social cognition, such as the amygdala, prefrontal cortex, and limbic system. These abnormalities are linked to impaired emotion processing and interpersonal functioning in PDs. This review focuses on how environmental factors shape maladaptive behaviours and endophenotypes central to many PDs. It explores the interaction between the Ras-ERK, p38, and mTOR molecular pathways in response to environmental stimuli, and examines the role of oxidative stress and mitochondrial metabolism in these processes.

Also reviewed are various types of PDs and existing animal models that replicate key endophenotypes, highlighting changes in neurotransmitters and neurohormones. Identifying molecular biomarkers can lead to the development of "enviromimetic" drugs, which mimic environmental influences to activate molecular pathways, facilitating targeted, personalized treatments based on the molecular profiles of individuals with PDs. Ultimately, understanding the molecular mechanisms of PDs promises to enhance diagnostic accuracy, prognosis, and therapeutic outcomes for affected individuals.

1. The clinical-preclinical gap: animal models of personality disorders

Personality disorders (PD) in humans are defined as long-term patterns of behaviour that significantly differ from the population average. For example, People with PD may differ in the way they about oneself and others, respond emotionally, relate to other people, and struggle to control behaviour. Within the clinical literature, there are ten specific types of personality disorders (DSM-5-TR) (American Psychiatric, 2022; Fisher and Hany, 2024) (Table 1).

Human PDs are very complex and are challenging to correctly diagnose. Many of these involve higher cognitive functions such as complex inter-specific social interplay.

To recapitulate in animal models the full phenotype of any of the PDs has been very challenging and presented several limitations insofar that animal models can only display one of more endophenotypes of such disorder or disorders (Table I). A good attempt has been from (Corniquel et al., 2019) which recapitulates some of the endophenotypes of BPD achieved by early life stressors in rodents. There is a requirement for better animal models for PD's endophenotypes (Table 2).

A practical method to assess one of the endophenotypes of PDs is to evaluate intra-specific aggression (Bortolato et al., 2011; Bortolato et al.,

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Table 1
The ten clinically acknowledged personality disorders (Vanwoerden and Stepp, 2022; Widiger and Hines, 2022).

Personality Disorder	Clinical Definition
Antisocial Personality Disorder (APD)	Defined as a pattern of disregarding or violating the rights of others. APD subjects may not conform to social norms, may repeatedly lie and deceive, and act impulsively.
Avoidant personality disorder (AvPD)	Defined as a pattern of extreme shyness, feelings of inadequacy and extreme sensitivity to criticism. AvPD subjects may be unwilling to get involved with others unless they are certain of being liked. They are constantly preoccupied with being criticized or rejected and may view themselves as not being good enough or socially inept.
Borderline personality disorder (BPD)	Characterised as a pattern of instability in personal relationships, intense emotions, poor self-image and impulsivity. BPD subjects may go to great lengths to avoid being abandoned, have repeated suicide attempts, display inappropriate intense anger and have feelings of emptiness.
Dependent personality disorder (DPD)	Characterised as a pattern of needing to be taken care of and being submissive and clingy behaviour. DPD subjects may have difficulty making daily decisions without reassurance from others or may feel uncomfortable or helpless when alone.
Histrionic personality disorder (HPD)	Defined as a pattern of excessive emotion and attention-seeking. HPD subjects may be uncomfortable when not at the centre of the attention, may use physical appearance to draw attention and have rapidly shifting or exaggerated emotions.
Narcissistic personality disorder (NPD)	Characterised as a pattern of need for admiration and lack of empathy for others. NPD subjects may have a grandiose sense of self-importance, entitlement and often take advantage of others.
Obsessive-compulsive personality disorder (OCPD)	Distinct disorder form Obsessive Compulsive Disorder, is characterised as a pattern of preoccupation with orderliness, perfection and control. OCPD subjects may be overly focused on details and schedules, may work excessively and so neglect leisure and friends, they may also be inflexible in their morality and values.
Paranoid personality disorder (PPD)	Characterised as a pattern of suspiciousness and seeing others as mean or spiteful. PPD subjects often assume people will harm or deceive them and do not confide in others.
Schizoid personality disorder (SPD)	Characterised as being detached from social relationships and expressing little emotion. SPD subjects typically do not seek close relationships and do not care about praise or criticism from others.
Schizotypal personality disorder (ScPD)	Characterised as a pattern of being very uncomfortable in close relationships, distorted thinking and eccentricism. ScPD subject may have odd beliefs and peculiar behaviours and excessive social anxiety.

2018; Frau et al., 2022; Godar et al., 2014; Godar et al., 2016; Nedic Erjavec et al., 2022; Richey et al., 2016). This behaviour is highly stereotyped in both male and female mice (Brain et al., 1981) and is commonly assessed using the resident-intruder paradigm (Olivier and Mos, 1992), However, significant sex differences in aggression are observed, likely due to hormonal influences (More, 2008). Despite its limitations, aggression has become the gold standard endophenotype for studying PD traits in preclinical models, owing to the lack of better tools (Shaw et al., 2020).

Typically, adult male mice exhibit aggression toward conspecific adult males but not toward females (in either oestrus or dioestrus) or prepubertal mice (Bartolomucci et al., 2004; de Almeida et al., 2005; Ferrari et al., 1996, 1998). In contrast, a PD mouse model demonstrates aggression toward a broader range of targets, including dioestrus females and prepubertal mice, while sparing oestrus females.

Adult female mice generally show aggression only toward other adult females, and only if raised in isolation for an extended period (More, 2008). This behaviour may be modulated by anti-aggression pheromones in group-housed females (More, 2006). Interestingly, while group-housed females tend to synchronize their oestrous cycles, isolation-induced aggression correlates more closely with cycle regularity than ovulation status (More, 2008). A PD model in females would, therefore, involve group-housed females attacking intruder females, regardless of their reproductive stage, but not adult intact males.

Although intra-specific aggression does not encompass the full spectrum of PD phenotypes (see Table II), it remains an invaluable tool for studying antisocial traits in mice. Aggressive behaviour inherently involves a risk of severe injuries, which in natural settings could result in death. It is important to note that male mice exhibit a highly stereotyped pattern of aggression, typically targeting the back and tail of the opponent—behaviours that rarely result in fatal injuries. Conversely, female aggression, though less frequent, often targets the snout and throat, significantly increasing the risk of lethality (More, 2008).

2. The neuropharmacology of personality disorders

Several neurotransmitters and neurohormones have been implicated in the aetiopathogenesis of PDs, these include serotonin, dopamine, adrenaline and oxytocin and vasopressin.

Serotonin is a monoamine neurotransmitter which modulates a wide array of physiological and behavioural processes. Impulsivity is a core feature of several PDs, including antisocial, borderline, and narcissistic PDs. Serotoninergic dysfunction has been linked to impulsivity in patients through its role in inhibiting impulsive behaviours and modulating executive control processes mediated by the prefrontal cortex (Cattarinussi et al., 2022; Salani et al., 2023).

Alterations in serotoninergic function have been implicated in affective dysregulation observed in PDs such as borderline personality disorder (BPD) and histrionic personality disorder (HPD), further serotoninergic abnormalities contribute to interpersonal dysfunction by impairing social cognition, empathy, and the ability to form and maintain stable attachments (Leichsenring et al., 2023; Mishra et al., 2023).

Pharmacological interventions targeting serotoninergic pathways in patients, such as selective serotonin reuptake inhibitors (SSRIs), have shown promise in ameliorating certain symptoms associated with PDs, particularly affective instability and impulsivity (Hankin et al., 2011; Raj, 2004; Sah et al., 2021; Salinas et al., 2020; Tadic et al., 2010; Wagner et al., 2009).

Dopamine is primarily produced in dopaminergic neurons located in the substantia nigra and ventral tegmental area of the midbrain. Dopamine plays a crucial role in reward processing, motivation, movement, and cognitive function, exerting its effects through a diverse array of

Table 2
A summary of available pre-clinical models for PD phenotypes.

Phenotype	Existing Model	Assessment
Poor impulse control	Delayed Discounting:	Choice of small early vs. large or small frequent vs. large infrequent rewards
Affect instability	Habituation to stimuli:	Extinction acquisition/recall
Unstable relationships	Social interaction test:	3-chamber social interaction
Empathy	Emotional contagion:	Observed foot-shock following Conditioned Stimulus (Cue)
Unstable self-image	None	N/A
Suicidal Behaviour	None	N/A
Feelings of emptiness	None	N/A
Worries of abandonment	None	N/A
Dissociation/ Paranoia	None	N/A

dopamine receptor subtypes distributed throughout the brain (da Costa Azevedo et al., 2022; Khalifa et al., 2020; Rafiei and Kolla, 2021; Rosell et al., 2015; Thompson et al., 2014; Thompson et al., 2020).

Dysregulated dopamine signalling has been implicated in aberrant reward processing observed in PDs, including heightened sensitivity to reward, reduced reward anticipation, and deficits in reward learning. Altered dopaminergic function contributes to impulsive behaviours and substance abuse commonly associated with PDs especially in antisocial and borderline personality disorders (Bandelow et al., 2010; Cuartas Arias et al., 2011).

Dysregulation of dopamine transmission in patients, particularly in the mesolimbic and mesocortical pathways, underlies impulsivity, another key feature of several PDs, through its effects on incentive salience, response inhibition, and delay discounting (Friedel, 2004; Lazzaretti et al., 2013).

Dopamine dysfunction, particularly alterations in the mesolimbic dopamine signalling contributes to affective dysregulation in mice by modulating the salience of emotional stimuli, reward responsiveness, and the processing of aversive experiences (Baptista-de-Souza et al., 2022)

Pharmacological interventions targeting dopaminergic pathways, such as antipsychotics and dopamine modulators, have shown efficacy in patients affected by PDs by ameliorating certain symptoms, including impulsivity and psychotic features (Alliani and Tarantelli, 2009; Bellino et al., 2011; Friedel, 2004; Garbutt et al., 1987).

Noradrenaline (norepinephrine) is synthesized from dopamine in the locus coeruleus, and it plays a critical role in modulating arousal, attention, vigilance, and stress response. Noradrenaline exerts its effects through activation of adrenergic receptors distributed throughout the CNS influencing a wide range of physiological and behavioural processes (Kulkarni et al., 2018).

Dysregulated noradrenergic function has been implicated in arousal dysregulation and emotional instability in patients with PDs, particularly borderline and antisocial PDs. Heightened noradrenergic activity contributes to hyperarousal, emotional reactivity, and difficulties in emotional regulation, leading to mood lability and impulsivity (Bellino et al., 2010).

Dysregulated noradrenergic signalling may enhance behavioural disinhibition, increase response to threat cues, and promote impulsive and aggressive behaviours, so clearly noradrenaline is implicated in the modulation of impulsivity and aggression in humans which core features of several PDs, including antisocial, borderline, and narcissistic PDs (Kulkarni et al., 2018).

Dysregulated noradrenergic function may also contribute to aberrant stress responses and maladaptive coping mechanisms observed in PDs, exacerbating symptoms and impairing adaptive functioning (Gerra et al., 2003; Jannini et al., 2022).

Pharmacological interventions targeting noradrenergic pathways, such as alpha-2 adrenergic receptor agonists or noradrenaline reuptake inhibitors, are promising as adjunctive treatments for PD symptoms in patients, particularly those related to arousal dysregulation, impulsivity, and aggression (Gerra et al., 2003; Southwick et al., 1990a, 1990b).

Oxytocin and vasopressin are neuropeptides synthesized in the hypothalamus and released into the bloodstream and brain in response to social and environmental cues. Oxytocin is primarily associated with social bonding, empathy, and affiliation, while vasopressin is implicated in aggression, territoriality, and pair bonding in humans (Jeung-Maarse et al., 2023; Kohlhoff et al., 2022; Maoz et al., 2024; Marazziti et al., 2022; Plett et al., 2023).

Dysregulated oxytocin signalling has been implicated in deficits in social behaviour and attachment observed in PDs, particularly borderline and avoidant PDs. Oxytocin promotes social bonding, trust, and affiliation in both mice and patients, and alterations in oxytocinergic function may contribute to interpersonal difficulties and attachment insecurities characteristic of these disorders (Baptista-de-Souza et al., 2022; Byrd et al., 2021; Gedeon et al., 2019; Jeung-Maarse et al., 2023; Zhang et al., 2020).

Oxytocin and vasopressin play a role in the regulation of emotional responses and stress reactivity and a dysregulated neuropeptide signalling has been linked to affective dysregulation and emotional instability observed in PDs, including borderline and histrionic PDs. Oxytocinergic dysfunction in humans may impair the ability to modulate emotional responses and cope with interpersonal stressors (Brune, 2016; Lee et al., 2009; Mancke et al., 2015; Stanley and Siever, 2010).

Vasopressin, particularly the vasopressin 1A receptor subtype, has been implicated in aggressive behaviour and impulsivity. Dysregulated vasopressinergic function contributes to impulsive aggression in patients with PDs, such as antisocial and narcissistic PDs, where aggression is a prominent feature (Brydges et al., 2019; Lee et al., 2009; Olabi and Hall, 2010; Vollebregt et al., 2021).

The synthesis of Serotonin and Dopamine, two of the key neurotransmitters involved in both depression and PD, have been recently linked to mitochondrial bioenergetic metabolism in mice (Monchaux de Oliveira et al., 2023; Vancassel et al., 2018).

3. Mitochondrial bioenergetic metabolism and redox status in personality disorders

3.1. Overview

Brain physiology and behaviour are tied together by mitochondrial bioenergetic metabolism, which underpins the energy demanding neural networks and glial cells (Brunetti et al., 2021; Rose et al., 2020; Ulgen et al., 2023). Large amounts of glucose, but also ketones, are used by neuronal and glial mitochondria to generate ATP via oxidative phosphorylation (Dienel, 2019a, 2019b). Beyond supporting cellular energy requirements, mitochondria are central to the coordination of synaptic function in the brain (Duarte et al., 2023).

Mitochondria play a pivotal role in various aspects of brain structure and function, including neurogenesis, dendritic and axonal branch formation, the inflammatory response, and synaptic neurotransmitter release (Courchet et al., 2013; Joshi et al., 2019; Khacho et al., 2019; Ugur et al., 2017). A mitochondrial phenotype has been observed in murine models of anxiety antisocial behaviours, suggesting that environmental stimuli may lead to behavioural changes via alterations in mitochondrial function (Rosenberg et al., 2023; Shaw et al., 2020).

3.2. Mitochondrial bioenergetic metabolism in behavioural disorders

The association between changes in mitochondrial function and behavioural disorders, such as APD, is increasingly appreciated. The outer mitochondrial membrane enzyme monoamine oxidase A (MAOA), which is involved in neurotransmitter inactivation, is already known to be implicated in the development of APD (Kolla et al., 2017). Various other genes related to mitochondrial respiration and bioenergetic function have recently been shown to be downregulated in the orbitofrontal cortex of individuals with APD postmortem (Piras et al., 2023).

Mitochondrial gene expression was found altered in the prefrontal cortex of mice subjected to chronic stress, a crucial vulnerability factor for the development of depression (Weger et al., 2020). Consistently, dysregulated mitochondrial bioenergetics are increasingly viewed as a mechanistic link between stress and anxiety, as supported by studies in patients with anxiety and animal models (Filiou and Sandi, 2019). Mitochondrial dysfunction has been shown to link anxiety and social subordination, sociability, and social status in rats (Hollis et al., 2015). It has been clinically observed that individuals with APD have altered glucose metabolism; however, the relationship between behavioural disorders and metabolism is complex and yet to be elucidated (Virkkunen et al., 2007).

18F-fluorodeoxyglucose (FDG) injection positron emission tomography (PET) studies showed changes in glucose metabolism across cortical and subcortical regions of the frontal and prefrontal regions in

patients with antisocial personality (Park et al., 2016). It has been suggested a link between violent behaviour and insulin-mediated glucose metabolism in human pluripotent stem cells (iPSC) derived cortical neurons and astrocytes derived from antisocial and violent offenders, although this link remains weakly tested (Tiihonen et al., 2020). However, decreased glucose in the frontal cortex has been observed in patients affected by other disorders characterised by impulsivity and aggression, such as borderline personality disorder (BPD) (Soloff et al., 2003). The emerging roles of brain metabolism in behavioural and neuropsychiatric disorders are garnering interest, as bioenergetic and metabolic pathways present numerous potential therapeutic targets as reviewed in (Morella et al., 2022).

3.3. Mitochondrial redox changes in behavioural disorders

Reactive oxygen species (ROS) are class of both radical and non-radical oxygen-based molecules that a normal byproduct of mitochondrial bioenergetic oxidative metabolism of glucose but are also produced by "professional" cellular ROS generating enzymes like NADPH oxidases. In the brain, redox changes are thought to mediate synaptic plasticity and memory and changes in transcriptional regulation via phosphorylation of CREB (Beckhauser et al., 2016).

Increased ROS generation to damage, ageing, and disease can lead to the overwhelming of enzymatic antioxidant systems (such as glutathione (GSH)) and the onset of overt oxidative stress, with myriad consequences for neurones (Cobley et al., 2018). However, ROS generation and GSH concentrations vary widely, not only between cellular compartments, but across regions of the brain (Vinokurov et al., 2021; Wojtovich et al., 2019).

In microglia, ROS have been shown to mediate behavioural responses in mice subjected to chronic social defeat (Lehmann et al., 2018). Moreover, in this model, administration of N-acetylcysteine (NAC), which increases glutathione availability and alleviates oxidative stress, normalised stress-induced behavioural defects highlighting the importance of understanding the mechanistic role redox changes in the brain for therapeutic purposes (Lehmann et al., 2019).

3.4. Possible role of tetrahydrobiopterin in behavioural disorders

The pteridine tetrahydrobiopterin (BH_4) is well-characterised cofactor for nitric oxide synthase (NOS) enzymes, which are responsible for production of the radical gas nitric oxide (NO) (Bendall et al., 2014). However, it is also a cofactor for enzymes tryptophan hydroxylase and tyrosine hydroxylase, the enzymes responsible in the production of 5-HT and L-DOPA (the precursor to dopamine) respectively. BH_4 is a redox-sensitive molecule and its oxidation to dihydrobiopterin (BH_2) abrogates its cofactor role, leading to NO and neurotransmitter deficiency. Moreover, BH_4 is a redox-sensitive molecule that can induce ROS independent of its cofactor role (Bailey et al., 2017).

The possible role of BH4 in neuropsychiatric disorders is now being recognised and the interaction between the redox state of cellular compartments and corresponding BH_4:BH_2 ratios may present an attractive target for the treatment of behavioural disorders (Fanet et al., 2021). Moreover, the cyclical link between BH_4 and redox metabolism is now being appreciated, with decreased BH_4 availability leading to NOS uncoupling and the production of ROS instead of NO. In the brain, these redox changes may have profound effects on neurotransmitter balance and synaptic communication (Kim and Han, 2020). As APD is increasingly viewed as a neurodevelopmental disorder that encompasses changes in both 5-HT and dopamine, it seems prudent to investigate the effects of redox changes on BH_4 availability on neurotransmitter synthesis in the developing APD brain (Raine, 2018).

3.4.1. Link between OS and monoamines synthesis, a key role for BH_4 pathway

Cytokine production in response to an immune challenge stimulates the activation of GTP-cyclohydrolase-1 (GCH1), 6-pyruvoyl-tetrahydropterin synthase (PTPS), and sepiapterin reductase (SR) through the *de novo* synthesis pathway, leading to the production of tetrahydrobiopterin (BH4). The activity of GCH1 is regulated by the interaction of GTP-cyclohydrolase feedback protein (GFRP) with effector molecules, BH4 and phenylalanine (Vancassel et al., 2018).

BH_4 is quickly oxidized to BH_2, which is then reduced back to BH4 by the enzyme dihydrofolate reductase (DHFR) in what is known as the "salvage" pathway.

In humans, PTPS becomes the rate-limiting factor during inflammation, promoting neopterin formation at the expense of BH_4 production. During inflammatory conditions, BH_4 is primarily utilized as a cofactor for nitric oxide synthase (NOS) to produce nitric oxide (NO), reducing its availability for phenylalanine hydroxylase (PAH), tyrosine hydroxylase (TH), and tryptophan hydroxylase (TrypOH) activities, thereby diminishing the synthesis of monoamines (Vancassel et al., 2018).

NH2TP refers to 7,8-dihydroneopterin triphosphate, and 6PTP refers to 6-pyruvoyl-tetrahydrobiopterin.

4. CNS molecular pathways responsible for the embodiment of the environmental stimuli adaptation

4.1. Ras-ERK

The Ras-ERK pathway acts as a key regulator of fundamental cellular processes, such as survival, proliferation and differentiation (Lavoie et al., 2020; Rubinfeld and Seger, 2005). In the central nervous system (CNS), the Ras-ERK pathway is activated by stimuli associated with synaptic activity and targeting a broad range of receptors, including G proteins-coupled receptors, ion channels and tyrosine kinase receptors (TRKs). These signals converge onto Ras-exchange factors, such as Ras-GRF and Son of Sevenless (Sos), which facilitate the conversion of Ras GTPases into their active form, thus enabling the activation of Raf kinase. This event initiates the sequential activation of MEK, ERK1 and ERK2. Upon phosphorylation, ERK1 and ERK2 can either activate cytoplasmic targets or translocate into the nucleus to activate various transcription factors (e.g., Elk1 and CREB), leading to the transcription of immediate early genes (IEGs), including c-Fos and c-Jun (Albert-Gasco et al., 2020).

Early evidence demonstrated the primary role of Ras-ERK signalling in long-term potentiation (English and Sweatt, 1996, 1997) and memory formation (Atkins et al., 1998; Brambilla et al., 1997; Silva et al., 1997). Since then, the Ras-ERK pathway has been linked to several behavioural processes (Fasano and Brambilla, 2011). Due to the central role of this signalling pathway in neuronal development and synaptic plasticity, dysregulation of Ras-ERK signalling has been associated with a spectrum of pathological conditions, including neurodevelopmental disorders, anxiety, depression as well as obsessive-compulsive disorder (OCD) (Iroegbu et al., 2021; Ullrich et al., 2018; Wang and Mao, 2019). Interestingly, the Ras-ERK pathway has been also proposed to be a crucial mediator of adaptations to environmental enrichment in mice via MSK1, a kinase downstream to ERK cascade, and CREB (Daumas et al., 2017; Karelina et al., 2012). Few reports also suggest the implication of ERK pathway in aggression. In particular, ERK downregulation achieved via conditional ERK2 knock-out (ERK2 cKO) in the CNS in mice was associated with behavioural anomalies, including deficits in social behaviour and high levels of aggression (Satoh et al., 2011). This finding may be in line with an early report showing that the genetic hemizygous ablation of Brain Neurotrophic Factor (BDNF), acting on TrkB receptors, leads to increased aggression levels that correlates with serotoninergic dysfunction (Lyons et al., 1999).

Understanding Ras-ERK pathway regulation is critical to inform the design of novel therapeutic approaches for behavioural disorders. So far, pharmacological approaches targeting the Ras-ERK pathway have been based on MEK inhibition or cell permeable peptides inhibiting specific

components of Ras-ERK pathway in preclinical models (Papale et al., 2016, 2017; Pucilowska et al., 2015). Recently, a cell permeable peptide selectively activating ERK pathway has been also designed (Indrigo et al., 2023).

However, since this signalling cascade is triggered by different receptor systems there might be several potential strategies for targeted intervention in behavioural disorders.

4.2. p38

Understanding the p38 molecular pathway to full extent is essential for future therapeutic interventions, as this pathway is believed to diminish sociability levels in individuals with behavioural disorders (Robson et al., 2018; Wu et al., 2024).

p38 MAPK pathway is activated by different stressors, such as pro-inflammatory cytokines, UV irradiation and oxidative stress (Asih et al., 2020). Four p38 isoforms have been identified: p38α, p38β, p38g and p38d (Raman et al., 2007). Activation of p38 MAPK hinges on phosphorylation within a flexible region, called the activation loop, which prompt conformational changes that enable substrate binding (Cuadrado and Nebreda, 2010). p38 activation is mediated by MAP2Ks, like MKK3, MKK6 and sometimes MKK4, with different selectivity for p38 MAPKs isoforms. In addition, p38 can be activated by MAP3Ks, including ASK1, DLK1, TAO1/2, MLK3, TPL2, MEKK3/4 and ZAK1 (Cuadrado and Nebreda, 2010). The regulation of MAP3Ks involves phosphorylation by STE20 family kinases, binding of Rho family GTP-binding proteins, and ubiquitination (Zhou et al., 2018). These kinases can respond to multiple stimuli and integrate p38 MAPK activation with other signalling pathways to phosphorylate their downstream targets. This is a key area to investigate, as the activation of other molecular pathways could cause side effects of medicinal drugs targeting this pathway. Several pharmacological compounds have been designed with drugs that can either inhibit or promote p38 activity, although they still carry some non-specific effects. Thus, more targeted design is needed (Asih et al., 2020; Nguyen et al., 2022).

p38 activation affects several cellular processes, including cell growth, cell death, proliferation and has a primary role in inflammation by regulating the production of cytokines (Asih et al., 2020). In the CNS, p38 is a mediator of synaptic plasticity by inducing long-term depression (LTD) and inhibiting long-term potentiation (LTP) (Guan et al., 2003; Krapivinsky et al., 2004). Moreover, several lines of evidence support the role of p38 in the modulation of neuronal excitability, synaptic development, and cytoskeletal organization (Asih et al., 2020).

Specific MAP3Ks are linked to particular stimuli; for instance, MEKK1 in Drosophila cells is associated with UV or peptidoglycan-induced p38 MAPK activation, whereas mammalian ASK1 is crucial for oxidative stress responses. The TRAF family of E3 ubiquitin ligases, especially TRAF6, is important in TAK1 activation, which mediates p38 MAPK activation by cytokine receptors (Nguyen et al., 2022). TAK1, activated by TRAF6, also plays a role in the NF-κB anti-apoptotic pathway in response to TNFα. The activation of MAP3Ks such as MEKK1 or TAK1 by TNF receptor family members involves complex formation at receptor intracellular domains (Zhou et al., 2018).

Recently, a potential role of p38 in aggression is starting to emerge. This link between p38 and aggressive behaviour is particularly interesting, considering the role of p38 in inflammation, a process increasingly implicated in aggression in both humans and animal models (Takahashi et al., 2018). Previous findings from animal models already demonstrated the role of p38 in mediating the maladaptive responses to stressful experiences (Bruchas et al., 2007; Peng et al., 2013), that are known environmental determinants of aggressive behaviours. In line with this evidence, selective ablation of p38 in serotoninergic neurons confers resilience to social defeat stress, thus further supporting the role of this kinase in modulating affective behaviours (Bruchas et al., 2007). In addition, social interaction reward exerts an anti-stress effect by reducing p38 phosphorylation in the nucleus accumbens shell of rats (Salti et al., 2015). In recent years, significant efforts have been made to understand the genetic causes of aggression in humans, although with some limitations associated with genome wide association studies (GWAS) (Vassos et al., 2014). However, the first transcriptomic characterization of genetic and behavioural mouse models of aggression identified 51 strongly dysregulated genes. Further network analysis on these genes revealed two pathways, centred on p38 MAPK and ubiquitin that might be implicated in aggression (Malki et al., 2016).

In conclusion, the complex p38 pathway consists of many sub-units responsible for many cellular functions and with potential causative links with behavioural disorders, including aggression. Thus, understanding the modulation of signalling pathway will be necessary to design novel interventions.

4.3. mTOR

The mechanistic Target of Rapamycin (mTOR) signalling pathway stands as a central regulator of cellular metabolism, growth, and survival, responding to a variety of environmental cues including nutrients, energy status, and growth factors (Zhao et al., 2023). Within this signalling framework, two distinct complexes, mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2), orchestrate a wide range of physiological processes through their unique and overlapping functions (Fakhri et al., 2021). mTORC1 is renowned for its sensitivity to the antibiotic rapamycin and plays a pivotal role in promoting anabolic processes when resources are abundant (Zhao et al., 2023). This complex integrates signals from growth factors, amino acids, oxygen, and energy status to regulate biosynthetic pathways, including protein and lipid synthesis, while simultaneously inhibiting catabolic processes such as autophagy (Graber et al., 2013).

Activation of mTORC1 occurs through a well-characterized pathway involving the PI3K/AKT signalling cascade, which, upon stimulation by growth factors, leads to the inhibition of the TSC1/TSC2 complex, a negative regulator of mTORC1 (Fakhri et al., 2021). Furthermore, mTORC1 activity is modulated by the availability of amino acids, particularly through the direct action of the Rag GTPases, and is also sensitive to cellular energy levels, with AMP-activated protein kinase (AMPK) serving as a key energy sensor that can inhibit mTORC1 under conditions of low energy (Wang et al., 2020b). In contrast, mTORC2, which is generally considered insensitive to acute rapamycin treatment, is implicated in the regulation of cell survival, proliferation, and cytoskeletal organization. Although less is understood about the activation mechanisms of mTORC2, it is known to be stimulated by growth factors and possibly other signals not yet fully elucidated. mTORC2's critical functions include the phosphorylation and subsequent activation of AKT, SGK1, and PKC, proteins involved in cell survival and proliferation pathways (Wang et al., 2020b).

Recent studies demonstrated that mTOR pathway is a central hub with functions in nerve growth, synapse formation and plasticity. Given its pivotal role in synaptic proteins synthesis, mTOR dysregulation has been associated with various mental illnesses, such as Alzheimer's disease, depression and neurodevelopmental disorders (Borrie et al., 2017; Chen et al., 2024; Hoeffer and Klann, 2010).

Emerging evidence supports the role of mTOR signalling pathway in stress-induced psychopathology. In particular, an elevation of mTOR levels has been shown to confer stress-resilience in rodent models of chronic stress (Liao et al., 2021; Yan et al., 2023; Zhu et al., 2019) and this effect appears to be mediated by BDNF-TrkB signalling (Zhu et al., 2019). In addition, a recent study demonstrated that impairment in mTORC1-mediated signalling induced by chronic stress in mice mediates hippocampal synapse loss by suppressing synaptic proteins synthesis (Luo et al., 2021).

Interestingly, early life stress, a key vulnerability factor for developing mental illnesses in the adulthood, induces downregulation of mTOR signalling in mice leading to decreased synaptic protein synthesis and behavioural deficits (Wang et al., 2020a). More work is needed to

fully elucidate the role of mTOR signalling in behavioural disorders. In particular, the implication of this pathway in aggression remains elusive, although a recent study on female hamsters found a transient dephosphorylation of mTOR in the medial prefrontal cortex, concomitantly with ERK1/2 activation in the nucleus accumbens, during aggressive interactions (Borland et al., 2023).

Different stimuli from G-proteins coupled receptors, Trk receptors or ion channel, such as NMDA and AMPA receptors, can promote the conversion of Ras from the inactive, GDP-bound form to the active, GTP-bound form. This process is mediated by Guanine Exchange Factors (GEF), whereas Ras inactivation is mediated by the GTPase-activating proteins (GAP). Ras activation triggers Raf/MEK/ERK1 and ERK2 cascade. Once phosphorylated, ERK1 and ERK2 can activate cytoplasmic proteins, such as Mnk and RSK, thereby promoting translation. Upon activation, ERK1 and ERK2 can also translocate into the nucleus to phosphorylate other transcription factors and kinases. For instance, the transcription factor Elk-1, upon ERK1 and 2-mediated phosphorylation, binds to the Serum Response Element (SRE) to promote the transcription of the Immediate Early Genes (IEGs). Another nuclear target of phospho-ERK1 and phospho-ERK2 is the kinase MSK-1, which in turn activates the transcription factor CREB. After binding to the cAMP Response Element (CRE), CREB regulates the transcription of IEGs (Gasco and Munoz-Fernandez, 2020).

In addition, MSK-1 phosphorylates histone H3 thus mediating chromatin remodelling (Sattarifard et al., 2023). p38 pathway is mainly triggered by UV irradiation, oxidative stress and inflammation. These stimuli converge on MAP3Ks and MKK3/4/6 leading to p38 activation (Cuadrado and Nebreda, 2010). The mTOR pathway integrates various stimuli including growth factors, nutrient, energy status and oxygen availability.

mTOR is found in two structurally and functionally different complexes: mTORC1 and mTORC2. Hormones and growth factors stimulating the production of phosphatidylinositol-3,4,5-triphosphate (PIP3) activates mTORC2 which in turn promotes PKC and AKT activation. Hormones and growth factors, via Trk receptors, stimulate PI3K/AKT pathway which in turn phosphorylates Tuberous Sclerosis Complex protein 2 (TSC2), leading to the dissociation of TSC1/TSC2 from the lysosome thus allowing Rheb-GTP loading and mTORC1 activation. In addition to growth factors and hormones, mTORC1 is also activated by nutrients and amino acids and inactivated by hypoxia and stress.

The main effectors of mTORC1 are translational regulators, such as S6 kinase (S6K) and the translational repressor 4EBP-2. 4EBP-2 phosphorylation promotes its dissociation from EIF4E, thus allowing the assembly of the translational machinery. Activated S6K phosphorylates S6 ribosomal protein (rpS6) and EIF4B, promoting its association with the translational machinery complex (Mieulet et al., 2007). This schematic was created with Biorender.com.

5. Nootropics acting on the Ras-ERK pathways as a tool to improving social cognition

5.1. CX929 ampakine as unspecific Ras-ERK potentiator

Ampakines can cross the blood-brain barrier and exhibit neuroprotective properties, potentially offering therapeutic benefits in a range of neurological and psychiatric disorders (Simmons et al., 2011), although their potential in enhancing sociability remains still unexplored.

Ampakines are a class of compounds that enhance synaptic transmission by modulating the activity of AMPA receptors. The mechanism of action of ampakines involves the positive allosteric modulation of AMPA receptors and unlike direct agonists, ampakines bind to a distinct site on the receptor, enhancing its response to endogenous glutamate without directly activating the receptor (Lauterborn et al., 2016).

Upon binding to the allosteric site, ampakines stabilize the open state of the AMPA receptor channels, increasing their conductance and prolonging the duration of excitatory postsynaptic currents (EPSCs). This results in an increased influx of sodium ions (Na+) and, to a lesser extent, calcium ions (Ca^{2+}), leading to enhanced synaptic strength and plasticity. This mechanism facilitates long-term potentiation (LTP) (Rex et al., 2006).

Ampakines also reduce receptor desensitization, allowing for sustained receptor activation during repetitive synaptic activity. This effect is particularly beneficial in enhancing cognitive functions, as it promotes more efficient synaptic transmission and communication within neural networks involved in learning and memory processes (Seese et al., 2020).

Ampakines activate the Ras-ERK pathway via increasing calcium-dependent signalling which activates Ras which in turn initiates the MAPK/ERK pathway by activating Raf kinase, which in then phosphorylates and activates MEK (MAPK/ERK kinase) (Kramar et al., 2012).

MEK-induced ERK phosphorylation leads to ERK activation and its subsequent translocation into the nucleus, where ERK phosphorylates various transcription factors such as CREB, via the action of MSK1, and eventually enhances the transcription of genes involved in synaptic plasticity, neuronal survival, and growth (Hunter et al., 2017; Cooper and Frenguelli, 2021).

5.2. Nutraceuticals as prosocial nootropics

Nutraceuticals are bioactive compounds found in foods which have gained attention for their potential therapeutic effects on neurological health. Their mechanisms of action in the nervous system are diverse and multifaceted and they may provide cognitive enhancing and increase sociability by stimulating the gut-muscle-brain axis (Morella et al., 2023; Vancassel et al., 2018; Vancassel et al., 2022).

Many nutraceuticals, such as omega-3 fatty acids, polyphenols, and vitamins, exert nootropic effects through their antioxidant properties, neutralizing free radicals and reducing oxidative stress, which is implicated in neurodegenerative diseases and in altering the BH_4:BH_2 balance as aforementioned (Fig. 1) (Vancassel et al., 2018, 2022).

Emotional alterations have been associated with activation of inflammatory processes seen as brain expression of microglial activation markers (IL-1β, IL-6, CD11b, CD74) in mice (Cardinal et al., 2021). Omega-3 fatty acids, for example, are integral to neuronal membrane fluidity and function, and they modulate inflammatory pathways by inhibiting pro-inflammatory cytokines and promoting the production of anti-inflammatory molecules (Laye et al., 2018). Among others, Saffron administration in mice counteracts lipopolysaccharide-induced activation of kynurenine pathway, assessed through the expression of BH4, thus reducing both inflammation and major depression endophenotypes, which may suggest a possible action on PD patients (Cardinal et al., 2021).

Nutraceuticals can also influence neurogenesis and synaptic plasticity; flavonoids and polyunsaturated fatty acids have been found to enhance brain-derived neurotrophic factor (BDNF) signalling (Bakoyiannis et al., 2019; Sun et al., 2018) which supports neuronal survival, differentiation, and synaptic plasticity (Hunter et al., 2017). This can contribute to improved cognitive function and resilience against neurodegenerative processes and ageing (More et al., 2023; Privitera et al., 2020) by enhancing the many beneficial effects of an environmental enrichment protocols whose main molecular target is the TrkB receptor and the potentiation of the Ras-ERK pathway (Correa et al., 2012; Morella et al., 2023; Morella et al., 2022). These effects remain elusive regarding their ability to increase pro-social behaviours (or decrease aggression) as we believe that it is a selective enhancement of the Ras-ERK pathway which could lead to a decrease in aggression via its anti-oxidative activity (Fig. 2) (see Fig. 3).

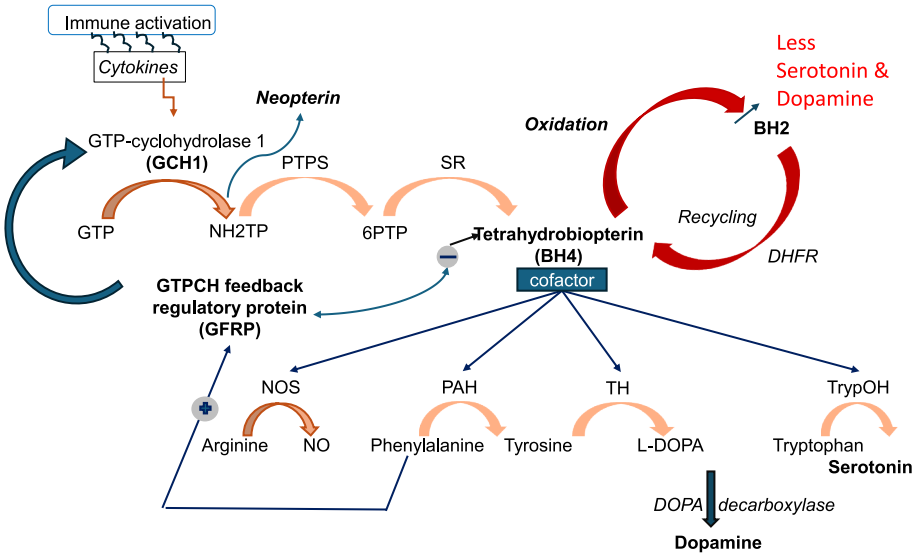

Fig. 1. The role of BH4 in NO and monoamine neurotransmitter synthesis (adapted from Vancassel et al., 2018).

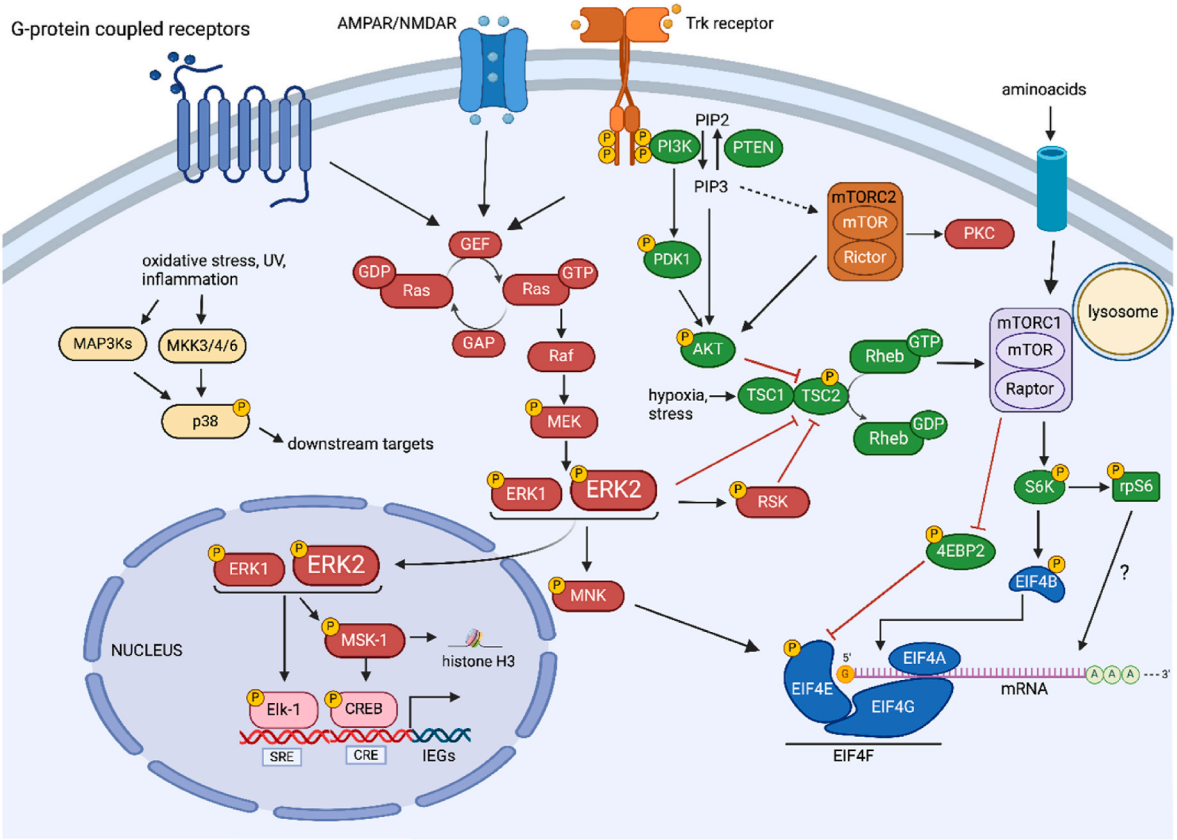

Fig. 2. A schematic representation of Ras-ERK, p38 and mTOR signalling pathways.

5.3. RB5, a cell penetrating peptide, enhances nuclear ERK signalling by Mimicking ERK1 deficiency

The dynamic regulation of extracellular signal-regulated kinases (ERK1/2) is pivotal for cellular responses to environmental cues, impacting cellular proliferation, differentiation, survival and synaptic activity in neurones (Brami-Cherrier et al., 2007; Chwang et al., 2007). The nuanced control of ERK1/2 localization and activation plays a critical role in these processes, making it a focal point for therapeutic intervention (Indrigo et al., 2023). A novel cell-penetrating peptide, RB5, derived from the N-terminus of ERK1, has been shown to interfere with ERK1 function, thereby modulating ERK signalling in a manner that recapitulates the phenotypic consequences of ERK1 deficiency (Indrigo et al., 2023).

RB5's efficacy in manipulating ERK signalling pathways was demonstrated through its selective enhancement of ERK phosphorylation without altering the kinase levels of ERK1/2 or affecting closely related kinases such as JNK (Indrigo et al., 2023). This specificity

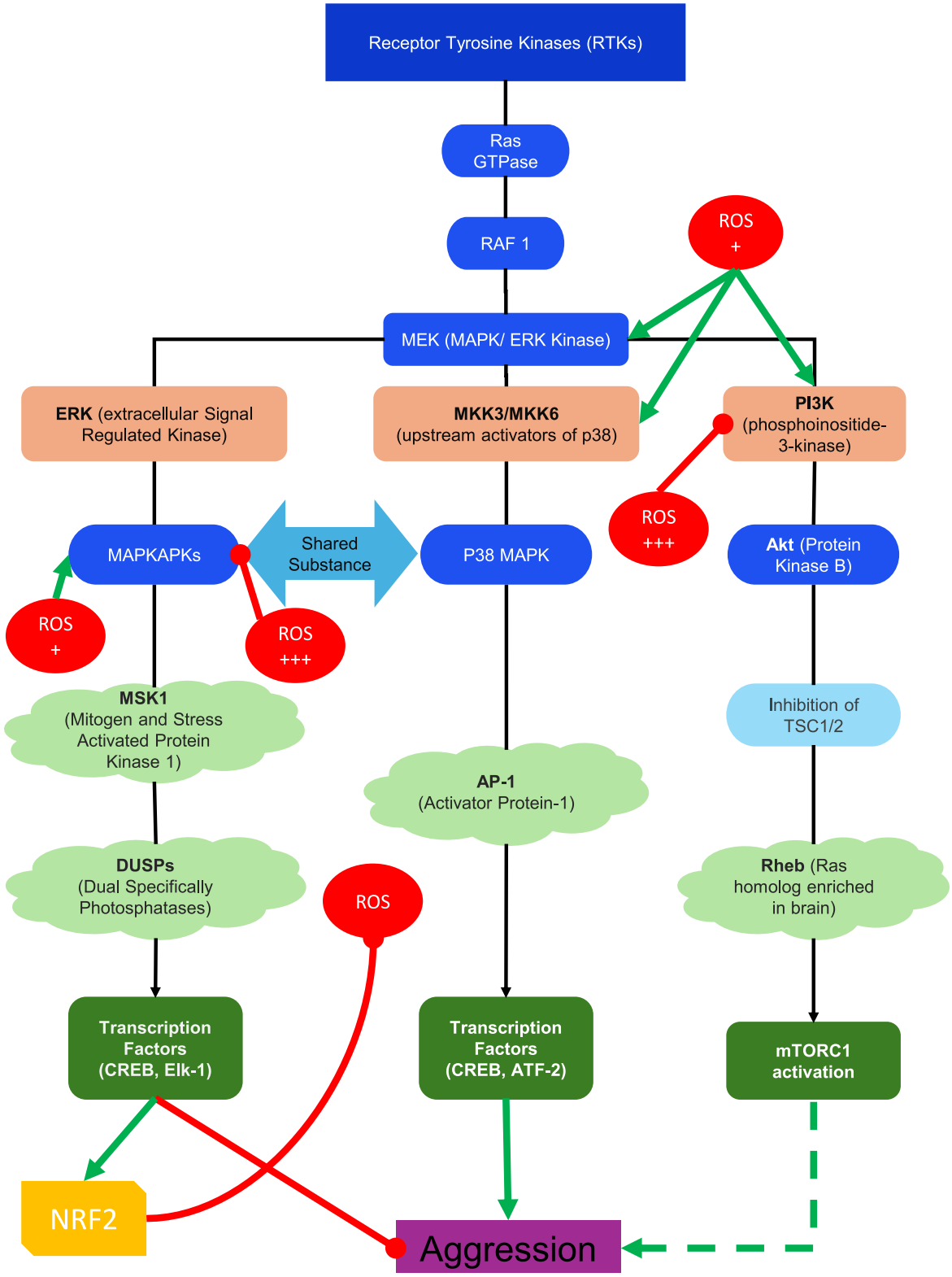

Fig. 3. A schematic of how the RAS-ERK, P38, and mTOR pathway and ROS action leading to decrease and increased aggression levels. Key to note that all the pathways originate from receptors tyrosine kinases and follow a similar route until they differentiate at their complementary molecules, that being ERK, MKK3/6 or PI3K. NRF2 regulates antioxidant response elements, crucial for regulation of cellular homeostasis. Transcription factors Elk-1, Cyclic AMP-Responsive Element-Binding Protein (CREB) and Activating transcription protein 2 (ATF-2) link oxidative stress to differential gene expression. Blue boxes: Signalling molecules; Orange boxes: Molecular pathways (mTor, Ras-ERK and p38); Green clouds: Transcription regulators; Red circles: Reactive oxygen species (ROS) at different levels (+ or +++); Green arrows: Activation or positive regulation; Red arrows: Inhibition or negative feedback; NRF2: Nuclear Factor Erythroid 2-related factor 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

underscores the peptide's potential as a targeted therapeutic tool. By facilitating the nuclear translocation and activation of ERK1/2, RB5 mimics the effects of ERK1 deficiency, which is known to shift the balance towards enhanced ERK2 activity, thus influencing nuclear signalling pathways that are crucial for gene expression and cellular responses (More et al., 2022; Olateju et al., 2021).

A pharmacokinetic and pharmacodynamic characterization of RB5 reveals its promising profile with sustained ERK phosphorylation, brain bioavailability, and a half-life supporting its use in in vivo studies (Cuadrado and Nebreda, 2010; Indrigo et al., 2023). The peptide's ability to selectively activate nuclear ERK-dependent signalling pathways without affecting cytoplasmic targets further highlights its specificity and potential therapeutic value. The study delves deeper into the mechanistic aspects of RB5's action, pinpointing Importinα1/KPNA2 as a differential mediator of ERK1 and ERK2 nuclear transport. This discovery suggests that RB5 can modulate the interactions between ERK1/2 and their nuclear transport machinery, thus influencing their subcellular localization and function. RB5's ability to decrease ERK1 binding to KPNA2 while increasing ERK2's interaction underscores a sophisticated mechanism by which RB5 modulates ERK signalling dynamics, promoting a bias towards nuclear ERK2 activities (Indrigo et al., 2023).

By selectively enhancing nuclear ERK signalling, RB5 opens avenues for therapeutic strategies aimed at diseases where dysregulated of ERK signalling is a hallmark, which we argue are many Personality Disorders. The identification of KPNA2 as a key player in this process highlights potential targets for further drug development, eventually leading to an "enviromometic drug" or "enviropill" (Notaras et al., 2021) which would be able to selectively and precisely stimulate key components of the complex molecular machinery which are normally activated by positive interactions with the environment during early development (Cooper and Frenguelli, 2021; Correa et al., 2012), aberrations of which may give rise to many PD conditions (Shaw et al., 2020).

5.4. Summary

This comprehensive review highlights the intricate interplay between genetic predispositions, neurobiological pathways, and environmental factors in shaping the development and manifestation of personality disorders (PDs). Through a detailed exploration of key molecular mechanisms, including the Ras-ERK, p38, and mTOR pathways, we underscore the role of these signalling cascades in modulating oxidative stress, neurotransmitter balance, and neurodevelopmental processes. The evidence presented supports the hypothesis that environmental stimuli and their interaction with molecular pathways significantly influence the expression of antisocial traits and other maladaptive behaviours.

Moreover, the identification of potential therapeutic targets, such as the modulation of mitochondrial bioenergetics and redox states, opens avenues for innovative pharmacological interventions. The concept of enviromimetic drugs, which mimic beneficial environmental influences at the molecular level, represents a promising frontier in the personalized treatment of PDs. Finally, the development of improved animal models that accurately replicate PD endophenotypes remains crucial for advancing our understanding of these disorders and their underlying mechanisms.

By integrating insights from neurobiology, molecular research, and clinical observations, this review provides a foundation for future studies aimed at enhancing diagnostic accuracy, therapeutic outcomes, and ultimately the quality of life for individuals affected by personality disorders.

CRediT authorship contribution statement

Patryk M. Adamczyk: Writing – review & editing, Investigation. **Andrew Shaw:** Writing – review & editing, Writing – original draft, Validation. **Ilaria M. Morella:** Writing – review & editing, Validation. **Lorenzo More:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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