Integrative neurochemistry and neurobiology of social recognition and behavior analyzed with respect to CD38-dependent brain oxytocin secretion

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Abstract:

This review summarizes the literature and our own data regarding the role of NAD^+-glycohydrolase/CD38-controlled molecular mechanisms of hypothalamic and pituitary oxytocin secretion in social behavior regulation. Current approaches to the modulation of both CD38 expression and brain cell activity that represent prospective treatments for disorders associated with altered social behavior are discussed.

Catalytic properties of NAD^+-glycohydrolase/CD38

NAD^+ metabolism in brain cells is tightly coupled to their functional activity, viability, and the development of neuroplasticity [1, 2]. NAD^+ release from brain cells corresponds to neuronal activity and might have biological significance. Recent data suggest that NAD^+ may be a novel candidate neurotransmitter translating metabolic signals into changes in gene transcription via the CD38/NAD^+/cyclic ADPR/Ca^{2+} pathway [3, 4, 5].

NAD+ acts as a substrate for NAD^+-converting enzymes located outside or inside the cells. Among all the NAD^+-degrading enzymes expressed in brain cells, including (poly(ADP-ribose) polymerase and ADP-ribosyltransferase (?)), NAD^+-glycohydrolase/CD38 is in the focus of thorough investigations in last 20 years. Because its expression is modified in neuronal and glial cells associated with brain development, neurotransmitters action, and various pathophysiological conditions. This molecule has also been implicated in the regulation of intercellular communication, apoptosis, cell migration, and neurosecretion [5, 6, 7].

Two kinetic mechanisms are involved in enzymatic activities of CD38: cyclization of NAD^+ into cyclic ADP-ribose (cADPR) followed by its hydrolysis to ADP-ribose (ADPR); conversion of $NADP^+$ in the presence of nicotinic acid into nicotinic acid adenine dinucleotide phosphate (NAADP). The most studied enzymatic activity of CD38 in various tissues is the formation of cADPR with calcium-mobilizing activity and of ADPR that may be further used for mon- or poly-ADP-ribosylation of functional proteins [8, 9, 10, 11, 12, 13]. Formation of cADPR leads to Ca^{2+}mobilization from intracellular Ca^{2+} stores in the inositol-1,4,5-trisphosphate-sensitive and ryanodine-depending endoplasmic reticulum, while NAADP acts at the different set of Ca^{2+} stores [7, 14].

In addition, CD38 may act as a receptor interacting with the non-substrate ligand (i.e. CD31) on the cell surface [15, 16, 17]. In certain cases, ligand-induced CD38 internalization occurs, allowing the production of intracellular cADPR. Recently, it has been shown that the catalytic domain of CD38 may be oriented either to the cytosol or the extracellular space [18,19]. The form of CD38 that is constructed as a type III protein (in which the C-terminal catalytic domain and the N-terminal tail would face the cytoplasm and the outside of the cell, respectively) is catalytically active in increasing cellular cADPR concentrations. For long time it has been known that CD38 is found in intracellular organelles in which cases CD38 is in the type III orientation. Therefore, a flipping mechanism could affect CD38 signaling activity [18]. Ratio of plasma membrane and intracellular CD38 may depend on the cell type and function. Associated molecules (i.e. Cx43) may act as nucleotide transporting channels providing access of NAD^+ to CD38 [UH Kim? Or De Flora?]. It is believed that CD38 acting either at the cell

surface or inside the cell may serve as a redox-sensor or as a NAD^+-sensor adjusting cell metabolic activity to the current needs [19, 20]. Thus, catalytic activity of CD38 might be tightly coupled to other NAD^+-consuming or NAD^+-dependent processes in cells including DNA replication and repair, epigenetic regulation, posttranslational modification of proteins, and energy metabolism etc.

CD38 expression and brain cell activity

In brain cells, CD38 is expressed on the surface of the plasma membrane and in various intracellular compartments, including mitochondria, the endoplasmic reticulum ribosomes, and the nucleus. Synaptic vesicles have been found to be immunopositive for CD38 [21]. In the central nervous system, CD38 is expressed in various brain regions, including the cortex and limbic system, and the pituitary [15]. CD38 expression occurs during an early period of embryonic development [16, 22] and during the postnatal period of brain development [5]. CD38 expression in neurons and glia can be affected by multiple factors; however, it is generally assumed that neurons, astroglia and microglia express significant levels of CD38, especially when stimulated with neurotransmitters (for neurons and astrocytes) or pro-inflammatory molecules (for microglia). Intracellular localization may also differ in these cell types: neurons express CD38 in the cytosol, while astrocytes and microglial cells express CD38 oriented towards the extracellular space. No clear information regarding CD38 expression in oligodendrocytes or NSCs has been published.

In various mammalian cells, CD38 expression is regulated by retinoic acid, thyroid hormones, estrogens and other hormones, glutamate, interleukins, and TNF-α [17]. Receptor-regulated activation of NAD^+-glycohydrolase/CD38 activity in the central nervous system is well-described [23, 24]. Excitable cells may depend on other types of CD38 biological activity including redox sensing [25] and NAD^+-sensing [20].

It should be noted that brain cells have a vast spectrum of enzymes involved in maintaining NAD^+ homeostasis [26]. In 2006, Aksoy et al. proposed a key role of CD38 in the regulation of intracellular levels of NAD^+ and of other related molecules in various mammalian cells including brain cells [27]. This hypothesis was later verified [28]. Therefore, CD38 activity may affect the following NAD^+-converting enzymes and molecular targets of cyclic ADP-ribose, which are responsible for the regulation of pivotal cellular functions, which are described below:

a) Sirtuins (NAD^+-dependent histone deacetylases) control synaptic plasticity, memory consolidation, brain aging, and neurodegeneration [29,30,31]. CD38 may regulate NAD^+-bioavailability for sirtuins in the cell nucleus [32]. *Cd38*$^{-/-}$ mice exhibit altered metabolic

circadian rhythms associated with behavioral abnormalities [33], which are likely due to elevated levels of intracellular NAD^+;

b) Poly(ADP-ribose)polymerase (PARP) exhibits the strongest known NAD^+-consuming ability among all other intracellular NAD^+-converting enzymes. PARP acts as a competitor to sirtuins in accessing the intracellular NAD^+ pool [34]. Little is known regarding the possible roles of CD38 in the functional connection between these two types of enzymes; however, one may propose that in normal physiological conditions, CD38 and sirtuins may play a dominant role in the regulation of intracellular NAD^+ levels, while in pathological contexts (i.e., oxidative stress) NAD^+ is mainly consumed by PARP;

c) The molecular targets of cyclic ADP-ribose include type 2 and 3 ryanodine receptors, which use cyclic ADPR for calcium release from intracellular stores [35, 36]. TRPM ion channels regulate Ca^{2+} influx and act as oxidative stress sensors [37, 38] that are controlled by cyclic ADPR [39]. The latter mechanism was previously demonstrated in oxytocin-mediated Ca^{2+}-dependent secretion in NG108-15 cells [40];

d) The activity of P2X7 purinergic receptors is involved in the transmembrane transfer of ions and nucleotides by two processes: i) NADH transport across the astrocyte plasma membrane, and, ii) NAD^+/cADPR conversion to P2X7-targeting diadenosine homodinucleotides. Bifunctional P2X7 receptors for extracellular ATP mediate NADH transport across the astrocyte's plasma membrane. P2X7 receptors form either cation-selective channels or nonselective pores with large conductance, depending on the levels of activation. However, the regulatory mechanism for the channel opening and pore formation of P2X7 receptors are not well understood [41].

NAD^+ levels could be regulated by the CD38-mediated production of cyclic ADPR followed by its conversion to diadenosine homonucleotides (isomers of diadenosine diphosphate) via Ca^{2+}-mobilizing activity [42]. In addition, extracellular NAD^+ can act as a substrate for ecto-ADP- ribosyltransferase at the plasma membrane. Thus, possibly, P2X7 receptors can be ADP-ribosylated [43], suggesting other cellular applications for CD38-mediated production of ADP-ribose. P2X7 receptors are functionally coupled to pannexin-1, and their interactions play an important role in controlling membrane permeability. It is generally believed that the cellular responses triggered by P2X7 depend on the structure of signaling complex formed by P2X7 and its associated molecules, including pannexin-1 [44]. Pannexin-1 acts as an ATP-permeant channel and is expressed in neurons, astrocytes, and pituitary cells [45]. This result suggests that there is a physiological role of pannexins' tight coupling to P2X7 receptors, which is regulated by cADPR in the brain. This action is likely supported by the activity of

connexins that provide regulated transport of NAD^+, ATP, and neurotransmitters [46]. Recent data regarding treatments targeting P2X7 receptors to correct autism-like behavioral abnormalities in an animal model have indirectly confirmed this action [47].

Alterations in social behavior due to neurosecretory dysfunction in the hypothalamic-pituitary-limbic system

Neuropeptides, neurotransmitters and multiple steroid hormones play a central role in regulating social behavior in mammals. Several behavior-regulating neuropeptides have been described [48]; in recent decades, much attention has been paid to oxytocin (OT) and arginine vasopressin (AVP) in the context of social recognition, social memory, mood regulation, aggression, and social behavior [49, 50]. The effects of these peptides are important in a variety of species and are moderated by receptor densities in the brain and the efficacy of neurosecretory events of the hypothalamus and pituitary [51]. The majority of OT and AVP biological effects in the central nervous system are concentrated in limbic regions (particularly, in the amygdala and the hippocampus), which are implicated in social affiliation, cognition, emotions, motivation, and sexual behavior.

Casual relationships between OT and AVP and social behavior have been intensively studied in experimental models and in humans. The results of these studies suggest that OT acts as a regulator of responses to social stress and facilitator of approach behavior, while AVP is mainly considered to be a mediator of anxiogenic action and modulator of male-typical social behaviors, including aggression and pair-bond formation [48, 49]. However, such functional differentiation is relative. At present, OT is implicated in the regulation of social recognition, memory and bonding, adjustment of the hypothalamic-pituitary-adrenal (HPA) axis under stressful conditions, maternal behavior (including maternal aggression), male and female sexual behaviors, empathy-based group formation, paternal and maternal care, feelings of attachment, development of more constructive behavioral approaches, and the establishment of social distance between males and females [50-60]. Balanced activity of both brain neuropeptide systems is important for appropriate emotional behavior [61]. In the coordination of parental care, mothers show greater amygdala activation and correlations between amygdala responses and OT, while fathers exhibit greater activation in social-cognitive circuits that are correlated with AVP [62].

OT attenuates stress-induced HPA activity and may produce anti-stress effects. It is suggested that the adaptation mechanism to chronic stress may involve up-regulation of oxytocin expression in the hypothalamus [63]. Chronic isolation stress results in increased plasma OT

levels and OTR mRNA in the hypothalamus in females, but not in males [64]. Central OT, but not AVP, attenuates both stress-induced neuroendocrine and molecular HPA axis responses and the dorsal hippocampus and paraventricular nuclei (PVN) constitute an OT-sensitive forebrain stress circuit [65]. Sexually dimorphic mechanisms of action for OT and AVP may underlie anxiety and repetitive behaviors commonly observed in children with ASD [66].

Different patterns of intracerebral release and action of OT may influence its regulatory activity in social behavior to a greater extent than do differences in OT receptor (OTR) levels in the brain. In the brain, OT is produced and released by magnocellular neurons of the PVN and supraoptic nuclei (SON) of the hypothalamus. In hypothalamic nuclei, OT gene expression and OT release is stimulated by hypertonic saline, parturition, suckling in lactating females, GABA, NO, glutamate, ATP, norepinephrine, IL-1β, estradiol and neurosteroids, maternal behavior, prostaglandins, angiotensin II, dopamine, and various stressors [67-69]. Some of these factors act in an age-dependent manner: more OT can be released from the SON in young rodents compared to older individuals [70].

OT in neurosecretory cells of the PVN and SON are packaged into specialized organelles: large dense-cored vesicles are transported via the microtubule cytoskeleton to the secretory sites of axon terminals or dendrites. The involvement of SNARE proteins in OT release remains controversial. The neurohypophyseal nerve terminals possess at least two functionally distinct and acutely releasable secretory granule pools that differ in size and Ca^{2+} sensitivity: 1) the immediately releasable pool and 2) the readily releasable pool (Ca^{2+}-dependent) [71].

OT is released in the brain from magnocellular neuronal dendrites in very large quantities; this type of release may be regulated independently from axonal secretion [72]. OT and AVP release are closely correlated with intracellular Ca^{2+} dynamics, which are mainly controlled by intracellular Ca^{2+} stores (endoplasmic reticulum) [73] and cytoskeletal remodeling [74]. Both types of OT secretion (dendritic and axonal) are triggered by increases in intracellular Ca^{2+} levels. However, dendritic release, but not axonal release, can be primed for further activity-dependent release by mobilizing Ca^{2+} from intracellular stores [75]. Recently, different compositions of voltage-gated Ca^{2+} channels (VGCC) were found in the two types of hypothalamic neurosecretory terminals: L, N, and Q in AVP terminals vs. L, N, and R in OT terminals. However, these channels do not differ greatly in relation to specific aspects of their release mechanisms. The only difference observed was attributed to the expression of purinergic receptors that affect VGCC functioning in these cells [76].

We recently found a novel CD38-dependent mechanism of intracellular Ca^{2+} mobilization, which plays a key role in OT release from the soma and axonal terminals of

hypothalamic neurons. This mechanism was related to profound changes in various social behaviors and did not play a role in AVP secretion (Figure 1). There is growing evidence that OT may be related to autism [77 - 80]. Defective OT and AVP function have been reported to play a role in the development of autism spectrum disorders (ASD) [81, 82]; genetic and epigenetic changes in OTR as well as changes in plasma OT levels have been discovered in patients with ASD [83].

Data from our laboratories demonstrate that impairment of the CD38/cADP-ribose system in the hypothalamo-neurohypophyseal system results in changes in OT secretion, but not AVP secretion, in humans [84] and in mice [85, 86, 87]. Impairments of this system have also been associated with abnormal social behavior in mice [85, 86]; this suggests new clues to understanding the pathogenesis of neurodevelopmental disorders [11, 30]. CD38 is highly expressed in the rodent and human hypothalamus [88]. Retinoic acid, an inducer of CD38 expression in various cell types, was recently discovered in the rat hypothalamus (PVN) [89], and retinoic acid synthesizing enzyme retinaldehyde dehydrogenase 1 is expressed in the hypothalamus. This is analogous to results reported by Stoney et al. [90], who demonstrated that increasing hypothalamic retinoic acid levels are sufficient to up-regulate various responsive genes: we can propose that retinoic acid metabolizing enzymatic machinery in the hypothalamus could provide enough retinoic acid to up-regulate CD38 expression. However, this must be confirmed experimentally.

CD38-controlled mechanisms revealed in Cd38 knockout mice

In CD38 gene knockout mice [91], we demonstrated that CD38-dependent cADPR- and NAADP-sensitive intracellular Ca^{2+} mobilization plays a key role in OT release from the soma and axonal terminals of hypothalamic neurons and exhibits profound modulation of social behaviors. Altered Ca^{2+} signaling observed in *Cd38*$^{-/-}$ mice was correlated with reduced ADP-ribosyl cyclase activity in the examined brain regions. Immunohistochemical analysis also demonstrated reduced CD38 immunoreactivity in hypothalamic periventricular regions. Plasma and cerebrospinal fluid (CSF) OT levels were lower in *Cd38*$^{-/-}$ mice than in *Cd38*$^{+/+}$ mice, and OT was extensively packaged in the hypothalamus and pituitary in *Cd38*$^{-/-}$ mice due to alterations in the Ca^{2+}-mediated release of OT-containing vesicles [85, 92]. We found that *Cd38*$^{-/-}$ mice exhibited altered communicative behaviors that were similar to those observed in *Oxt*$^{-/-}$ and *Oxtr*$^{-/-}$ mice. In these mice, both the injection of OT and the expression of CD38 were able to restore the observed social memory deficits [88].

Interestingly, CD38-controlled mechanisms of central OT release are clearly dependent on reproductive experience in female mice, and in male mice, associations between peripheral OT levels and parenting and paternal care have been described [93]. In support of our experimental findings, reproductive experience improves parental behavior in *Cd38*$^{-/-}$ male mice (even to a lower extent than in *Cd38*$^{-/-}$ females), thus, experience-mediated remodeling of the neuroendocrine system and neurosecretory events may be controlled, at least in part, by the CD38/cyclic ADPR system.

OT itself can elicit dendritic peptide release without increasing neuronal electrical activity [72]. The activation of peptide receptors on the dendrites or soma elevates intracellular Ca^{2+} concentrations and triggers exocytosis. Once dendritic peptide release is triggered, feedback allows for self-sustaining and long-lasting release to occur. We found that CD38 is also involved into the autoregulation of OT secretion in the hypothalamus and pituitary of rodents [87]. Our data on parental behavior, social recognition, and the findings of our in vitro study have indicated that social experiences lead to consecutive stimulation of OT neurons, the activation of CD38/ADP-ribosyl cyclase activity, Ca^{2+} mobilization from intracellular stores, OT release, and the activation of positive feedback in PKC- and cADPR-dependent manners [88, 94].

In accordance with our experimental findings in mice, a mutation in the CD38 gene is found to be associated with lower plasma OT levels in humans [84]. Similar allele frequencies for the genotyped SNPs in men and women are comparable. Additionally, similar correlations between plasma OT, CD38, and human OTR SNP variants and parenting behavior have been observed between mothers and fathers [95]. Positive feedback of OT-induced OT release has been previously confirmed in humans [96, 97].

Other NAD^+-dependent mechanisms may also be involved in the regulation of OT and AVP-producing neurons, including differential expression of NAD^+-dependent histone deacetylases in monoaminergic and neuropeptidergic neurons [98].

Specific patterns of OTR expression in hypothesized social brain regions correlate to functional characteristics of these areas obtained using fMRI [99, 100]. The role of OT in the regulation of the limbic system as a major social brain region has been confirmed in numerous experimental studies: corticosteroids regulate binding of OT to OTR in hippocampus [101], and this mechanism is responsible for OT-controlled behavioral hippocampal responses [102]; OT is secreted in the hippocampus during complex behavioral reactions [103]; activation of OTR in the medial amygdala is required for social recognition in mice [104]; and the positive effects of OT in socially-stimulated learning depends on amygdala functional activity in humans [105]. In the hypothalamic nuclei, OT is mainly released from dendrites; in the pituitary and the hippocampus,

OT is released from axonal terminals [106]. Data regarding local OT release in the amygdala remains controversial [107, 108]. Abnormal amygdaloid structure has been implicated in the pathophysiology of ASD and depression; therefore, OT release and action in the amygdala may be of interest in integrative neurochemistry and the neurobiology of social behavior.

Differences in the molecular mechanisms controlling OT and AVP release in the hypothalamus and pituitary (CD38 controls OT, but not AVP release) may have implications considering OT and AVP release and action in the amygdala. CD38 is expressed in the amygdala; however, expression levels are significantly lower in the amygdala than in the hypothalamus [109], and cyclic ADP-ribose-controlled TRPM2 channels are also expressed in amygdala [110]. The activation of amygdala AVP and OT receptors have opposing effects on fear and anxiety-related behaviors: AVP enhances aggressiveness, anxiety, and stress levels and the consolidation of fearful memories, while OT decreases anxiety and stress and facilitates social encounters, maternal care, and the extinction of conditioned avoidance behavior. It was previously shown that OT and AVP stimulate different populations of neurons in the central amygdala, thus modulating the integration limbic and cortical information [111]. This result strongly supports OT and AVP act as antagonists in the regulation of social behavior: OR reduces anxiety and stress-stimulated behavioral responses, while AVP mediates defensive behavior.

Postulated roles of CD38 in the amygdala

The amygdala is highly connected to other areas of the brain. Hypothalamic OT, hypocretin and melanin-concentrating hormone neurons have many projections to the central amygdala, thereby regulating region-associated behaviors and personality traits [108, 112, 113]. Estrogens have been shown to regulate OTR expression in this part of the limbic system. OT effects on amygdala are numerous: OT can facilitate amygdala-dependent, socially reinforced learning and emotional empathy in humans [105] and can modulate the expression of evaluative conditioning for socially relevant faces via influences on the amygdala and fusiform gyrus. The latter effect may explain prosocial activity of OT [114].

Amygdala-hypothalamus interconnection is mediated by OT-dependent mechanisms, and establishing medial amygdala-controlled inter-male aggressive behavior is associated with immediate early gene expression in OT neurons located in specific brain regions [115]. OT acts in the medial amygdala during an initial exposure to facilitate social recognition; OT given before, but not after, an initial encounter restores social recognition in *Oxt*$^{-/-}$ mice [104]. It is

well-known that the medial amygdala modulates female social recognition. Antisense oligonucleotides specific for OTR administered into the medial amygdala several days prior to testing has been shown to significantly reduce social recognition in females. This indicates that OTR expression in this region is necessary for proper social recognition [116]. Furthermore, a model of social cognitive dysfunction was recently proposed that comprises abnormalities in oxytocinergic and dopaminergic signaling in the amygdala, resulting in impaired emotional salience processing and consequent social cognitive deficits in schizophrenia [117].

Many authors believe that OT primarily reduces amygdala activity [118], and certain studies indicate that OT is able to increase amygdala activation for pleasant stimuli. Thus, the amygdala might be a key structure mediating not only the positive influence of social feedback in general but also the specific influence of OT on socially-reinforced learning [119]. OT can facilitate amygdala-dependent emotional empathy in humans [105]. In stressful conditions, the oxytocinergic system of the amygdala is significantly activated in stress-coping strategies [120]. OTR polymorphism affects amygdala volume, most likely due to greater cortisol exposure [121]. OT and AVP in the medial amygdala mediate approach and avoidance behavior; however, the manner in which these behaviors are mediated differ significantly [122].

Alterations of central OT release and action in the deregulation of brain development

Autism is a neurodevelopmental disorder characterized by prominent alterations in social interactions, communication, and the appearance of stereotyped repetitive behaviors with restricted interests [123, 124]. Defects in neurotransmitters release and reception, synaptic proteins, mitochondrial function, signal transduction pathways, and innate immune responses have been implicated in the complex pathogenesis of autism.

Neurodevelopmental disorders have origins in early life, and more classical conceptions have recently been replaced with the theory of complex interactions between genes and the environment, resulting in the phenomenon of early life programming [125]. Early life stresses (including prenatal exposure to toxic or immunogenic agents, perinatal stress itself), nutritional status at the perinatal period, and changes in regulatory neuroendocrine networks could result in postponed alterations in cognition and social behavior. NAD^+ metabolism in brain cells has recently been attributed to the development of this phenomenon, with a special focus on NAD^+-dependent histone deacetylases as epigenetic regulators [126] or NAD^+-converting enzymes affecting neuronal fate [127].

Little, and occasionally controversial, information is available regarding development-associated changes in brain expression of CD38 and its associated molecules in relation to behavioral alterations occurring later in the life. Ceni et al. [128] found dramatic elevations of ADP-ribosyl cyclase activity in the adult rodent brain compared to that observed on postnatal day 1. The same team later revealed that *Cd38*$^{-/-}$ mouse brains have high intracellular ADP-ribosyl cyclase activity and that higher levels of activity are detected in synaptosomes purified from neonates than in those of adult animals. These authors found this to be consistent with the observation that endogenous brain cyclic ADPR concentrations, which are definitively not related to the presence of the CD38 protein, are higher in the developing brain and decline in adult tissue over time [16]. We have demonstrated dynamic changes in CD38 expression in the cortex of rodents from postnatal day 1 to postnatal day 48 and that such changes were correlated with NAD^+ levels and apoptosis of brain cells [22, 129].

Birth-related surges in maternal OT may regulate synchronization of children's hippocampal neurons and may be important for the transitions from prenatal to postnatal life. Thus, this mechanism may induce long-lasting behavioral endophenotypes [130]. The OT system continues to mature after birth and may be especially sensitive to the factors affecting brain development during the perinatal and neonatal periods. Hypothalamo-neurohypophysial neurons secreting OT and AVP migrate early in the development of the PVN and SON and send their axons to the neurohypophysis. The neurogenesis of OT- and AVP-producing neurons continues in the adult hypothalamus and is stimulated by conditions requiring higher neuropeptide levels for adequate neuroendocrine responses [131, 132].

Reduced OT plasma concentrations mark not only ASD but also borderline personality disorder, which is believed to be closely related to traumatic childhood experiences and is characterized by (para)suicidal behaviors as well as aggressive outbursts. However, OT-mediated links between early life stress and the development of borderline personality disorder are not confirmed [133].

Generally, social behavior may be viewed as a situation associated with dramatic changes in the neurogenesis of various brain regions (i.e., olfactory bulbs, hippocampus, amygdala, hypothalamus, subventricular zone, cortex, and nucleus accumbens) [134]. This has been clearly demonstrated in parental behavior [135], paternal recognition of offspring [136], and social interactions of females with male, but not female conspecifics [137]. It is interesting that maternal behavior is not affected when neurogenesis is impaired in the olfactory system but spared in the hippocampus [138].

OT itself can powerfully stimulate proliferation of neural progenitors in the adult hippocampus [139], but whether the same activity occurs with respect to neurogenesis in the hypothalamus is unknown. OT, but not AVP, stimulates adult neurogenesis in the hippocampus of rats subjected to stress [140]. Due to its action in cytoskeletal structure, OT was proposed to act as a growth factor for neurons [141].

Experiences in the first few days of the life are mediated by sexually dimorphic changes in OT and OTR levels. This is highly sensitive to different animal handling regimens and provides a basis for establishing behavioral reactions occurring within the phenomenon of early life programming [142]. Early life chronic social stress has long-term effects on maternal care (due to changes in OT and prolactin levels), leading to decreased nursing efficiency in adult dams [143]. This may result in the formation of "*circulus vitiosus*" in the pathogenesis of neurodevelopmental disorders: when dams are stressed in their early life, they will provide less maternal care and thus provoke early life stress in their offspring. Neonatal exposure to OT may influence receptor expression for neuropeptides of transmitters that have been implicated in social behavior, and such effects are region-specific and sexually dimorphic [144, 145].

Short-term maternal separation (a widely used experimental model of early life stress) results in significantly lower OT levels in the rat hypothalamus and amygdala and elevated levels in the pituitary gland in juvenile rats, while in adult rats hypothalamic expression of OT is not changed. OT expression was found to be the most sensitive parameter in maternal separation-induced neurochemical alterations [146], and the AVP system was not affected by maternal separation. As expected, early interactions with the mother and peers resulted in elevated levels of OTR in the amygdala and enhanced adult affiliation behavior [147].

A recently proposed theory states that OT stimulates prosocial behavior by facilitating the connectivity between different brain regions (i.e., posterior cingulate cortex, cerebellum, postcentral gyrus) and that this effect is modulated by the experience of maternal love withdrawal [148]. A well designed study by Feldman [149] clearly demonstrated that OT functioning is transferred from parent to child through patterns of parental care: children's social contact with peers is associated with OT plasma levels, the expression of the OT gene in the mother, and the quality of social contact between the mother and child. Additionally, low child OT levels can be predicted by the interaction of maternal high-risk CD38 alleles and diminished maternal care in infancy.

Extremely limited information exists regarding the changes in the OT system that are associated with aging. Aging affects neurocognitive and socio-emotional processes, which are likely due to alterations in OT release and signaling in the amygdala [150].

Current approaches to pharmacological modulation of CD38 expression and activity in mammalian cells

The only existing pathogenetically proven pharmacological strategy by which to improve the CD38-controlled behaviors observed in ASD is the application of intranasal OT [151, 152]. However, the data are conflicting: numerous studies report positive results, but one study of intranasal OT administration in early life found that it led to the development of aggressive behaviors [153]. Thus, OT is not effective for all patients but may be beneficial for specific individuals and/or conditions [154, 155].

Deciphering the molecular mechanisms of central OT release provides novel approaches to treat ASD with high efficacy (Figure 2). Pharmacological modulation of CD38 expression and activity could theoretically be achieved via cADPR and its analogs. However, the clinical utility of cADPR as a pharmacological tool is limited by the rapid hydrolysis of this metabolite in the cells, therefore much attention is paid to the prospects for using various modulators of ryanodine receptors activity (caffeine, ryanodine, procaine, ruthenium red), FKBP ligands, and NAD^+-glycohydrolase inhibitors.

Among all of the cyclic ADPR antagonistic derivatives, 8-amino-cADPR is the most potent antagonist and can block Ca^{2+} release-inducing cADPR activity in the nanomolar range [156]. Wagner et al. [157] produced cyclization of the dinucleotide of the nicotinamide 8-bromo-hypoxanthine at the nitrogen 1-position to yield cyclic 8-bromo-inosine diphosphoribose. Similarly, Gu et al. [158] synthesized N1-[(5"-O-Phosphorylethoxy)methyl]-5'-O-phosphorylinosine 5',5"-cyclic pyrophosphate (cIDPRE) and the 8-substituted derivatives 8-azido-, and 8-amino-cIDPRE as membrane-permeable mimics of cyclic ADPR. Cyclic aristeromycin diphosphate ribose, which contains oxygen in the ribosyl ring of the adenine ribose that can be replaced by carbon, is highly resistant to hydrolysis by cADPR hydrolase. It is thereby able to prolong the physiological action of cyclic ADPR; the same result could be achieved by converting the 7-nitrogen of the adenine ring to carbon, as in 7-deaza-cADPR [159]. Among analogs of cyclic ADPR, adenosine diphospho-carbocyclic-ribose significantly induces Ca^{2+} release, whereas cyclic aristeromycin diphosphoribose is slightly more active than the endogenous cyclic adenosine diphosphoribose. Shuto et al. [160, 161] have described derivatives of cyclic ADP-carbocyclic-ribose and their respective biological activity as well as the structure-activity relationships for selective analogs of cADPR.

Inhibition of CD38 activity can be achieved by various approaches. Nicotinamide 2'-deoxyriboside and 5-methylnicotinamide 2'-deoxyriboside can affect the formation of common covalent intermediates in the soluble domain of CD38. This domain is the site of NAD^+ conversion to cADPR and further to ADPR [162]. Carbocyclic NAD^+ analogs, in which 2,3-dihydroxycyclopentane methanol replaces the β-D-ribonucleotide ring of the nicotinamide riboside moiety of NAD^+ (i.e., carbo-NAD^+ and pseudocarbo-NAD^+), are resistant to enzymatic cleavage of the pyridinium-carbon bond. These analogs also act as NAD^+-glycohydorlase inhibitors; the same activity has been reported for arabinosyl-NAD^+ and 2-fluoroarabinosyl-NAD^+ [163]. Nicotinamide acts as a strong but non-specific inhibitor of NAD+-consuming enzymes. Small-molecule inhibitors (4,4'-dihydroazobenzene and 2,2'-dihydroazobenzene) have been shown to be effective suppressors of ADPR-cyclase [164]. Catalysis-based inhibitors of CD38 have been previously synthesized (arabinosyl-2'-fluoro-2'-deoxynicotinamide mononucleotide, etc.) [165]. One study reported that CD38 activity can be inhibited by micromolar concentrations of flavonoids (luteolinidin, kuromanin, luteolin) [166]. Novel approaches to manipulate CD38-mediated cADPR metabolism in vivo were recently proposed [167].

The group headed by Lee [168] has tested novel inhibitors of CD38 (N-substituted nicotinamide derivatives), and demonstrated that 1-(|2-(4-phenoxy-phenoxy)ethoxy|methyl}-3-(aminocarbonyl)-pyridinium chloride is highly potent; its nicotinamide portion binds to CD38 in a manner that is identical to that exhibited by NAD^+. The authors cite that replacement of highly charged moieties of NAD^+ with aromatic groups provides membrane permeability.

In contrast to CD38 inhibitors, stimulation of CD38 expression and increased CD38 activity can be attained with very few compounds. Retinoic acid has been shown to induce high levels of CD38 antigen expression in leukemia cells due to the activation of CD38 gene transcription [169]. Retinoic acid can also modulate CD38 expression in the rat brain after perinatal hypoxic-ischemic injury [156]. It may also modulate CD38 expression in lymphocytes obtained from patients with ASD [170]. However, the potential mechanisms that underlie up-regulation of CD38 expression in brain cells are not well studied [171]. It is interesting that alterations in the expression of the *Rai* gene (encoding for retinoic acid-induced transcription factor) are associated with neurodevelopmental disorders [172, 173], including ASD [174]. Chronic administration of retinoic acid results in abnormal behavior (decreased exploratory activity and elevated anxiety), most likely due to hyper-activation of the HPA axis [175]. Considering the important role of astrocytes as a source of endogenous brain retinoic acid that

affects neuronal proliferation and differentiation [176], the existing data provide a novel approach to manipulate CD38 activity in the brain under normal and pathological conditions.

Recently, sildenafil was reported to induce OT release from the pituitary [177], but this effect is mediated through modulation of phosphodiesterase activity and has no direct relationship to Ca^{2+}-dependent OT release.

Conclusion

A vast volume of recent data indicate that CD38-controlled homeostasis of NAD^+ and CD38-catalyzed cADPR formation are the important components of signal transduction pathways implicated in the regulation of pivotal brain cell functions (intercellular communication, excitability, proliferation, differentiation, migration, apoptosis) and neuroplasticity, in general. It is known that CD38 expression and activity in the brain are frequently altered by impaired interaction between neurons and glial cells at the sites of acute and/or chronic neurodegeneration, which may lead to pathological conditions during brain development and neuroinflammation [5, 7, 129, 178, 179, 180]. Furthermore, our recent findings regarding CD38-controlled neurosecretory activity of hypothalamic and pituitary cells [40, 92, 181, 182] open a new chapter in elucidating the role of CD38 in integrative brain functions and provide novel approaches to identify molecular targets for the pharmacological treatment of disorders associated with social behavioral alterations.

List of abbreviations

ADPR – adenosine diphosphate ribose

ASD – autism spectrum disorder

ATP - adenosine triphosphate

AVP – arginine vasopressin

cADPR – cyclic adenosine diphosphate ribose

CD38 – NAD^+-glycohydrolase/CD38

NAD^+ - nicotinamide adenine dinucleotide

NAADP - nicotinic acid adenine dinucleotide phosphate

NADH – nicotinamide adenine dinucleotide reduced

OT - oxytocin

OTR – oxytocin receptor

P2X7 – purinergic receptor 7

PARP – poly(adenosine diphosphate ribose)polymerase

PVN – paraventricular nucleus

RyR – ryanodine receptor

SNARE – soluble NSF attachment receptor

SON – supraoptic nucleus

TNFα – tumor necrosis factor α

TRPM – transient receptor potential cation channel, subfamily M, member 2

VGCC – voltage-gated calcium channel

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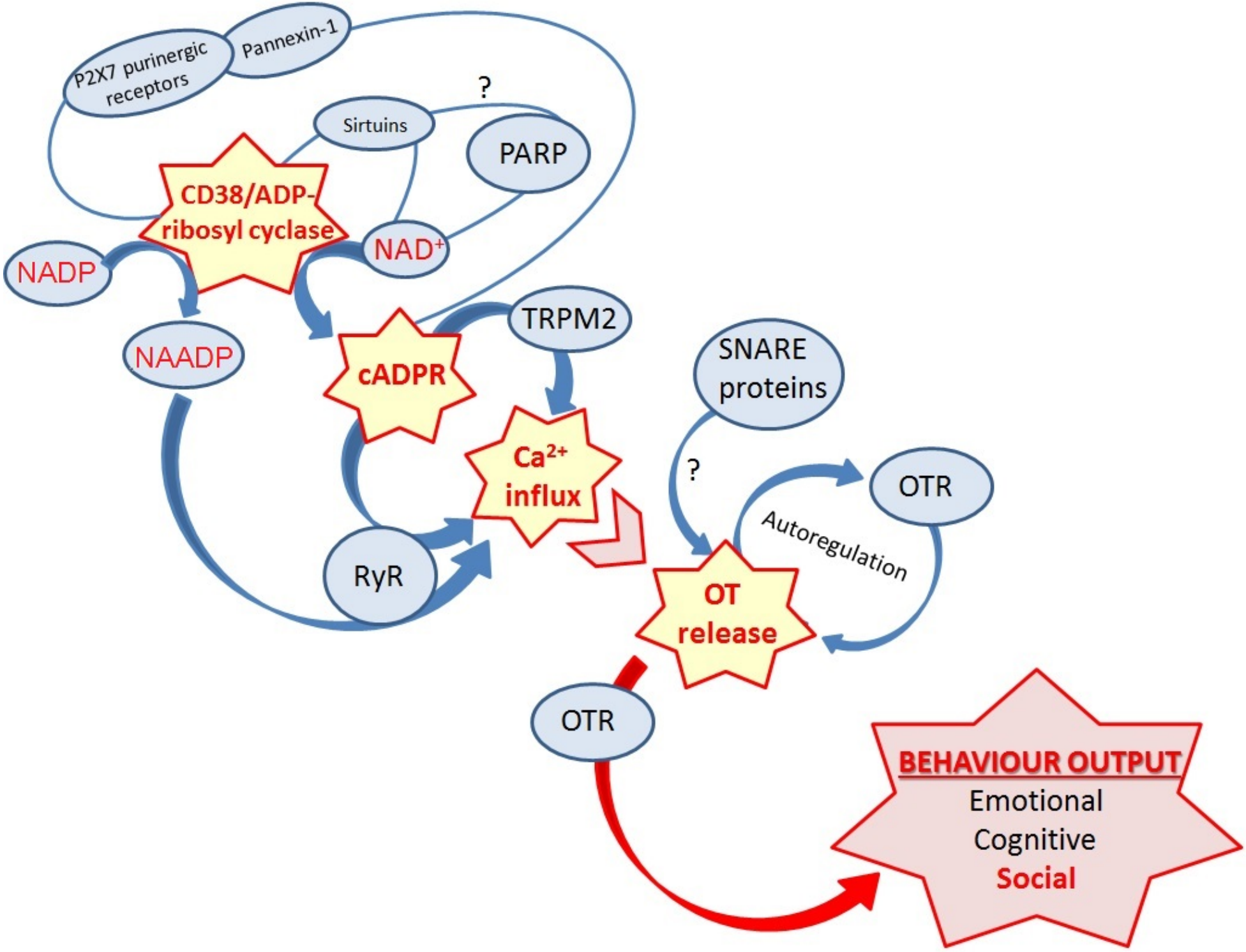
Figure legends:

Fig.1. CD38-controlled mechanisms in the regulation of social behavior. A schematic representation of a key role of CD38 in different social behavior outputs by molecular pathways of oxytocin secretion, including NAD^+ and NADP transformation, cyclic ADP-ribose formation, and Ca^{2+} release from ryanodine receptors.

Fig. 2. Pathophysiology of CD38-controlled social behavior: novel molecular targets for pharmacological amelioration.


P2X7 purinergic receptors
Pannexin-1
?
Sirtuins
PARP
CD38/ADP-ribosyl cyclase
NAD+
NADP
NAADP
cADPR
TRPM2
SNARE proteins
Ca2+ influx
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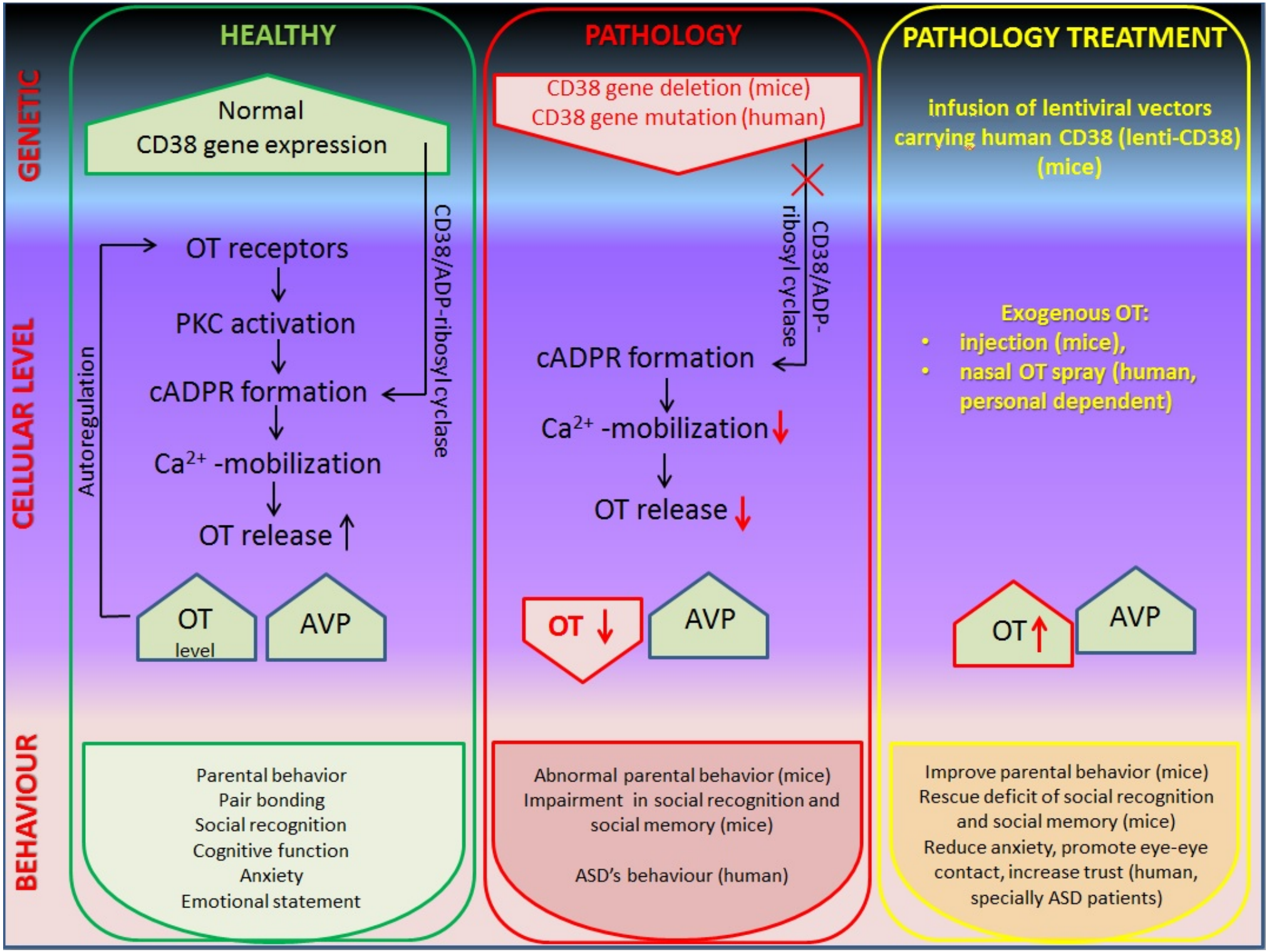
OTR
Autoregulation
RyR
OT release
OTR
BEHAVIOUR OUTPUT
Emotional
Cognitive
Social


GENETIC
CELLULAR LEVEL
BEHAVIOUR
HEALTHY
Normal
CD38 gene expression
CD38/ADP-ribosyl cyclase
OT receptors
PKC activation
cADPR formation
Ca2+ -mobilization
OT release
Autoregulation
OT
level
AVP
Parental behavior
Pair bonding
Social recognition
Cognitive function
Anxiety
Emotional statement
PATHOLOGY
CD38 gene deletion (mice)
CD38 gene mutation (human)
CD38/ADP-ribosyl cyclase
cADPR formation
Ca2+ -mobilization
OT release
OT
AVP
Abnormal parental behavior (mice)
Impairment in social recognition and social memory (mice)
ASD's behaviour (human)
PATHOLOGY TREATMENT
infusion of lentiviral vectors carrying human CD38 (lenti-CD38) (mice)
Exogenous OT:
injection (mice),
nasal OT spray (human, personal dependent)
OT
AVP
Improve parental behavior (mice)
Rescue deficit of social recognition and social memory (mice)
Reduce anxiety, promote eye-eye contact, increase trust (human, specially ASD patients)