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Towards the convergent therapeutic potential of G protein-coupled receptors in autism spectrum disorders

Anil Annamneedi^{1,2,3}  | Caroline Gora¹ | Ana Dudas¹ | Xavier Leray^{1,4}  |
Véronique Bozon¹ | Pascale Crépieux^{1,4}  | Lucie P. Pellissier¹ 

¹Team Biology of GPCR Signaling Systems (BIOS), CNRS, IFCE, INRAE, Université de Tours, Nouzilly, France

²LE STUDIUM Loire Valley Institute for Advanced Studies, Orléans, France

³Department of Biotechnology, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, Tamil Nadu, India

⁴Inria, Inria Saclay-Ile-de-France, Palaiseau, France

Correspondence

Lucie P. Pellissier, Team Biology of GPCR Signaling Systems (BIOS), CNRS, IFCE, INRAE, Université de Tours, PRC, F-37380, Nouzilly, France.

Email: lucie.pellissier@inrae.fr

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Abstract

Autism spectrum disorders (ASDs) are diagnosed in 1/100 children worldwide, based on two core symptoms: deficits in social interaction and communication, and stereotyped behaviours. G protein-coupled receptors (GPCRs) are the largest family of cell-surface receptors that transduce extracellular signals to convergent intracellular signalling and downstream cellular responses that are commonly dysregulated in ASD. Despite hundreds of GPCRs being expressed in the brain, only 23 are genetically associated with ASD according to the Simons Foundation Autism Research Initiative (SFARI) gene database: oxytocin OTR; vasopressin V_{1A} and V_{1B}; metabotropic glutamate mGlu₅ and mGlu₇; GABA_{B2}; dopamine D₁, D₂ and D₃; serotonergic 5-HT_{1B}; β₂-adrenoceptor; cholinergic M₃; adenosine A_{2A} and A₃; angiotensin AT₂; cannabinoid CB₁; chemokine CX₃CR1; orphan GPR37 and GPR85; and olfactory OR1C1, OR2M4, OR2T10 and OR52M1. Here, we review the therapeutic potential of these 23 GPCRs, as well as 5-HT_{2A} and 5-HT₇, for ASD. For each GPCR, we discuss its genetic association, genetic and pharmacological manipulation in animal models, pharmacopoeia for core symptoms of ASD and rank them based on these factors. Among these GPCRs, we highlight D₂, 5-HT_{2A}, CB₁, OTR and V_{1A} as the more promising targets for ASD. We discuss that the dysregulation of GPCRs and their signalling is a convergent pathological mechanism of ASD. Their therapeutic potential has only begun as multiple GPCRs could mitigate ASD.

KEYWORDS

autism spectrum disorder, brain, G protein-coupled receptors, neurotransmitter, signalling pathways, social interaction

Abbreviations: ASD, autism spectrum disorder; cKO, conditional knock-out; CNV, copy number variant; FXS, fragile X syndrome; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; NAM, negative allosteric modulator; OR, olfactory receptor; PAM, positive allosteric modulator; PD, Parkinson's disease; RTT, Rett syndrome; UTR, untranslated region.

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1 | INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder diagnosed around the age of 3 with a worldwide prevalence of around 1/100 child births (Zeidan et al., 2022). Core clinical symptoms are defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013): social interaction and communication deficits and stereotyped behaviours, restrained or compulsive activities and interests. ASD is often associated with comorbid symptoms, such as anxiety, epilepsy, sleep disturbances, motor coordination impairment, gastrointestinal disorders, or intellectual disability. Its aetiology is partially resolved, because 70% of cases remain sporadic, highlighting the polygenic, epigenetic and environmental complexity of the disease (Cheroni et al., 2020; Lacivita et al., 2017; Saxena et al., 2020). To date, no pharmacological treatment exists for the core social symptoms of ASD. Currently, only **risperidone** and **aripiprazole** antipsychotics are approved for irritability, aggressive behaviours and self-injury comorbid symptoms, and they frequently present side effects (McCracken et al., 2002; McDougle et al., 2005; Owen et al., 2009; Varni et al., 2012). Administration of antidepressant compounds (e.g., **fluoxetine**) improves stereotyped and repetitive behaviours and compulsive activities in patients, despite having limited efficacy and important side effects (Lacivita et al., 2017). Early behavioural intervention programmes have shown some efficacy on core social symptoms. However, they are costly, they are highly demanding to children and their families, they need intensive training, they should start as early as possible and their outcome remains uncertain (Estes et al., 2015; Linstead et al., 2017; Smith et al., 2015). Therefore, the discovery of new and effective drugs relies on the identification of new targets that remain the main gaps in the ASD field so far.

Various types of ionotropic (**NMDA**, **nicotinic acetylcholine** and **GABA_A** receptors), metabotropic or G protein-coupled receptors (**GPCRs**) (**glutamate**, **GABA_B**, **serotonin** and **oxytocin (OT)-vasopressin** systems), **Toll-like (TLR)** and **insulin growth factor 1 (IGF1)** receptors or intracellular signalling molecules (**mTOR**, **ROCK** and **GSK3B**) have been targeted in ASD preclinical and clinical trials (Lacivita et al., 2017). So far, these clinical trials have failed at the phase 2b/3 stage of clinical trials, because of an important placebo effect, lack of efficacy, and/or the large heterogeneity of patients (Daniels et al., 2023; Lacivita et al., 2017). New advances need to overcome these challenges. First, subtypes of patients determined on their genetic or neuropathological mechanism profile should be tested rather than patients from the whole spectrum. Second, the identification of robust therapeutic targets and the development of potent drugs should thwart the placebo effect. More than a thousand candidate genes are listed in the Simons Foundation Autism Research Initiative (SFARI) database (<https://gene.sfari.org>), and rather than a single mutation, accumulation of deleterious alleles and copy number variants (CNVs) may underlie the pathological process among affected individuals (Manoli & State, 2021). Recent genome wide association studies of large ASD cohorts robustly identified hundreds of candidate genes that fall in two main convergent neurobiological mechanisms,

namely 'gene expression regulation' or 'neuronal communication, signalling or plasticity' (De Rubeis et al., 2014; Satterstrom et al., 2020; Pintacuda et al., 2023). GPCRs are master regulators of these convergent mechanisms. In addition, their fine-tuned pharmacology and diversity may represent the greatest therapeutic potential for ASD, leading to successful clinical trials. In this review, we demonstrate why this receptor family meets all criteria of convergent therapeutic targets for ASD.

1.1 | GPCRs and their signalling are dysregulated in ASD

Canonical GPCRs display an extracellular domain composed of the N-terminus and three extracellular loops (EL1–3) that connect seven transmembrane (TM) helices. Occupancy of the ligand binding pocket leads to conformational changes in the helices that transmit activation to the intracellular domain, that is composed of three intracellular loops (IL1–3) and a C-terminus region with an eighth helix parallel to the plasma membrane (Figure 1). This intracellular domain is involved in the recruitment and activation of direct transducers that activate downstream intracellular signalling. GPCRs are translated inside the membrane of the endoplasmic reticulum (ER) and are actively exported to the plasma membrane. Due to their molecular complexity, they are often prone to misfolding or lack of ER export, which may result in cell toxicity (Beerepoot et al., 2017). Most GPCRs and their transducers are expressed in the central nervous system (CNS) (Marti-Solano et al., 2020; Regard et al., 2008), with over 200 variants in GPCR genes associated with ASD (SFARI). Furthermore, transcriptomic data and meta-analysis from prefrontal cortex tissue showed that GPCRs are the most frequently dysregulated genes in ASD and revealed around 200 GPCRs potentially linked to ASD (Hormozdiari et al., 2015; Monfared et al., 2021). Among these genes, serotonin **HTR2A**, adenosine **ADORA1** and adrenergic **ADRA1D** are the most dysregulated.

GPCRs and their downstream signalling pathways are also affected in ASD. Upon activation, GPCRs couple to several heterotrimeric G proteins (comprising α , β and γ subunits) and recruit β -arrestins that impact on the kinetics of intracellular signalling pathways, such as extracellular signal-regulated kinases (**ERKs**) or promote receptor endocytosis (Figure 1a). $G_{\alpha_{s/olf}}$ protein activates **adenylyl cyclases** that hydrolyse **ATP** into **cAMP**, which is degraded by **phosphodiesterases** into **AMP**. cAMP activates the exchange protein activated by cAMP (**EPAC**), **calcium ion channels** (Ca_v) and protein kinase A (**PKA**). Conversely, $G_{\alpha_{i/o}}$ inhibits adenylyl cyclases and cAMP production and mostly modulates calcium channels. $G_{\alpha_{q/11}}$ proteins activate **phospholipases C β** , which hydrolyses phosphatidylinositol-4,5-bisphosphate (**PIP₂**) into diacylglycerol (DAG) and inositol-1,4,5-triphosphate (**IP₃**). Released **IP₃** binds to **ryanodine receptors** (RyRs) on the ER, which leads to calcium release from this subcellular location. Both calcium and DAG activate protein kinase C (**PKC**) and its effectors, such as **Akt** (protein kinase B, PKB) or ERK. $G_{\alpha_{12/13}}$ activates Rho guanine nucleotide exchange factor (**GEF**) and RhoA, which

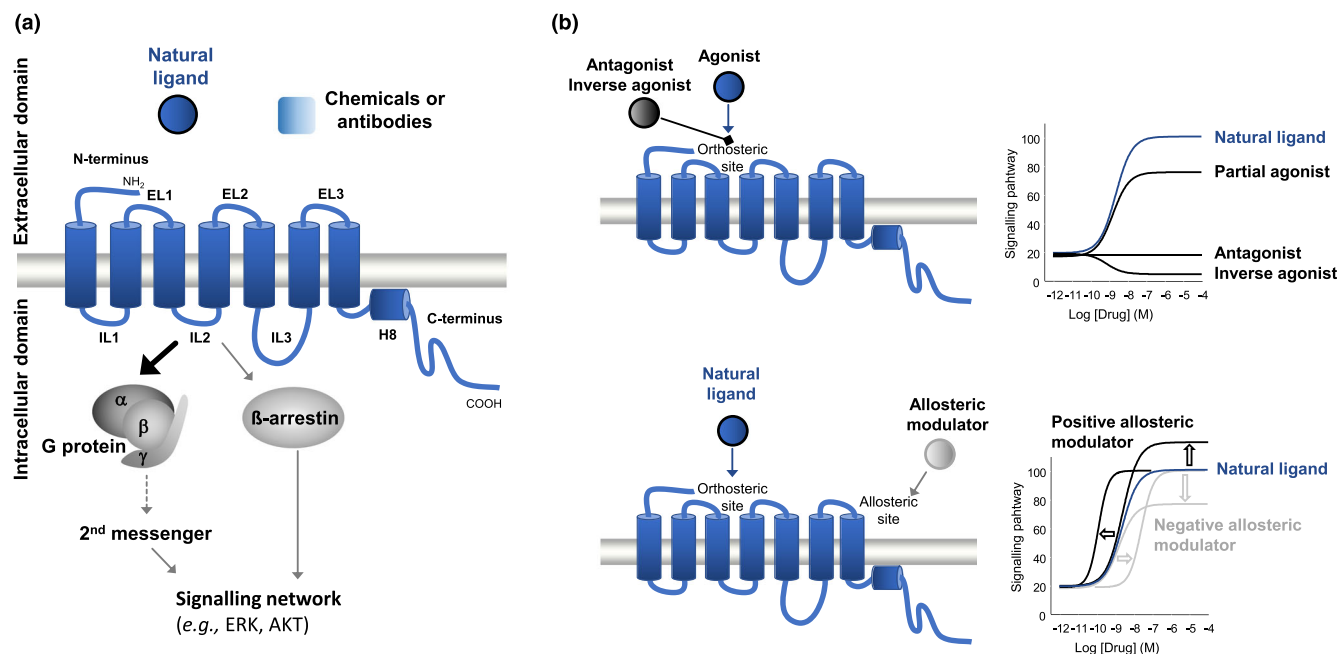


FIGURE 1 G protein-coupled receptor (GPCR) signalling and pharmacology. (a) GPCRs are composed of seven transmembrane domains connecting the extracellular domain (N-terminus and extracellular loops [EL] 1–3) where various ligands bind the receptor (e.g., natural ligands and chemicals/antibodies), to the intracellular domain (intracellular loops [IL] 1–3, helix H8 and C-terminus) that recruit the direct transducers, which activate a signalling network (e.g., Akt and extracellular signal-regulated kinase [ERK]) and integrated cellular processes. A biased ligand has the particular pharmacological profile to favour signalling pathways within the complex receptor signalling network. Here, a G protein-biased ligand that favours G protein coupling (black arrow) over β -arrestin recruitment (grey arrow) is shown. (b) GPCRs display a rich pharmacopoeia of ligands, with agonists, antagonists and inverse agonists that bind to the orthosteric binding site (e.g., the binding site of the natural ligand) to, respectively, activate or prevent the agonist binding and inactivate the receptor. Other ligands bind to allosteric sites that increase or decrease the efficacy and/or potency of the natural ligand, respectively, called positive or negative allosteric modulators.

acts on the cytoskeleton to promote neurite formation. G $\beta\gamma$ proteins also participate in downstream signalling through activation of G protein-coupled inwardly rectifying potassium channels (GIRK) and other ion channels. The most affected transducers in ASD are G α_i and G $\alpha_{12/13}$ proteins (Monfared et al., 2021). Following activation, GPCRs are internalised in intracellular compartments (e.g., endosomes) together with their transducers and participate in the signalling cascades (Villardaga et al., 2023). Downstream intracellular signalling networks lead to integrated cellular processes, translation of specific mRNAs (León et al., 2014; Musnier et al., 2012; Tréfier et al., 2018) and gene transcription. The profile of gene expression and transcript translation depends on the specific activation of GPCRs and the cellular context. For example, G α_s -dependent GPCRs activate the transcription factor cAMP-responsive element binding protein (CREB), among many others. Globally, GPCRs are key upstream regulators of Wnt/ β -catenin, ERK, PKC, PI3K/Akt, CREB, PTEN and mTOR intracellular pathways that are convergently dysregulated in ASD (Gazestani et al., 2019; O'Roak et al., 2012; Pintacuda et al., 2023). In an attempt to estimate their potential as master regulators of genes involved in ASD, we confronted 'Kyoto Encyclopedia of Genes and Genomes' (KEGG) pathways, 'Reactome' pathways, 'Gene Ontology' (GO) terms and our knowledge (Supporting Information) to the 1045 ASD candidate genes from the SFARI list. In this list, we identified 23 GPCRs and 129 genes linked to GPCRs (Figure 2 and

Table S1), accounting for at least 15% of all the candidate genes. Interestingly, two orphan GPR37 and GPR85 and four olfactory OR1C1, OR2M4, OR2T10 and OR52M1 receptors with relatively unknown functions in the brain belong to this list. This proportion of candidate genes might increase with future knowledge on signalling and cellular processes under the control of GPCRs, especially their effect on translation and transcription.

1.2 | GPCRs are relevant druggable targets for ASD

GPCRs respond to diverse natural signals ranging from photons, amino acids, peptides up to large glycosylated proteins. This receptor family comprises more than 800 GPCRs, subdivided into five classes according to the International Union of Basic & Clinical Pharmacology (IUPHAR) nomenclature and classification (Alexander et al., 2021): the largest rhodopsin-like class A, the secretin/class B, the glutamate/class C, the Frizzled class and the adhesion class. Sensory GPCRs (olfactory, vision, taste and pheromone receptors), which account for most GPCR genes, are included mostly in class A and a few in class C. Although hundreds of GPCRs remain without any identified ligand, 24% of these so-called 'orphan receptors' (including olfactory receptors [ORs]) are dysregulated in ASD. In addition to natural ligands,

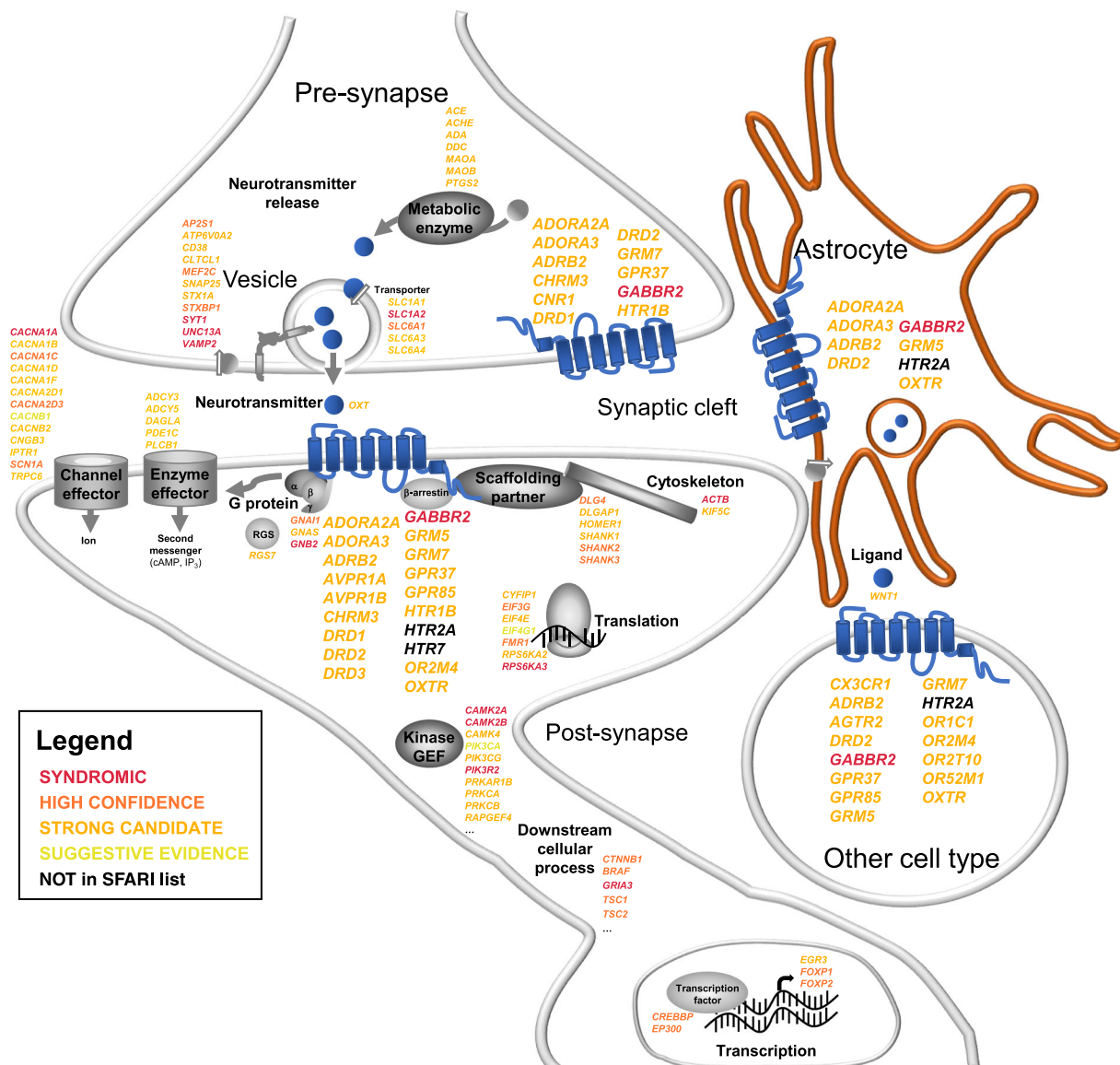


FIGURE 2 At least 15% of Simons Foundation Autism Research Initiative (SFARI) genes participate in G protein-coupled receptor (GPCR) activity and signalling processes. GPCR ligands are synthesised by metabolic enzymes, loaded by their transporters into synaptic vesicles that fuse with the presynaptic membrane upon increase of intracellular calcium, leading to neurotransmitter release in the synaptic cleft. These neurotransmitters or ligands are either recaptured by membrane transporters, degraded or bind and activate their cognate GPCR. Even in the absence of ligand, GPCRs are present in preformed higher complexes with scaffolding partners, channels, cytoskeleton and signalling transducers. Upon GPCR activation, transducers activate enzyme and channel effectors to produce second messengers. These second messengers activate major kinases and guanine nucleotide exchange factor (GEF) that tune up or down downstream cellular processes, including translation and transcription. Syndromic (in red), high confidence (Category 1 in dark orange), strong candidate (Category 2 in light orange) and suggestive evidence (Category 3 in green) genes are coloured according to SFARI gene scoring and colour code (gene.sfari.org/about-gene-scoring; Table S1) and additional GPCR genes are in black. GPCRs are localised at presynaptic and/or postsynaptic compartment of neurons, in astrocytes or in unknown or other cell types (see text and Figure 3 for their widespread or specific expression pattern in the different structures).

drugs can modulate GPCR activity, inducing diverse pharmacological profiles (Figure 1b). They can either be chemical compounds, peptides, large autoantibodies and more recently, antibody fragments (Mujic-Delic et al., 2014). Orthosteric agonists, inverse agonists and antagonists occupy the natural ligand binding pocket and activate, inactivate the receptor and/or prevent the binding of the endogenous ligand respectively. In contrast, by binding to allosteric sites, positive

(PAM) or negative (NAM) allosteric modulators enhance or decrease GPCR activity only in the presence of agonists. While their intrinsic instability has been a major issue for resolving their three-dimensional structure, many GPCR structures in inactive, intermediate and active conformations became available with the development of cryo-electron microscopy. These recent advances facilitate in silico design of more selective drugs. Finally, GPCRs are modulated by interacting

partners. They can form cell-specific homo- or hetero-oligomers depending on the GPCR composition and subcellular localisation in a particular cell type. Each GPCR in the oligomer, or co-expressed in the same cell, may influence the signalling network of other GPCRs, opening a new area of GPCR pharmacology. Their activity also is modulated through reciprocal functional interactions with scaffolding protein partners (e.g., Shank1–3), **ion channels** and **tyrosine kinase receptors**. Different ligands may favour one coupling or protein partner interaction, leading to what is called ‘signalling bias’ (Figure 1a). This pharmacological property of GPCRs may be of great interest for therapeutic applications, because one biased drug can promote one signalling cascade over all others, hence possibly avoiding side effects. Considering their unique characteristics, GPCRs offer many levels of leveraging as therapeutic targets for neurological disorders. More than 30% of the drugs approved on the global market target GPCRs in various disorders, including neurological conditions by 20% of them (Alexander et al., 2021; Hauser et al., 2017). This proportion will increase because nearly half of GPCRs in the CNS remain orphan. So far, no pharmaceutical agent has reached the market to improve core symptoms of ASD. The few GPCRs that have been tested in clinical trials are **mGlu₅**, **GABA_B**, **V_{1A}** and **CB₁**, all of which are listed in the SFARI database (Table S1). Therefore, the therapeutic potential of GPCRs has only begun. In this review, we explored the therapeutic values of 23 GPCRs identified above and in the SFARI list. We further included 5-HT_{2A} and 5-HT₇ receptors because both receptors are associated with ASD and they are listed in another autism database (<http://autism.mindspec.org/autdb>). We studied the potential deleterious effect of different variants associated with ASD and their dysregulation in ASD post-mortem tissues to conclude on their potential

contribution in the aetiology of ASD (Table S2). We addressed the behavioural consequences of their genetic and pharmacological manipulation in animal models (Table S3) and whether these models fulfil the validity criteria defined for psychiatric diseases applied to ASD (Chadman et al., 2019). We analysed their pharmacological landscape (e.g., specific drugs on the market or in clinical trials), the availability of GPCR structures and where available, the results of clinical trials (Table S4). We also reported their known downstream signalling and their interacting partners (Table S5). Finally, we reviewed their expression profile in the different brain cell types and structures (widespread vs. specific localisation; Figures 2 and 3 and Table S6). Based on this evidence, we conclude on the therapeutic potential of 25 candidate GPCRs (Figure 4).

2 | OXYTOCIN AND VASOPRESSIN RECEPTORS

Oxytocin (OT) was first described in the 1960s for its effects on reproduction and maternal behaviours (Froemke & Young, 2021). In the mammalian CNS, OT and its paralogue **arginine vasopressin** (AVP) modulate social recognition and memory, defensive behaviours, trust, empathy and maternal attachment (Macdonald & Macdonald, 2010; Rae et al., 2022). Mice lacking OT peptide (Oxt knock-out [KO] mice) display aggressive and anxious-like behaviours and social memory impairment (Table S3) (DeVries et al., 1997; Ferguson et al., 2000; Ragnauth et al., 2005; Winslow et al., 2000), but these phenotypes vary across laboratories and parental genotypes. Administration of OT in the lateral ventricles or in the medial amygdala of Oxt KO mice

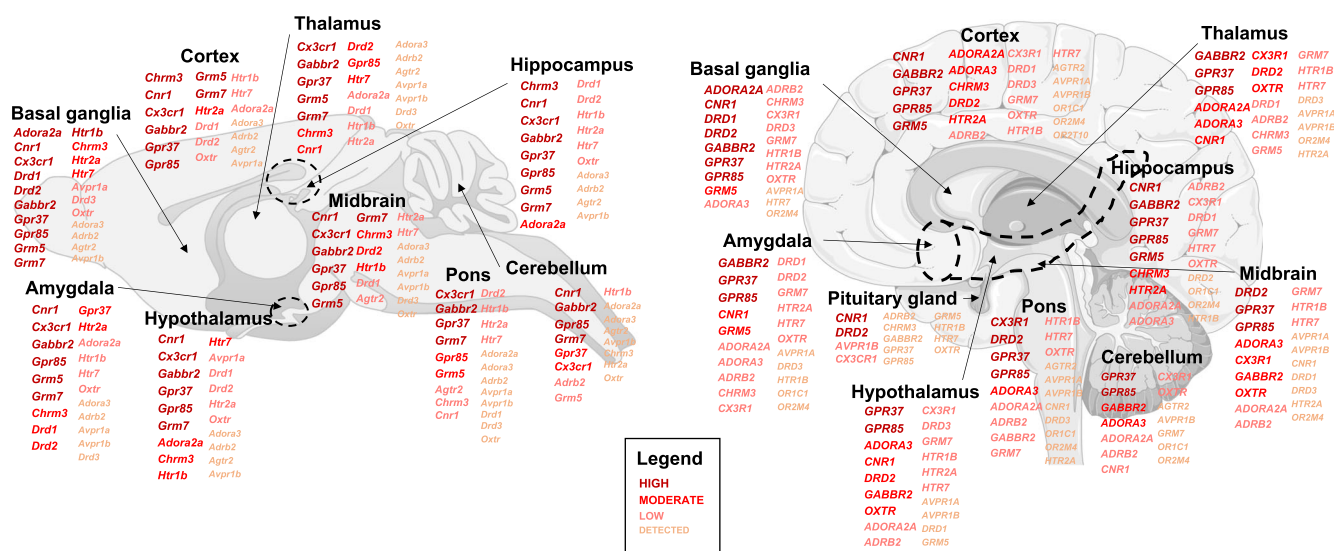


FIGURE 3 G protein-coupled receptor (GPCR) localisation and expression in the human and mouse brain. Relative expression and localisation of the 25 GPCRs are presented on the murine and human brain templates from the protein atlas database (www.proteinatlas.org). After comparison with protein expression for consistency (only available for the 5-HT_{1B}, 5-HT_{2A}, 5-HT₇, A_{2A}, V_{1B}, M₃, CB₁, CX₃CR₁, D₂, GABA_{B2} and GPR37), relative RNA levels are represented as high (brown, over 20 normalised transcript expression values [nTPM]), moderate (red, 10–20 nTPM), low (pink, 2–10 nTPM) and just detectable (light pink, 0.1–2 nTPM) expression in the CNS (expression in the other organs are indicated in Tables S4 and S6). Brain templates are from Servier Medical Art.

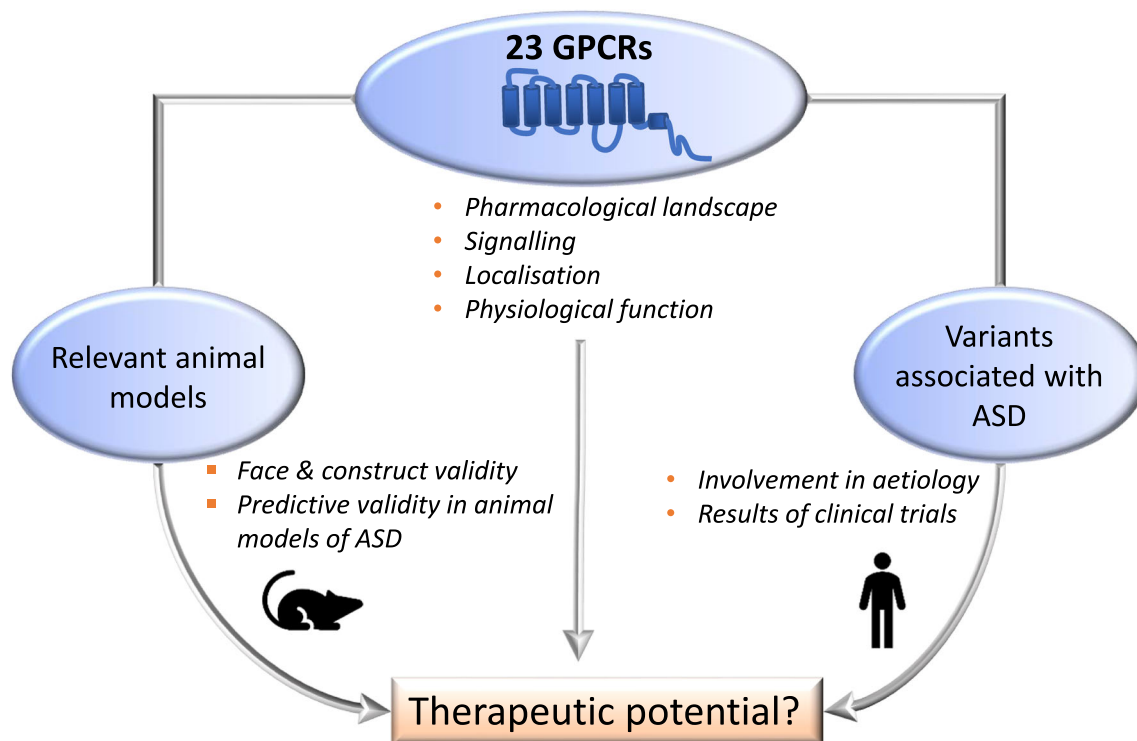


FIGURE 4 Workflow to assess the relevance to autism spectrum disorder (ASD) of G protein-coupled receptor (GPCR) genes extracted from the Simons Foundation Autism Research Initiative (SFARI) database and their therapeutic potential.

restores anxious-like behaviour and social recognition (Ferguson et al., 2001; Mantella et al., 2003). Brattleboro rats, which carry a frameshift deletion in the *Avp* gene and loss of AVP, display social preference impairment (Surget & Belzung, 2008) whereas *Avp* full deletion in mice is lethal in the absence of peripheral AVP administration (Zelena, 2017).

Many studies have investigated the therapeutic potential of either OT or AVP for ASD, because they regulate social behaviours and OT plasma levels are lower in ASD children (Cataldo et al., 2018; John & Jaeggi, 2021; Rae et al., 2022). Administration of OT or AVP normalises social skills and/or stereotyped behaviours in *Cdh8*, *Pogz*, *Cntnap2*, *Oxtr*, *Magel2* and *Fmr1* KO mouse models of ASD but not in 16p11.2 deletion and *Shank3* KO mice (Cherepanov et al., 2021; Kitagawa et al., 2021; Lindenmaier et al., 2022; Meziane et al., 2015; Peñagarikano et al., 2015; Sala et al., 2011). Differences in dose, acute versus chronic treatment, and/or way of administration in these studies prevent generalising the beneficial effects reported. Furthermore, chronic exposure to OT abolishes sociability and induces stereotyped behaviours in wild-type (WT) animals (Bales et al., 2013; Zhang et al., 2015). Intranasal administration of OT at low dose improves emotion recognition in young men with ASD (Guastella, Einfeld, et al., 2010), increased trust and interactions in adults with ASD (Andari et al., 2010), and reduced severe repetitive behaviours (Hollander et al., 2003). Unexpectedly, administration of OT failed to improve social abilities over placebo in phase 2 clinical trials and induced frequent side effects in several studies (Leppanen et al., 2018; Sikich et al., 2021; Witte et al., 2022). In fact, OT

administration may not be effective in all patients but rather only in subtypes of patients with OT deficiency, or should be combined with behavioural intervention programmes (Daniels et al., 2023). Interestingly, administration of AVP in healthy men improves the recognition of happy and angry social faces compared with neutral faces (Guastella, Kenyon, et al., 2010). A phase 2 clinical trial showed that 4 weeks of intranasal administration of AVP in 30 ASD children improved their social skills and reduced anxiety and repetitive behaviours, with minimal side effects (Parker et al., 2019). Whereas AVP remains to be tested in a large cohort of patients, the first results indicate that it might be more efficient than OT to provide pro-social effects. Thus, despite mixed results, the OT-AVP family remains of interest for ASD. Actually, OT and AVP might not be ideal treatments. Both peptides bind and activate with nanomolar affinity the four highly conserved OT receptor (OTR), vasopressin V_{1A} and V_{1B} receptors in the CNS and V_2 receptor in the periphery. Therefore, in the following section, we review the therapeutic potential of OTR, V_{1A} and V_{1B} for ASD.

2.1 | OTR

The OTR gene (*OXTR*) spans over four exons and encodes five splicing transcript variants that differ in their 5' untranslated region (UTR) leading to only one receptor, OTR. Decades of research have identified several agonists of OTR (Table S4), such as the potent peptide agonist **Thr⁴Gly⁷-OT** (TGOT) (Elands et al., 1988), the G_{α_q} -biased

agonist **carbetocin** (Passoni et al., 2016) and the first chemical agonist **LIT001** (Frantz et al., 2018). However, all these ligands also bind to vasopressin receptors. OTR expression is found in CNS regions critical for the regulation of social behaviour and emotion (Figure 3) and might be sexually dimorphic depending on the brain region and species (Dumais et al., 2013). In humans, *OXTR* transcript levels peak after birth, during all infancy and reduce in adolescents and adults (Kang et al., 2011). This corresponds to oxytocinergic neuron development in the same critical period in mice (Soumier et al., 2022). OTR is involved in complex social behaviours, like maternal care, social recognition, aggression, mating and pair bonding. It also favors empathy and can exert anxiolytic effects (Jurek & Neumann, 2018). *Oxtr* KO mice or conditional KO (cKO) in forebrain neurons have an autism-like phenotype, with both social and communication deficits and stereotyped behaviours, whereas heterozygous mice express only social deficits (Table S3) (Lee et al., 2008; Pobbe et al., 2012; Sala et al., 2013; Takayanagi et al., 2005). However, results in self-grooming, anxious-like behaviours and cognitive inflexibility vary through laboratories or mouse lines. In addition, *Oxtr* KO in monogamous prairie voles leads to deficits only in social novelty and increased compulsive behaviours but no impairment in social interactions, vocalisations or maternal behaviour (Berendzen et al., 2023; Horie et al., 2019). Interestingly, intraventricular administration of either OT or AVP restores the social deficits in *Oxtr* KO mice via V_{1A} receptors (Sala et al., 2011). This finding highlights the crosstalk within this GPCR family. More than 20 variants in the *OXTR* gene have been associated with ASD (Table S2). Interestingly, variants are mostly located outside the receptor coding region, leading to potential receptor expression dysregulation.

2.2 | Vasopressin V_{1A} and V_{1B} receptors

AVP is well known as the antidiuretic hormone via the activation of V_2 receptors, but also binds to V_{1A} and V_{1B} receptors in the CNS. *AVPR1A* and *AVPR1B* genes encode only one transcript variant each and their V_{1A} and V_{1B} receptors, respectively.

V_{1A} receptor is involved in maternal care, social recognition, affiliative behaviour and pair bonding (Koshimizu et al., 2012). Administration of the V_{1A} antagonist **d(CH₂)₅Tyr(Me)AVP** into the medial amygdala of rats affects maternal memory (Nephew & Bridges, 2008). Furthermore, *Avpr1a* KO mice and hamsters display defective social memory, interaction and communication, reduced anxious-like behaviours and inconsistent levels of aggressive behaviour across species (Table S3) (Bielsky et al., 2004, 2005; Egashira et al., 2007; Taylor et al., 2022; Wersinger et al., 2007). Several studies have associated the length of the promoter and the 5'UTR of the *AVPR1A* gene, which regulate V_{1A} expression levels, with important social deficits. Indeed, most variants associated with ASD risk are identified in these regions (Table S2), which influence human relationships and altruism (Meyer-Lindenberg et al., 2009; Walum et al., 2008), personality in non-human primates (Hopkins et al., 2012) or social behaviour in rodents (Hammock et al., 2005). Recently, administration of the selective V_{1A} antagonists, either **RG7713** or **balovaptan**, improved

socialisation and communication in men with ASD (Bolognani et al., 2019; Schnider et al., 2020; Umbricht et al., 2017). Despite these promising results in phase 2 clinical trials, balovaptan failed to improve social abilities over placebo in phase 3 trials (Jacob et al., 2022). Further investigations are still required to understand the therapeutic potential of the V_{1A} receptor because it remains unclear if either activation or inhibition would improve social skills.

V_{1B} receptor deletion in mice (*Avpr1b* KO) leads to increased dominance, impaired aggressive behaviour, vocalisations, social motivation and memory (Table S3) (Albers, 2012; Scattoni et al., 2008; Wersinger et al., 2007). Three independent studies have identified variants in the *AVPR1B* gene linked to ASD (Table S2), mood disorders and aggressive behaviour. Accordingly, administration of the antagonist **nelivaptan** (Table S4) normalises aggressive, chasing and anxious-like behaviours in rodents (Blanchard et al., 2005; Salomé et al., 2006). Oral administration of nelivaptan is currently in clinical trials for anxiety and depression.

In conclusion, data in animals and humans support that OTR and V_{1A} receptors may be involved in the aetiology of autism and are major therapeutic targets for ASD, whereas V_{1B} might be of interest for aggressive and anxious-like behaviours. Nevertheless, so far, clinical trials failed to bypass the placebo effect observed in patients. Regarding their conservation, their crosstalk and the existence of homo- and hetero-oligomers of these three receptors (Dekan et al., 2021; Terrillon et al., 2003), further investigations are needed to identify the most suitable targets (e.g., which receptor or oligomer, which signalling pathway).

3 | METABOTROPIC GLUTAMATE AND GABA RECEPTORS

Glutamate and γ -aminobutyric acid (**GABA**) are the two major neurotransmitters in the CNS. They bind to their cognate class C GPCRs, the metabotropic glutamate mGluRs and GABA_B receptors, respectively. In contrast to class A GPCRs, glutamate and GABA bind to the large extracellular N-terminal domain called the Venus Fly Trap, which closes upon activation. In addition, they form constitutive oligomers, which lead to specific rearrangements of subunits during activation. They are mainly expressed in presynaptic and postsynaptic compartments in the brain (Figures 2 and 3) and participate in the excitatory and inhibitory balance in the CNS (Nelson & Valakh, 2015), which is hypothesised to be dysregulated in ASD.

3.1 | mGlu₅

The *GRM5* gene encodes two splice variants of mGlu₅ (mGlu_{5a} and mGlu_{5b}), with the mGlu_{5b} receptor expressed predominantly during the adult stage (Table S6). Activation of mGlu₅ induces synaptic plasticity, which requires de novo mRNA translation through phosphorylation of eukaryotic initiation factor-2 (eIF2 α) (Di Prisco et al., 2014). *Grm5* KO mice display ASD-related core symptoms (Table S3), deficits

in social interaction, increased stereotyped and compulsive behaviours (Xu et al., 2021). Furthermore, they show hyperactivity, reduced anxious-like behaviours and sensorimotor gating deficits (Brody et al., 2004; Xu et al., 2021). Five independent studies have identified over 20 rare variants in the *GRM5* gene of ASD patients (Table S2), highlighting *GRM5* as one of the most susceptible genes in ASD (Nisar et al., 2022). Alterations in mGlu₅ receptor signalling or expression affect synaptic and neuronal development, trademarks of ASD and intellectual disability (D'Antoni et al., 2014). Thus, administration of the selective antagonist **mavoglurant** and the NAM **basimglurant** in the fragile X syndrome (FXS) mouse model (*Fmr1* KO) (Table S4) improved its broad range of phenotypes (Scharf et al., 2015). However, administration of these compounds failed to provide similar therapeutic benefits in FXS patients in phase 2b/3 clinical trials (Jacquemont et al., 2011, 2014; Lozano et al., 2015). These compounds are still in clinical trials for dyskinesia, obsessive-compulsive disorders and depression. Altogether, data favour the role of mGlu₅ in ASD pathogenesis. However, targeting mGlu₅ with a selective negative allosteric modulator did not pass the placebo effect in patients. Variations in mGlu₅ expression levels in patients might result from insufficient inhibition of excitatory outputs. Indeed, higher mGlu₅ protein expression was reported in different brain regions including cerebellar vermis region and superior frontal cortex in children with ASD (Fatemi et al., 2011) whereas higher and lower expression was observed in the prefrontal cortex of patients with FXS and ASD patients, respectively (Chana et al., 2015; Lohith et al., 2013). In addition, *GRM5* is one of the GPCR genes that display the highest number of variants altering drug efficacy (Hauser et al., 2018).

3.2 | mGlu₇

The *GRM7* gene encodes two isoforms (mGluR_{7a} and mGluR_{7b}) that differ in their C-terminus, potentially leading to different protein-protein interactions and receptor coupling. mGlu₇ is expressed during the critical neurodevelopmental period, when it augments synapse formation and stabilisation (Song et al., 2021). Compared with other mGluRs, mGlu₇ has lower affinity for glutamate, hence is considered as an 'emergency brake'. mGlu₇ receptors are predominantly localised at presynaptic sites and regulate neurotransmitter release of glutamate or GABA. Interestingly, the non-selective mGlu_{4/6/7} agonist **L-AP4** negatively regulates glutamate or GABA release whereas the selective PAM **AMN082** positively affects the extracellular glutamate levels and negatively the GABA levels (Li et al., 2008; Manahan-Vaughan & Reymann, 1995; Mitsukawa et al., 2005). *Grm7* KO mice display intact social interaction, but social memory deficits (Table S3) (Fisher et al., 2020), which might be explained by their global learning defects. Overall, *Grm7* KO mice and mice carrying the Ile154Thr mGlu₇ mutation identified in ASD patients recapitulate comorbid symptoms, such as anxious-like behaviours, motor coordination impairment and seizures (Fisher et al., 2020, 2021). Twenty-one single-nucleotide polymorphisms (SNPs) and CNVs in the *GRM7* gene have been associated with ASD (Table S2). In particular, the Ile154Thr,

Arg658Trp and Thr675Lys mutants lead to reduced mGlu₇ surface expression and/or degradation. Dysregulated levels of mGlu₇ results in lack of axonal growth due to altered cAMP-PKA-ERK signalling and reduced number of synapses in primary neuronal cultures, which is rescued by the PAM AMN082 (Song et al., 2021). This is in line with reduced expression of mGlu₇ in post-mortem motor cortex samples from patients with Rett syndrome (RTT) and in a mouse model of RTT (*Mecp2* KO) (Bedogni et al., 2016; Gogliotti et al., 2017). In conclusion, mGlu₇ is a promising target because it could contribute to ASD pathogenesis. Furthermore, selective agonists or PAMs (e.g., **AMN082**) already exist and normalise comorbid symptoms in mouse models of ASD via the regulation of glutamate and GABA release and possibly in patients as well.

3.3 | GABA_B receptor

Metabotropic GABA_B receptors are obligatory hetero-oligomers of **GABA_{B1}** and **GABA_{B2}** through their C-terminus coiled-coiled domain. Presynaptic GABA_B receptors suppress neurotransmitter release whereas postsynaptic receptors induce slow inhibitory postsynaptic currents, which shunt the excitatory currents (Lüscher et al., 1997). GABA_B receptor deletion in mice (*Gabbr1-Gabbr2* double KO) leads to emotional disturbances and increased anxious- and anti-depressive-like behaviours (Table S3) (Mombereau et al., 2005). The effect of *Gabbr2* deletion alone has not been reported yet on core ASD symptoms. However, *Xenopus tropicalis* tadpole larvae carrying the Ala567Thr, Ser695Ile and Ile705Asn GABA_{B2} mutants identified in ASD and epileptic patients, display increased seizure-like behaviour and altered swimming patterns that are partially rescued by the selective GABA_B agonist **baclofen** (Yoo et al., 2017). Of note, when expressed heterologously in HEK293 cells, these three mutants disrupt GABA_B activation. Four genomic studies revealed an association of the *GABBR2* gene with ASD and RTT (Table S2). Administration of baclofen normalises the behaviours observed in a mouse model of FXS, in an idiopathic BTBR mouse model of ASD and in the C58 inbred mouse strain (Henderson et al., 2012; Silverman et al., 2015). Despite its first beneficial effect and its good tolerance in FXS and ASD patients, baclofen clinical trials were discontinued after phase 2 for its lack of efficacy (Berry-Kravis et al., 2012; Veenstra-VanderWeele et al., 2017). Nevertheless, baclofen is currently tested for irritability as an adjuvant therapy to risperidone (Mahdavinassab et al., 2019). Finally, in agreement with the unbalanced GABA and glutamate transmission hypothesis in ASD, reduced expression levels of the GABA_B receptor were observed in the cerebellum, in the cingulate cortex and in the fusiform gyrus of ASD patients (Fatemi et al., 2009; Oblak et al., 2010).

In conclusion, GABA_B receptor remains a promising therapeutic target for ASD according to the genomic and genetic data in patients and in animal models. However, its efficacy might be greater in combination with the administration of other ligands, such as risperidone for irritability or drugs targeting mGluRs to restore the excitatory and inhibitory balance.

4 | BIOGENIC AMINE RECEPTORS

Biogenic amine receptors are class A GPCRs that interact with endogenous aminergic ligands, such as **adrenaline**, **noradrenaline**, **dopamine** and serotonin (5-hydroxytryptamine [5-HT]).

4.1 | Dopamine receptors

Dopaminergic D₁-like (D₁ and D₅) and D₂-like (D₂, D₃ and D₄) receptors regulate broad functions: locomotion including voluntary movement, reward processing, learning, motivated behaviour, action selection, sleep, attention, and decision making (Mishra et al., 2018), some of which, when dysregulated, are comorbid symptoms of ASD (DiCarlo et al., 2019).

D₁ receptors are particularly enriched in D₁ striato-nigral GABAergic medium spiny neurons of the striatum. They have the lowest dopamine affinity among all the dopaminergic receptors, suggesting that they are activated by high phasic dopamine release, while D₂-like receptors might detect low tonic dopamine levels (Beaulieu & Gainetdinov, 2011). D₁ receptors may have a role, although controversial, in social behaviours (Campi et al., 2014; Scerbina et al., 2012). Rats carrying the Ile116Ser mutation in the D₁ receptor and KO mice display deficits in social interaction and communication and reduced stereotyped behaviours and comorbid symptoms, respectively (Homberg et al., 2016; McNamara et al., 2003), while excessive activation of D₁ receptors in the dorsal striatum exhibits both symptoms in WT mice (Table S3) (Lee et al., 2018). Unbalanced D₁ over D₂ medium spiny neuron outputs on the circuitry probably explains this finding. Administration of the D₁ receptor antagonist **SCH23390** ameliorated stereotyped behaviours in mice lacking the **tyrosine hydroxylase** that catalyses dopamine synthesis (Chartoff et al., 2001). The D₁/D₅ antagonist **ecopipam** is currently in phase 2 clinical trials for the treatment of Tourette's syndrome, characterised by repetitive tics (Gilbert et al., 2018). Lastly, one study reported that three common SNPs located in the 5'UTR of the *DRD1* gene (Table S2) are associated with severe impairments in social interaction, non-verbal communication and increased motor stereotypies.

D₂ receptors encoded by the *DRD2* gene comprise two splicing isoforms, short D_{2S} and long D_{2L} differing in their IL3 loops. D_{2S} serves as an auto-receptor regulating dopamine release and dopamine synthesis whereas D_{2L} is a postsynaptic receptor (Negyessy & Goldman-Rakic, 2005). These receptors are mainly expressed in neurons, with the highest levels in GABAergic indirect D₂ striato-pallidal medium spiny neurons of the striatum, and in astrocytes and oligodendrocytes (Figure 2). *Drd2* KO mice show great impairments in social interaction and communication, social olfaction and stereotyped behaviours (Table S3) (Lee et al., 2018). Moreover, *Drd2* heterozygous mice exposed to early maternal separation stress also display social interaction deficits and stereotyped behaviours (Lee & Han, 2019). This phenotype seems exclusively mediated by the dorsal striatum as specific knock-down of the D₂ receptors in this structure is sufficient to recapitulate all the behavioural impairments

reported in *Drd2* KO mice (Lee et al., 2018). Conversely, D₂ receptor overexpression in the striatum and olfactory tubercle revealed impairment in sociability and communication only in female mice (Kabitzke et al., 2015). Among the dopamine receptors, the *DRD2* gene displays the highest number of SNPs associated with ASD (Table S2). Currently, the only approved drugs for comorbid ASD symptoms, aripiprazole or risperidone, antagonise the D₂ receptors as their primary target (Table S4) (McDougle et al., 2005; Varni et al., 2012). Antipsychotics might normalise the exacerbated activity of D₂ in the dorsal striatum of ASD patients (Brandenburg et al., 2020). Additionally, two other D₂ antagonists, **pimozide** and **olanzapine**, are antipsychotics used in clinics for schizophrenia and Tourette's syndrome, leading to potential amelioration of speech impairment (Maguire et al., 2004; Pringsheim & Marras, 2009).

D₃ receptor expression is conserved between humans and rodents and controls habituation to novelty (Mishra et al., 2018). *Drd3* KO mice display hyperactive and addictive behaviours, with particular vulnerability to alcohol and drug abuse (Table S3). Their social skills or stereotyped behaviours have not been reported yet. Three independent studies identified three SNPs in the *DRD3* gene associated with ASD (Table S2). The antipsychotic **cariprazine**, a partial agonist for D₃ that also binds D₂ receptors with lower affinity, is approved for the treatment of schizophrenia and bipolar disorder. Interestingly, administration of cariprazine improved social behaviours in a dose-dependent way, in male rat models of ASD exposed to **valproic acid** in utero (Román et al., 2021), which makes this ligand a potential treatment for ASD.

In conclusion, alteration in any of these three dopaminergic receptors results in autistic-like symptoms in animal models and in genetic association with ASD. However, approved ligands targeting the D₂ receptor are already on the market to ameliorate comorbid symptoms and could be tested for core symptoms. Nonetheless, other dopamine receptors might be of interest; for example, the less known *DRD5* gene that displays the highest number of distinct missense and loss of function variants in the general population (Hauser et al., 2018).

4.2 | Serotonin receptors

Dysregulation in 5-HT levels in different CNS structures has been observed in ASD (Pourhamzeh et al., 2022), whereas enhanced 5-HT release restores social deficits in several ASD mouse models (Walsh et al., 2021). The dup15q11-q13 mouse model of ASD displays reduced serotonergic activity in the dorsal raphe nucleus, associated with low 5-HT levels in all CNS regions and impaired social interaction (Farook et al., 2012; Nakai et al., 2017). Because more than 25% of the ASD patients show increased 5-HT blood levels, 5-HT is considered as a biomarker for a subgroup of patients (Gabriele et al., 2014; Muller et al., 2016). All 14 serotonin receptors occur as a GPCR, except the ion channel receptor 5-HT₃. These GPCRs modulate cognition, memory, sleep, appetite, respiration, thermo-regulation and mood (Berger et al., 2009).

The **5-HT_{1B} receptor** belongs to the 5-HT₁ receptor family that are encoded by seven genes (*HTR1A-F*). It exerts a consistent effect on anxious-like behaviours in rodents, because administration of the selective full agonist **CP94253** or antagonists **SB 216641** and **GR 127935** (Table S4) leads to either anxiogenic or anxiolytic effect, respectively. In addition, administration of CP94253 reduced aggressive behaviour in resident male mice, whereas anpirtoline, which also targets **5-HT₃** channels, restored isolation-induced impairments, increased pain threshold and exerted anti-depressive effects in mice (Fish et al., 1999; Schlicker et al., 1992). In agreement with pharmacological studies, *Htr1b* KO mice display decreased anxious-like behaviours, exacerbated aggressive behaviour, deficits in maternal behaviour, improved cognitive flexibility and vulnerability to drug abuse (Table S3) (Bouwknicht et al., 2001; Brunner et al., 1999). So far, only two variants associated with ASD have been reported from two independent studies (Table S2).

The **5-HT_{2A} receptor**, together with **5-HT_{2B}** and **5-HT_{2C}** receptors, modulates the activity of neurotransmitters, such as glutamate, dopamine, **acetylcholine** and noradrenaline. Mice lacking the 5-HT_{2A} receptor (*Htr2a* KO) display reduced anxious-like behaviour (Table S3), which can be normalised by restoration of 5-HT_{2A} expression in the cortex or reversed to depression-like behaviour by chronic exposure to corticosterone (Petit et al., 2014; Weisstaub et al., 2006). In addition, administration of **M100907**, a selective 5-HT_{2A} antagonist, reduces repetitive grooming in the BTBR mouse model of ASD (Amodeo et al., 2016). Two SNPs in the *HTR2A* gene are associated with ASD (Table S2). The most frequent SNP is the rs6311 variant located within the promoter region (Liu et al., 2021; Smith et al., 2014), which probably influences 5-HT_{2A} receptor levels. In addition, imaging and post-mortem studies revealed lower densities of 5-HT_{2A} in the fusiform gyrus, the cingulate cortex and the thalamus in ASD patients (Beversdorf et al., 2012; Goldberg et al., 2009; Murphy et al., 2006; Oblak et al., 2013). In particular, *HTR2A* transcripts are reduced in the platelets of patients with ASD as well as in patients with gastrointestinal disorders (Kazek et al., 2010). Because serotonin receptors tightly control gastrointestinal motility, it might explain the co-occurrence with this comorbid symptom. Finally, targeting 5-HT_{2A} receptors offers promise for ASD. On the one hand, the only two approved drugs for ASD, aripiprazole and risperidone (Table S4), antagonise 5-HT_{2A} (Alexander et al., 2021; McCracken et al., 2002; McDougale et al., 2005; Varni et al., 2012). On the other hand, psychedelics (e.g., **MDMA**, **LSD**, and **psilocybin**) that activate the receptor have beneficial effects in animal models and in case studies of ASD patients (Kwan et al., 2022). Regular clinical trials are required, notably to assess the risk associated with their administration.

5-HT₇ receptors encoded by the *HTR7* gene display three splicing isoforms that differ in their C-terminal domain (Marti-Solano et al., 2020). 5-HT₇ receptors promote neurite growth and synaptogenesis through their signalling (Table S5) (Kvachnina et al., 2005; Speranza et al., 2017). This serotonin receptor is involved in cognition, sleep, pain, circadian rhythm, hypothermia and mood. Deletion of 5-HT₇ in mice (*Htr7* KO) leads to decreased compulsive behaviours associated with reduced depressive-like behaviours and pain

thresholds and increased epileptic seizures and anxious-like behaviours (Table S3) (Hedlund & Sutcliffe, 2007). Moreover, activation of 5-HT₇ normalises repetitive and anxious-like behaviours in *Fmr1* and *Mecp2* KO mice (Costa et al., 2018; De Filippis et al., 2014). Whereas only one SNP in the coding sequence of the *HTR7* gene has been associated with ASD (Table S2) (Cukier et al., 2014), several selective 5-HT₇ ligands have been developed and/or are currently in clinical trials (Table S4). Administration of serodolin, a selective β -arrestin-biased agonist for inflammatory pain (El Khamlichi et al., 2022), might be beneficial in preclinical models, and eventually in patients, as α_5 -biased agonist increased self-grooming in *Shank3* KO mice (Lee et al., 2021).

Apart from the *HTR1B* gene, evidence highlights that the *HTR2A* and *HTR7* genes might also fulfil the criteria to be candidate genes in the SFARI database. Regarding the major 5-HT system dysfunctions in ASD, potentially all the 14 serotonin receptors are of interest. For example, targeting **5-HT₆** using a selective antagonist SLV improves core social symptoms in mouse models of ASD (de Bruin et al., 2016) and variants in the *HTR6* gene are associated with autism susceptibility (Hervás et al., 2014). Highly promising drugs targeting multiple 5-HT receptors, such as arylpiperazine derivative drugs (Lacivita et al., 2021) and the first 5-HT₇ biased agonist (El Khamlichi et al., 2022), could be tested to improve core ASD symptoms. Currently, the administration of antipsychotics (aripiprazole and risperidone) to treat irritability, aggressive and repetitive behaviours in ASD patients partially activates 5-HT_{1A} and inhibits 5-HT_{2A}.

4.3 | β_2 -Adrenoceptor

Noradrenaline and adrenaline activate the α_1 -, α_2 -, β_1 -, β_2 - and β_3 -**adrenoceptors** with different potencies. In the CNS, they control cognition, memory, emotions and stress-induced behaviours. Only the *ADRB2* gene is present in the SFARI list and encodes the **β_2 -adrenoceptor**. Despite its vital cardiac function, *Adrb2* KO mice are viable and fertile. They display increased anxious-like behaviours and decreased depressive-like behaviours (Table S3). Increased adrenergic neuron activity from the locus coeruleus or increased noradrenaline plasma concentration has been associated with aberrant attention and decreased interest in ASD individuals (Bast et al., 2018; Beversdorf, 2020). Accordingly, two common SNPs associated with ASD (Table S2) show enhanced **isoprenaline**-induced response. Furthermore, studies have suggested an association between prenatal exposure to β_2 -adrenoceptor agonists and ASD (Gidaya et al., 2016). Interestingly, administration of the approved β_2/β_3 -adrenergic antagonist **propranolol** improves verbal responses and social interactions and decreases anxiety in ASD patients (Hegarty et al., 2017). Therefore, the β_2 -adrenoceptor is an interesting target for ASD, and the approved β_1/β_2 -adrenoceptor antagonist propranolol (Table S4) may help to normalise core social symptoms. Further investigations also should address the potential interest in other members of this family, such as *ADRA1D*, one of the most down-regulated genes in the

prefrontal cortex of ASD patients (Monfared et al., 2021), whose targeting with **clonidine** improves hyperarousal, hyperactivity and social relationships in individuals with ASD (Ming et al., 2008).

5 | OTHER CLASS A RECEPTORS

5.1 | Adenosine receptors

Adenosine receptors are divided into four subtypes, namely, A_1 , A_{2A} , A_{2B} and A_3 , among which A_1 and A_{2A} show the highest affinity for adenosine (Alexander et al., 2021). Adenosine receptors in the CNS have important roles in neuroplasticity, sleep–wake cycle, locomotion and cognition (Wei et al., 2011).

A_{2A} receptor, which is encoded by the *ADORA2A* gene, stimulates glutamate release at presynaptic terminals and myelination by oligodendrocytes (De Nuccio et al., 2019). Postsynaptic A_{2A} receptors are highly enriched in D_2 GABAergic striato-pallidal medium spiny neurons of the striatum, to modulate locomotion and anxious-like behaviours (Coelho et al., 2014). Accordingly, *Adora2a* KO mice display motor impairment and anxious-like behaviours (Table S3). A_{2A} might act as a regulator of other GPCRs (Table S5), because it forms many different hetero-oligomers with D_2 , mGlu₅, δ opioid receptors and orphan **GPR88** (Ciruela et al., 2011; Laboute et al., 2020; Pellissier et al., 2018). During brain development, GABAergic synapses, which release **adenosine** and ATP in addition to GABA, are the first synapses to be formed and are crucial for the construction of the neural network. Activation of A_{2A} receptors is necessary and sufficient to prune GABAergic synapses during this period (Gomez-Castro et al., 2021). In contrast, any impairment in A_{2A} signalling or expression may result in GABAergic synapse alteration and cognitive deficits in adults, as observed in animals administered with A_{2A} antagonists during development. Spontaneous stereotypies often result from unbalanced cortical glutamatergic and GABAergic afferences (glutamate hyperactivity) on the striatum and decreased activation of the efferent subthalamic nucleus, as observed in ASD patients and animal models (Li & Pozzo-Miller, 2020). Consistently, administration of the selective A_{2A} agonist **CGS21680** normalises aberrant vertical repetitive behaviours in BTBR and C58 inbred mice (Amodeo et al., 2018; Lewis et al., 2019) via its action on D_2 medium spiny neurons, which in turn restore the neurotransmission of efferent subthalamic nucleus. So far, only one study has associated four SNPs in the *ADORA2A* gene with autism and severe anxiety (Table S2).

The A_3 receptor promotes expression of the serotonin transporter (**SERT**) to the cell surface (Campbell et al., 2013). Thus, lack of A_3 signalling decreases SERT cell-surface expression and leads to extracellular accumulation of serotonin, as observed in ASD patients (see Section 4.2 on serotonin). Actually, two variants in the *ADORA3* gene are associated with ASD (Table S2), with impaired adenosine binding (Campbell et al., 2013). However, the effect of *Adora3* deletion has not been studied for core or comorbid symptoms (Table S3).

In conclusion, A_{2A} shows the greatest promise in mitigating repetitive behaviours and anxiety in ASD. However, most A_{2A} agonists

have failed in clinical trials (Guerrero, 2018) due to severe side effects, including CNS excitotoxicity (Table S4). Only a few of them have been approved, such as the agonist **regadenoson**. An alternative strategy would be to consider other members of this family, such as the *ADORA1* gene, which is one of the most down-regulated GPCR genes in patients (Monfared et al., 2021) and whose targeting in combination to A_{2A} agonists improves stereotyped behaviours (Lewis et al., 2019). A better specificity also could be achieved by targeting A_{2A} hetero-oligomers such as D_2 - A_{2A} -mGluR₅ to avoid side effects.

5.2 | Angiotensin AT₂ receptor

Angiotensin receptors are divided into AT_1 and AT_2 subtypes. They are activated by different maturation products of angiotensinogen peptides, namely, **angiotensin II** and **angiotensin III**. Only the AT_2 receptor is implicated in different neurological disorders, such as ASD, schizophrenia, Parkinson's disease (PD) and Alzheimer's disease (Firouzabadi et al., 2016; Szczepanska-Sadowska et al., 2022). Its functions in the brain remain elusive. To date, no data from genetic or pharmacological manipulation supports a role of AT_2 in social or stereotyped behaviours (Table S3). However, *Agtr2* KO mice show impaired reward processing and locomotion. Interestingly, administration of the AT_2 receptor selective agonist **C21/M024** improves cognition in a mouse model of Alzheimer's disease (Jing et al., 2012). Finally, four independent studies have associated the *AGTR2* gene on the chromosome X with ASD and X-linked intellectual disability (Table S2). Therefore, together with its unknown expression and function in the CNS, further studies are required to conclude on the therapeutic potential of AT_2 .

5.3 | Cannabinoid CB₁ receptor

Endogenous cannabinoids regulate many brain functions, including learning and memory, locomotor activity or appetite (Irving et al., 2002). In dopamine circuits, they are crucial for reward processes, linked to addiction (Zhang et al., 2004). Cannabinoid receptors are composed of CB_1 and CB_2 . CB_1 mediates the central effects of cannabis and its derivatives and modulates synaptic transmission through its effect on neurotransmitter release. *Cnr1* KO mice show deficits in social interaction and communication, two core symptoms of ASD (Table S3) (Haller et al., 2004; Litvin et al., 2013). They also exhibit anxiogenic, context-dependent social aggressive and depressive-like behaviours and improved social memory. Interestingly, administration of anandamide **fatty acid amide hydrolase** (FAAH) inhibitor improves social interactions and cognitive deficits in BTBR and *Fmr1* KO mice and *Fmr1* Δ *exon8* rats, whereas administration of a CB_1 antagonist in the amygdala reverses only social impairment in the FXS rats (Schiavi et al., 2023; Wei et al., 2016). Three independent studies have reported more than 30 variants in the *CNR1* gene associated with ASD (Table S2). Some states in the United States have already authorised cannabis to treat self-injury or aggressive behaviours in ASD patients.

The first results of clinical trials with a combination of **cannabidiol** and **Δ^9 -THC** showed no side effects, but also mixed results (Aran et al., 2021). Few case studies have shown improvement of core and comorbid symptoms in children (Carreira et al., 2022). Thus, further testing is required and administration of CB₁ NAM cannabidiol or an endocannabinoid mix are currently in clinical trials for ASD (Aran et al., 2021). In conclusion, evidence highlights that the CB₁ receptor as one of the most promising GPCR targets to treat core and comorbid symptoms in ASD.

5.4 | Chemokine CX₃CR1 receptor

Chemokine receptors are a vast family of GPCRs involved in the immune system. Both secreted and membrane-bound chemokine **CX3CL1** activate the C-X₃-C motif chemokine receptor 1 (**CX₃CR1**, or GPR13). In humans, the **CX3CR1** gene encodes four transcript variants and two protein isoforms that differ in their N-terminus domain (Marti-Solano et al., 2020). CX₃CR1 is expressed on microglia where it is activated by CX3CL1 released from neurons upon inflammatory response and during synaptic maturation and pruning (Jung et al., 2000; Soriano et al., 2002; Zhan et al., 2014). *Cx3cr1* KO mice display social interaction deficits and increased motor stereotypies (Table S3) associated with decreased functional brain connectivity from the prefrontal cortex, similarly to observations in ASD patients (Pirainen et al., 2021; Zhan et al., 2014; Zhou et al., 2020). Moreover, in mice exposed to social isolation, levels of *Cx3cr1* transcripts were increased in the prefrontal cortex, nucleus accumbens and hippocampus (Zhou et al., 2020). Three rare missense deleterious mutations in the **CX3CR1** gene have been associated with schizophrenia and ASD (Table S2).

In conclusion, CX₃CR1 plays a major role in neuron–microglia mutual interaction, highlighting the growing evidence of microglia in neurodevelopmental disorders, including ASD (Lukens & Eyo, 2022). CX₃CR1 is a promising target to treat ASD. However, development of specific compounds will be necessary to demonstrate its beneficial effect.

5.5 | Muscarinic acetylcholine M₃ receptor

In addition to ionotropic receptors, acetylcholine activates five **muscarinic** M₁–M₅ GPCRs. Whereas many receptor ligands, including allosteric modulators, have been reported, few of them are selective for a receptor subtype (Table S4). The **CHRM3** gene is complex, spans over 550 kbp and includes seven exons, with only Exon 7 encoding the **M₃ receptor**. It has 10 described, and 21 predicted, transcript variants. Like other muscarinic receptors, M₃ modulates excitatory transmission, neuronal development including cellular proliferation and survival, neuronal differentiation, and controls food intake, learning and memory (Poulin et al., 2010; Yamada et al., 2001). *Chrm3* KO mice or knock-in of a mutant receptor whose IL3 loop cannot be phosphorylated, significantly altered hippocampus-dependent contextual fear

memory formation and decreased paradoxical sleep (Table S3). However, no study has investigated the ASD-like symptoms in these animals nor the therapeutic potential of muscarinic ligands. Seven variants have been associated with ASD in six independent studies (Table S2), suggesting the potential involvement of M₃ in ASD aetiology. Interstitial deletion in the 1q43 region, which mostly affects the **CHRM3** gene, is associated with ASD, intellectual disability, seizures, microcephaly and congenital malformations (Hiraki et al., 2008; van Bever et al., 2005). Whereas reduced cholinergic enzyme activity has been observed in cortical areas of ASD patients (Perry et al., 2001), further evidence is needed to conclude on the potential interest of muscarinic receptors as therapeutic targets for ASD.

6 | ORPHAN AND OLFACTORY RECEPTORS

Hundreds of orphan and olfactory GPCRs are expressed in the CNS and represent new potential therapeutic targets for neurological disorders (Khan & He, 2017) including ASD. Interestingly, orphan GPR37 and GPR85 are the top dysregulated GPCR genes in ASD tissues (Monfared et al., 2021). Except their classification by sequence homology to the class A of GPCRs, the study of orphan or olfactory receptors remains challenging due to the lack of any identified ligand or poorly known function.

6.1 | GPR37

GPR37 or parkin-associated endothelin-like receptor (Pael-R) is closely related to endothelin GPCRs. Several potential natural peptides have been reported to activate GPR37 (Table S4), but this remains to be confirmed. GPR37 is characterised by a poor export from ER to plasma membrane in heterologous cell lines, which is either rescued by deletion of its long N-terminus domain, oligomerization with A_{2A} or D₂ receptors, or interaction with syntenin 1 through their PDZ domain (Dunham et al., 2009; Hertz et al., 2019). GPR37 is up-regulated during oligodendrocyte differentiation, where it inhibits late-stage differentiation and myelination (Yang et al., 2016). GPR37 is also located in dopaminergic axon terminals of the substantia nigra, where it controls dopamine release through a direct interaction with the **dopamine transporter** (SLC6A3) (Marazziti et al., 2007). *Gpr37* KO mice display obsessive compulsive behaviours, decreased locomotion, reduced colon motility and abnormal sensorimotor gating (Table S3) (Imai et al., 2007; Mandillo et al., 2013; Marazziti et al., 2007, 2011). They may have increased anxious-like behaviours, but this phenotype varies depending on the tests, sex, and housing conditions. Conversely, transgenic mice overexpressing *Gpr37* show increased **methamphetamine**-induced stereotyped behaviours, motor coordination and locomotion (Imai et al., 2007). Although social interaction deficits remain to be investigated, *Gpr37* mice display a variety of comorbid symptoms of ASD that are associated with altered striatal dopamine signalling (Li & Pozzo-Miller, 2020). Interestingly, variants

of the dopamine transporter gene, its direct interactor, are also associated with ASD (DiCarlo et al., 2019) and lead to similar alterations of dopamine transmission in the striatum. The *GPR37* gene has been identified in the first autism locus (AUTS1) on chromosome 7q31–33. Since then, nine variants in this gene have been associated with ASD (Table S2). Therefore, several pieces of evidence confirm that *GPR37* may be an interesting target for ASD. However, selective ligands should be developed and tested in preclinical models to further strengthen its therapeutic potential for ASD.

6.2 | GPR85

GPR85/SREB2 belongs to the super-conserved receptor expressed in the brain (SREB) family. The *GPR85* gene encodes seven predicted and three transcript variants due to alternative splicing of the 3'UTR. They all encode the extremely conserved *GPR85*, which shares 100% homology and strong expression throughout the CNS in humans and mice (Figure 3). It is expressed in all types of neurons and microglia (Figure 2). At the molecular level, *GPR85* directly interacts with SHANK3 or PSD95 scaffolding partners through its PDZ domain in its C-terminus and indirectly with *neuroligin* through PSD95 (Fujita-Jimbo et al., 2015; Jin et al., 2018). In the adult hippocampus, *GPR85* negatively regulates neurogenesis and dendritic morphology, thus controlling brain size (Chen et al., 2012). *Gpr85* KO mice display increased neurogenesis associated with enlarged brain size and increased cognitive abilities in spatial tasks (Table S3). Conversely, mice overexpressing *Gpr85* in forebrain neurons show core symptoms of ASD, social interaction deficits and restrictive behaviours, in addition to cognitive inabilities, abnormal sensorimotor gating and reduced dendritic arborisation (Chen et al., 2012; Matsumoto et al., 2008). Two independent studies reported five variants in the human *GPR85* gene in Japanese ASD patients (Table S2), including one variant in the 3'UTR. Furthermore, two studies have found down-regulated *GPR85* transcripts and decreased *GPR85* splicing events in the cortex of ASD patients (Monfared et al., 2021; Voineagu et al., 2011). Interestingly, increased *Gpr85* mRNA levels have been found in the striatum and prefrontal cortex of mice overexpressing *Shank3* (Jin et al., 2018). Although studies on *GPR85* remain sparse and no drugs are available, data from mice and patients converge on its therapeutic potential to improve social interaction deficits.

6.3 | ORs

In humans, 387 genes encode ORs in addition to 462 pseudogenes. ORs, which are encoded by a single exon, are subdivided in aquatic ancestry class I receptors clustered on human chromosome 1 (OR1–15) and the largest terrestrial ancestry class II (OR51–56) located on different chromosomes (Olender et al., 2020). They detect odorant volatile molecules, although most of them remain orphans. Since their discovery, growing evidence has shown OR expression outside the olfactory epithelium, first in testis, then in most tissues, including

the CNS. Their roles in development, chemotaxis, tissue injury and regeneration are starting to be deciphered. While the strongest association with ASD for ORs has been observed in the *OR1C1* gene, few studies have associated the *OR2M4*, *OR2T10* and *OR52M1* genes with ASD (Table S2). Furthermore, other OR genes were identified in association studies (Ruzzo et al., 2019), in particular with schizophrenia. Often qualified as 'ectopic' outside the olfactory epithelium, their expression is rather conserved among species (De la Cruz et al., 2009; Olender et al., 2016). *OR1C1*, *OR2M4* and *OR2T10* are present in the CNS, in contrast to *OR52M1*, which is conserved between humans and rodents (Figures 2 and 3 and Table S4). *OR1C1* and *OR2T10*, specific to apes, are both detected in the cortex, with *OR1C1* also found in the pons, cerebellum, hippocampus and amygdala (Table S6). *OR2M4* is conserved in apes, cows and pigs and is detected in neurons of most CNS areas. Their function remains to be elucidated in the CNS because no ligands nor animal models are available. In conclusion, the function of orphans and ORs is only starting to be elucidated in the CNS, but they could be of interest for ASD in the future with the development of selective drugs.

7 | GENERAL CONCLUSIONS AND FUTURE DIRECTIONS

In this review, we highlighted the contribution of different GPCRs in the aetiology of ASD and emphasised their potential role as therapeutic targets. First, we analysed the effect of GPCR variants associated with ASD based on their level of expression, ligand binding, receptor folding or activation of downstream signalling pathways (Table S2). SNPs or CNVs located in introns, untranslated regions or coding regions of *mGlu₇*, *5-HT_{2A}*, *CB₁*, *GPR37* and *GPR85* receptor genes are consistent with the decreased levels of transcript expression observed in patients (Monfared et al., 2021). Based on evidence in ASD patients, their function, localisation (Figures 2 and 3 and Tables S2 and S6) and their behavioural predictive validity in animal models (Table S3), we identified *OTR*, *V_{1A}*, *mGlu₅*, *D₂*, *5-HT_{2A}*, *CB₁* and *GPR37* for their contribution to ASD aetiology. *V_{1A}* receptors display a clear potential for improving social interaction, *D₂* and *GPR37* for normalising stereotyped behaviours and *mGlu₅*, *OTR*, *CB₁* and *5-HT_{2A}* for both core ASD symptoms. Overall, it is surprising that out of around 800 GPCRs, only 23 are included in the SFARI list, and that these genes are only classified in the second category, namely, 'strong candidate gene'. We propose to move *OTR*, *CB₁* and *V_{1A}* receptors to the first category 'high confidence genes' and add *5-HT_{2A}* and *5-HT₇* to the list. We also propose *GABA_{B1}*, *5-HT₆*, *D₄* and *D₅* as potential candidates that deserve further consideration for their contribution to ASD. Overall, further investigation is required to identify all the GPCRs that contribute to the aetiology of the spectrum or subtypes of autism. Increasing evidence highlights functional crosstalk between GPCRs within a cell type to control a specific function, such as *D₂*, *A_{2A}* and *mGlu₅* for the control of motor activity (Ciruela et al., 2011). In fact, independently of their physical interaction, GPCRs are not individual entities but should rather be considered as combinations of

GPCRs and isoforms working together in a cell to orchestrate the different signals and regulate downstream signalling networks and related cellular processes. Up to hundreds of GPCRs are expressed in the same brain structures or cell types, with the highest diversity in the striatum, cortex and hypothalamus (Marti-Solano et al., 2020; Vassilatis et al., 2003). Over 30 thousands of missense variants and CNVs have been identified in GPCR genes in the global population (Hauser et al., 2018). Considering the potential impact of GPCR on downstream signalling and cellular processes (Table S5) that are altered in ASD (De Rubeis et al., 2014; Hormozdiari et al., 2015; Gazestani et al., 2019), any slight modification in a GPCR (van der Westhuizen, 2023) or combinations of GPCRs may lead to important signalling defects and neuronal pathogenicity in a given cell type and circuitry. Here, we found that at least 15% of the genes listed in the SFARI database are involved in the signalling networks and cellular downstream processes of GPCRs. Therefore, rather than individual gene, combinations of GPCRs expressed in a cell type or circuit that control signalling networks should be considered in order to understand the global contribution of GPCRs to ASD aetiology. These analyses would allow us to identify an exhaustive list of GPCRs. Therefore, the impact of GPCRs for autism research has only begun to be highlighted.

GPCRs meet the criteria of therapeutic targets for ASD to bypass the placebo effect observed in clinical trials. They contribute to the polygenic ASD aetiology, pathogenic variants are recessive, they are therapeutically rescuable, and they are *per essence* membrane receptors that display a large pharmacopoeia of safe and efficient drugs. Nevertheless, targeting GPCRs, that are not involved in ASD aetiology but could normalise core symptoms, would also offer therapeutic opportunities across the spectrum without loss of efficacy. Here, we analysed the therapeutic potential of 25 GPCRs and categorised them as 'high', 'moderate' and 'low' candidates, based on (1) the expected pharmacological profile for ASD, (2) drug development status (approved or tested for a related disorder; Table S4), (3) their beneficial effects in animal models of ASD or in clinical trials (Tables S3 and S4) and (4) their safety (see Tables S4 and S6) and/or potential therapeutic window of efficacy (e.g., during development or in adults). We classified mGlu₅, GABA_B, D₂ and 5-HT_{2A} as 'high' candidates and OTR, V_{1A}, mGlu₇, D₁, 5-HT_{1B}, M₃, 5-HT₇ and CB₁ as 'moderate' candidates. We excluded β₂-adrenoceptors, A_{2A} and AT₂ and mGlu₅ and GABA_B as toxicity and lack of efficacy have been reported in clinical trials, respectively. We did not exclude OTR and V_{1A}, because more selective compounds or other pharmacological profiles remain to be tested, especially in combination with behavioural intervention programmes (Daniels et al., 2023). Furthermore, Hauser et al. (2018) reported hundreds of missense variants and CNVs in GPCR genes, including mGlu₅, V_{1B}, D₁, D₂, D₃, 5-HT_{2A}, β₂-adrenoceptors and GABA_B. This area of research based on receptor bias is known as pharmacogenomics (e.g., all variants that might influence ligand binding or transducer recruitment; Table S2). In particular, variants reported in mGlu₅ and 5-HT_{2A} compromise their responsiveness to drugs (Hauser et al., 2018), which may explain why mGlu₅-targeted clinical trials did not reach significant results. Finally, despite their strong potential, orphan and olfactory receptors belong to the

'low' category as there are no natural ligands or drugs clearly identified. We also ranked CX3CR₁, V_{1B}, D₃ and A₃ as 'low' candidates, as no data on pharmacological and genetic manipulation in animals is available. Finally, based on their involvement in ASD aetiology and their 'high' or 'moderate' therapeutic potential (Figure 4), we conclude that D₂, 5-HT_{2A}, CB₁, OTR and V_{1A} remain the most promising targets. Nevertheless, investigations or trials are still ongoing (or should be done) for these targets (e.g., CB₁ on social scale).

In the future, targeting oligomers or multiple GPCRs in a given cell type or administration of allosteric modulators or biased compounds should offer great promise for ASD drug development. Whereas allosteric modulators have already been tested for widespread targets (e.g., mGlu₅ or GABA_B) in ASD, administration of biased agonists has only begun. The effect of one particular signalling pathway to a specific physio-pathological process (known as functional selectivity) has started to be unravelled (Kolb et al., 2022), including for ASD. Several examples of the effect of biased agonists showed very promising properties with limited side effects for other CNS applications. For example, β-arrestin-biased D₂ partial agonists normalised positive, negative and cognitive symptoms in two mouse models of schizophrenia, including social deficits, with reduced cataleptic side effects (Park et al., 2016). Gα_i-biased μOR agonists have been developed for pain, without tolerance and addictive values (Crowley et al., 2020; Stahl et al., 2021). In addition, functional selectivity could be fully addressed for the 5-HT₇ as both β-arrestin and Gα_s-biased agonists have been developed (El Khamlichi et al., 2022; Lee et al., 2021). Targeting oligomers or combinations of GPCRs in a given cell type using combination of drugs or a drug targeting multiple GPCRs would act synergically to achieve local and specific therapeutic effects. Such drugs already exist. For example, aripiprazole, risperidone, cariprazine or arylpiperazine derivatives target multiple dopamine, serotonin, histamine and/or adrenoceptors (Table S4) (Lacivita et al., 2021). The emergence of high throughput screening by DNA-based bar-coded chemical libraries should boost the identification of new drugs to target GPCRs with appropriate pharmacological profiles, including orphan and olfactory receptors (Madsen et al., 2020). Furthermore, the recent development of antibody fragments targeting GPCRs (Mujčić-Delić et al., 2014) offers multiple therapeutic advantages. They display all types of pharmacological profiles, and in addition, acting as chaperones, they could rescue deficient GPCR cell-surface expression. Furthermore, when reformatted in bi-specific or bivalents, they can target oligomers of GPCRs. Based on their fine-tune pharmacology and their diversity, GPCRs represent the greatest therapeutic options for ASD and hold the promise for successful clinical trials.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <https://www.guidetopharmacology.org> and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22: G protein-coupled receptors (Alexander et al., 2021).

AUTHOR CONTRIBUTIONS

All authors contributed to the review. *Conceptualization*: Anil Annamneedi and Lucie P. Pellissier. *The literature search, data analysis and writing—original draft preparation*: Anil Annamneedi, Caroline Gora, Ana Dudas, Xavier Leray, Véronique Bozon, Pascale Crépieux and Lucie P. Pellissier. *Writing—review and editing*: Anil Annamneedi, Pascale Crépieux and Lucie P. Pellissier. *Funding acquisition, project administration and supervision*: Lucie P. Pellissier. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

N/A-Review.

ORCID

Anil Annamneedi  <https://orcid.org/0000-0002-6743-8627>

Xavier Leray  <https://orcid.org/0000-0003-2107-6082>

Pascale Crépieux  <https://orcid.org/0000-0002-2712-5271>

Lucie P. Pellissier  <https://orcid.org/0000-0001-7085-3242>

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