

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

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18

19 **Abstract:**

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

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26

## *Catalytic properties of NAD<sup>+</sup>-glycohydrolase/CD38*

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

NAD<sup>+</sup> acts as a substrate for NAD<sup>+</sup>-converting enzymes located outside or inside the cells. Among all the NAD<sup>+</sup>-degrading enzymes expressed in brain cells, including (poly(ADP-ribose) polymerase and ADP-ribosyltransferase (?)), NAD<sup>+</sup>-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<sup>+</sup> into cyclic ADP-ribose (cADPR) followed by its hydrolysis to ADP-ribose (ADPR); conversion of NADP<sup>+</sup> 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<sup>2+</sup> mobilization from intracellular Ca<sup>2+</sup> stores in the inositol-1,4,5-trisphosphate-sensitive and ryanodine-dependending endoplasmic reticulum, while NAADP acts at the different set of Ca<sup>2+</sup> 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<sup>+</sup> to CD38 [UH Kim? Or De Flora?]. It is believed that CD38 acting either at the cell

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

### 7 *CD38 expression and brain cell activity*

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

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

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

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

1 circadian rhythms associated with behavioral abnormalities [33], which are likely due to elevated  
2 levels of intracellular  $\text{NAD}^+$ ;

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

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

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

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

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

4  
5 *Alterations in social behavior due to neurosecretory dysfunction*  
6 *in the hypothalamic-pituitary-limbic system*

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

17 Casual relationships between OT and AVP and social behavior have been intensively  
18 studied in experimental models and in humans. The results of these studies suggest that OT acts  
19 as a regulator of responses to social stress and facilitator of approach behavior, while AVP is  
20 mainly considered to be a mediator of anxiogenic action and modulator of male-typical social  
21 behaviors, including aggression and pair-bond formation [48, 49]. However, such functional  
22 differentiation is relative. At present, OT is implicated in the regulation of social recognition,  
23 memory and bonding, adjustment of the hypothalamic-pituitary-adrenal (HPA) axis under  
24 stressful conditions, maternal behavior (including maternal aggression), male and female sexual  
25 behaviors, empathy-based group formation, paternal and maternal care, feelings of attachment,  
26 development of more constructive behavioral approaches, and the establishment of social  
27 distance between males and females [50-60]. Balanced activity of both brain neuropeptide  
28 systems is important for appropriate emotional behavior [61]. In the coordination of parental care,  
29 mothers show greater amygdala activation and correlations between amygdala responses and OT,  
30 while fathers exhibit greater activation in social-cognitive circuits that are correlated with AVP  
31 [62].

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

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

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

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

21 OT is released in the brain from magnocellular neuronal dendrites in very large  
22 quantities; this type of release may be regulated independently from axonal secretion [72]. OT  
23 and AVP release are closely correlated with intracellular Ca<sup>2+</sup> dynamics, which are mainly  
24 controlled by intracellular Ca<sup>2+</sup> stores (endoplasmic reticulum) [73] and cytoskeletal remodeling  
25 [74]. Both types of OT secretion (dendritic and axonal) are triggered by increases in intracellular  
26 Ca<sup>2+</sup> levels. However, dendritic release, but not axonal release, can be primed for further  
27 activity-dependent release by mobilizing Ca<sup>2+</sup> from intracellular stores [75]. Recently, different  
28 compositions of voltage-gated Ca<sup>2+</sup> channels (VGCC) were found in the two types of  
29 hypothalamic neurosecretory terminals: L, N, and Q in AVP terminals vs. L, N, and R in OT  
30 terminals. However, these channels do not differ greatly in relation to specific aspects of their  
31 release mechanisms. The only difference observed was attributed to the expression of purinergic  
32 receptors that affect VGCC functioning in these cells [76].

33 We recently found a novel CD38-dependent mechanism of intracellular Ca<sup>2+</sup>  
34 mobilization, which plays a key role in OT release from the soma and axonal terminals of

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

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

20

### 21 *CD38-controlled mechanisms revealed in Cd38 knockout mice*

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



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

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

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

23           Other NAD<sup>+</sup>-dependent mechanisms may also be involved in the regulation of OT and  
24 AVP-producing neurons, including differential expression of NAD<sup>+</sup>-dependent histone  
25 deacetylases in monoaminergic and neuropeptidergic neurons [98].

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

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

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

### 19 20 *Postulated roles of CD38 in the amygdala*

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

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

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

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

### 17 18 *Alterations of central OT release and action in the deregulation of brain development*

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

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

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

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

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

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

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

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

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

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

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

1  
2 *Current approaches to pharmacological modulation of CD38 expression*  
3 *and activity in mammalian cells*

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

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

17 Among all of the cyclic ADPR antagonistic derivatives, 8-amino-cADPR is the most  
18 potent antagonist and can block Ca<sup>2+</sup> release-inducing cADPR activity in the nanomolar range  
19 [156]. Wagner et al. [157] produced cyclization of the dinucleotide of the nicotinamide 8-bromo-  
20 hypoxanthine at the nitrogen 1-position to yield cyclic 8-bromo-inosine diphosphoribose.  
21 Similarly, Gu et al. [158] synthesized N1-[(5"-O-Phosphorylethoxy)methyl]-5'-O-  
22 phosphorylinosine 5',5"-cyclic pyrophosphate (cIDPRE) and the 8-substituted derivatives 8-  
23 azido-, and 8-amino-cIDPRE as membrane-permeable mimics of cyclic ADPR. Cyclic  
24 aristeromycin diphosphate ribose, which contains oxygen in the ribosyl ring of the adenine  
25 ribose that can be replaced by carbon, is highly resistant to hydrolysis by cADPR hydrolase. It is  
26 thereby able to prolong the physiological action of cyclic ADPR; the same result could be  
27 achieved by converting the 7-nitrogen of the adenine ring to carbon, as in 7-deaza-cADPR [159].  
28 Among analogs of cyclic ADPR, adenosine diphospho-carbocyclic-ribose significantly induces  
29 Ca<sup>2+</sup> release, whereas cyclic aristeromycin diphosphoribose is slightly more active than the  
30 endogenous cyclic adenosine diphosphoribose. Shuto et al. [160, 161] have described derivatives  
31 of cyclic ADP-carbocyclic-ribose and their respective biological activity as well as the structure-  
32 activity relationships for selective analogs of cADPR.

1           Inhibition of CD38 activity can be achieved by various approaches. Nicotinamide 2'-  
2 deoxyriboside and 5-methylnicotinamide 2'-deoxyriboside can affect the formation of common  
3 covalent intermediates in the soluble domain of CD38. This domain is the site of NAD<sup>+</sup>  
4 conversion to cADPR and further to ADPR [162]. Carbocyclic NAD<sup>+</sup> analogs, in which 2,3-  
5 dihydroxycyclopentane methanol replaces the β-D-ribonucleotide ring of the nicotinamide  
6 riboside moiety of NAD<sup>+</sup> (i.e., carbo-NAD<sup>+</sup> and pseudocarbo-NAD<sup>+</sup>), are resistant to enzymatic  
7 cleavage of the pyridinium-carbon bond. These analogs also act as NAD<sup>+</sup>-glycohydrolase  
8 inhibitors; the same activity has been reported for arabinosyl-NAD<sup>+</sup> and 2-fluoroarabinosyl-  
9 NAD<sup>+</sup> [163]. Nicotinamide acts as a strong but non-specific inhibitor of NAD<sup>+</sup>-consuming  
10 enzymes. Small-molecule inhibitors (4,4'-dihydroazobenzene and 2,2'-dihydroazobenzene) have  
11 been shown to be effective suppressors of ADPR-cyclase [164]. Catalysis-based inhibitors of  
12 CD38 have been previously synthesized (arabinosyl-2'-fluoro-2'-deoxynicotinamide  
13 mononucleotide, etc.) [165]. One study reported that CD38 activity can be inhibited by  
14 micromolar concentrations of flavonoids (luteolinidin, kuromanin, luteolin) [166]. Novel  
15 approaches to manipulate CD38-mediated cADPR metabolism in vivo were recently proposed  
16 [167].

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

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

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

3 Recently, sildenafil was reported to induce OT release from the pituitary [177], but this  
4 effect is mediated through modulation of phosphodiesterase activity and has no direct  
5 relationship to Ca<sup>2+</sup>-dependent OT release.

### 7 *Conclusion*

8 A vast volume of recent data indicate that CD38-controlled homeostasis of NAD<sup>+</sup> and CD38-  
9 catalyzed cADPR formation are the important components of signal transduction pathways  
10 implicated in the regulation of pivotal brain cell functions (intercellular communication,  
11 excitability, proliferation, differentiation, migration, apoptosis) and neuroplasticity, in general. It  
12 is known that CD38 expression and activity in the brain are frequently altered by impaired  
13 interaction between neurons and glial cells at the sites of acute and/or chronic neurodegeneration,  
14 which may lead to pathological conditions during brain development and neuroinflammation [5,  
15 7, 129, 178, 179, 180]. Furthermore, our recent findings regarding CD38-controlled  
16 neurosecretory activity of hypothalamic and pituitary cells [40, 92, 181, 182] open a new chapter  
17 in elucidating the role of CD38 in integrative brain functions and provide novel approaches to  
18 identify molecular targets for the pharmacological treatment of disorders associated with social  
19 behavioral alterations.



- 1 **List of abbreviations**
- 2 ADPR – adenosine diphosphate ribose
- 3 ASD – autism spectrum disorder
- 4 ATP - adenosine triphosphate
- 5 AVP – arginine vasopressin
- 6 cADPR – cyclic adenosine diphosphate ribose
- 7 CD38 – NAD<sup>+</sup>-glycohydrolase/CD38
- 8 NAD<sup>+</sup> - nicotinamide adenine dinucleotide
- 9 NAADP - nicotinic acid adenine dinucleotide phosphate
- 10 NADH – nicotinamide adenine dinucleotide reduced
- 11 OT - oxytocin
- 12 OTR – oxytocin receptor
- 13 P2X7 – purinergic receptor 7
- 14 PARP – poly(adenosine diphosphate ribose)polymerase
- 15 PVN – paraventricular nucleus
- 16 RyR – ryanodine receptor
- 17 SNARE – soluble NSF attachment receptor
- 18 SON – supraoptic nucleus
- 19 TNF $\alpha$  – tumor necrosis factor  $\alpha$
- 20 TRPM – transient receptor potential cation channel, subfamily M, member 2
- 21 VGCC – voltage-gated calcium channel
- 22
- 23
- 24
- 25

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26

1 **Figure legends:**

2

3 **Fig.1.** CD38-controlled mechanisms in the regulation of social behavior. A schematic representation of a  
4 key role of CD38 in different social behavior outputs by molecular pathways of oxytocin secretion, including NAD<sup>+</sup>  
5 and NADP transformation, cyclic ADP-ribose formation, and Ca<sup>2+</sup> release from ryanodine receptors.

6

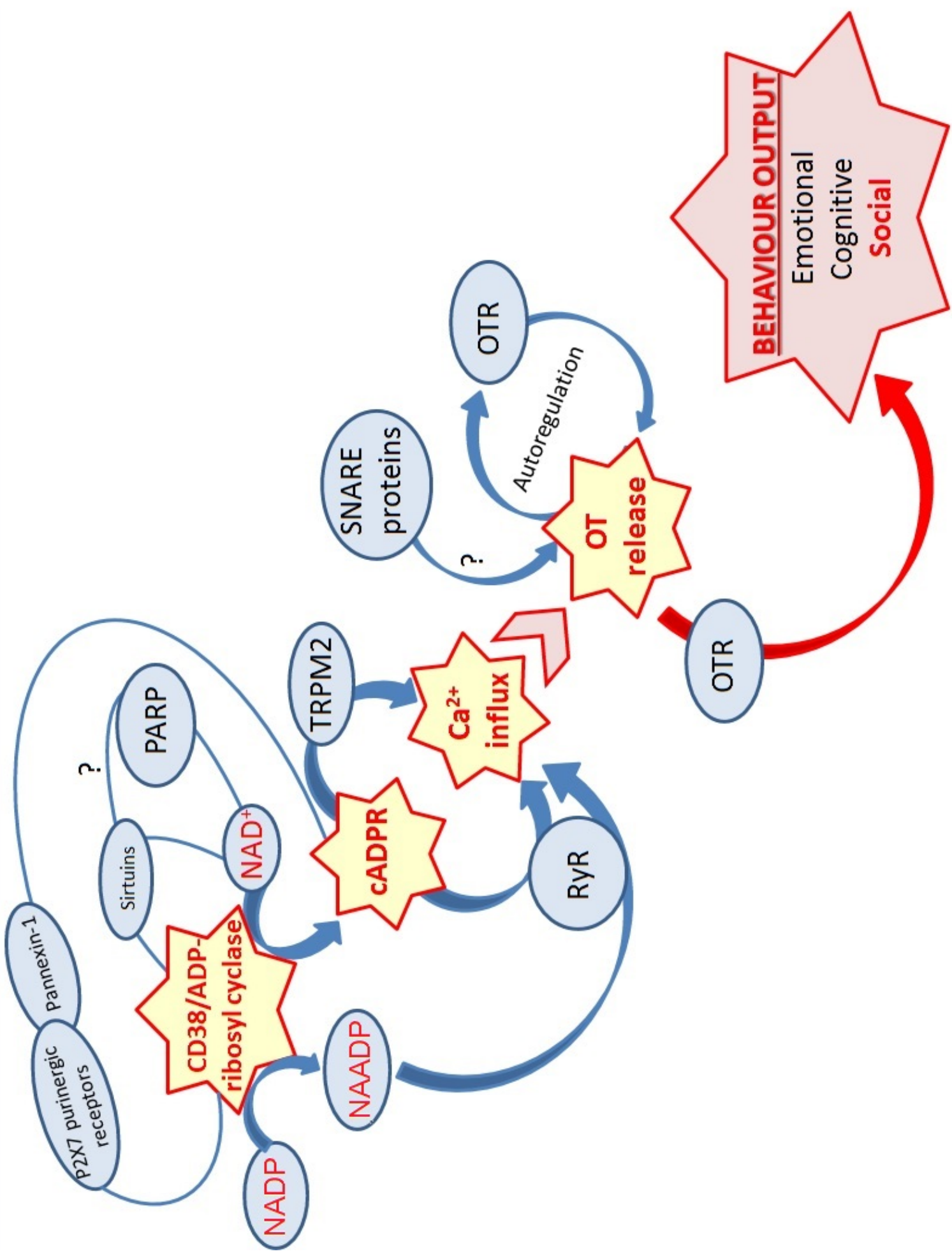
7

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

10

11





## HEALTHY

Normal  
CD38 gene expression

CD38/ADP-ribosyl cyclase

OT receptors

PKC activation

cADPR formation

Ca<sup>2+</sup> -mobilization

OT release ↑

OT  
level

AVP

Autoregulation

## BEHAVIOUR

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

Ca<sup>2+</sup> -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)

## GENETIC

## CELLULAR LEVEL