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Themed Issue: Complexity of GPCR Modulation and Signaling (ERNST)

THEMED ISSUE REVIEW

ERNEST COST action overview on the (patho)physiology of GPCRs and orphan GPCRs in the nervous system

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G protein-coupled receptors (GPCRs) are a large family of cell surface receptors that play a critical role in nervous system function by transmitting signals between cells and their environment. They are involved in many, if not all, nervous system processes, and their dysfunction has been linked to various neurological disorders representing important drug targets. This overview emphasises the GPCRs of the nervous system, which are the research focus of the members of ERNEST COST action (CA18133) working group 'Biological roles of signal transduction'. First, the (patho) physiological role of the nervous system GPCRs in the modulation of synapse function is discussed. We then debate the (patho)physiology and pharmacology of opioid, acetylcholine, chemokine, melatonin and adhesion GPCRs in the nervous system. Finally, we address the orphan GPCRs, their implication in the nervous system function and disease, and the challenges that need to be addressed to deorphanize them.

LINKED ARTICLES: This article is part of a themed issue Complexity of GPCR Modulation and Signaling (ERNST). To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v182.14/issuetoc

KEYWORDS
deorphanization, G protein-coupled receptors, glia, nervous system, nervous system disorders, neuron, orphan G protein-coupled receptors, physiology, signalling

Abbreviations: 7TM, seven-transmembrane; 7TMD, seven-transmembrane domain; 7TMH, seven-transmembrane helices; AD, Alzheimer's disease; CA1, cornu ammonis area 1; COST, European cooperation in science and technology; CTF, C-terminal fragments; CXCL, CXC chemokine ligand; ECD, extracellular domain; ECL, extracellular loop; ER, endoplasmic reticulum; ERNEST, European research network on signal transduction; FDA, food and drug administration; GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; GPR, predicted G protein-coupled receptor; GRK, G protein-coupled receptor kinase; ICD, intracellular domain; ICL, intracellular loop; NAc, nucleus accumbens; NAM, negative allosteric modulator; NFEPP, N-(3-fluoro-1-phenetylpiperidin-4-yl)-N-phenylpropionamide); NPC, neural progenitor cells; NTF, N-terminal fragments; oGPCRs, orphan G protein-coupled receptors; PAM, positive allosteric modulator; PD, Parkinson's disease; RhoGEF, Rho guanine nucleotide exchange factor.

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1 | INTRODUCTION

There are >800 human **G protein-coupled receptors** (**GPCRs**). Around half (~400) have sensory functions mediating olfaction, taste, light perception, and pheromone signalling. The remaining GPCRs are non-sensory, of which >90% are expressed in the nervous system and respond to hormones and neurotransmitters, regulating many physiological processes such as synapse function, brain metabolism, pain perception, mood, behaviour, memory, learning, immune response, neuroprotection, mechanosensation, myelination, cell differentiation, cell migration, nervous system development, axon guidance, dendritogenesis and vascularization.

The dysfunction of GPCRs in the nervous system has been linked to many neurological deficits, including neurodegeneration, psychiatric disorders, epilepsy, cancer and addiction (Wacker et al., 2017). As a consequence, GPCRs are the most common therapeutic target for the treatment of neurological disorders. In 2017 it was accounted that ~34% of all FDA-approved drugs are targeting GPCRs, acting as antagonists or agonists (Hauser et al., 2017). Moreover, many GPCR-based drugs are currently being evaluated in clinical trials (Shimada et al., 2019). As new functions for GPCRs are discovered, particularly for the ~100 orphan GPCRs (oGPCRs; Watkins & Orlandi, 2021) for which endogenous ligands and, to a great extent, their role in the cellular processes is currently unknown, the number of drugs targeting GPCRs is expected to increase. The elucidation of GPCR structures and the development of novel GPCR ligands are critical to better understand the role of each GPCR type in nervous system function and beyond.

This review is part of the European Cooperation in Science and Technology (COST) Action CA18133—European Research Network on Signal Transduction (ERNEST) special issue and focuses on the nervous system GPCRs in which the members of the ERNEST 'Biological roles of signal transduction' working group specialise (Sommer et al., 2020). European Union COST Actions provide a platform for researchers and experts from different European countries to collaborate and work together on specific research topics. The review covers the selected research topics of ERNEST members and summarises the related literature. First, the general structural and signalling characteristics of the GPCR families commonly found in the nervous system will be discussed (Figure 1 and Table 1). We will then focus on the (patho)physiology of nervous system GPCRs (**metabotropic glutamate receptors** [**mGluR**], **γ-aminobutyric acid B [$GABA_B$] receptors**, **[5-hydroxytryptamine {5-HT}] receptors**, metabotropic purinergic **P2Y receptors**, **dopamine receptors**) in the modulation of synapse function. Furthermore, we will discuss the (patho)physiology and pharmacology of **opioid receptors**, **muscarinic acetylcholine receptors (muscarinic)**, **chemokine receptors** and **melatonin receptors**. These receptors have been shown to play a role in various nervous system disorders and are important drug targets (see Table 2 for active and/or [not yet] recruiting clinical trials). In addition, we will discuss **adhesion GPCRs** (**aGPCRs**) and their emerging role in the nervous system function. Finally, we will address **orphan GPCRs** (**oGPCRs**) in nervous system function and disease with the remaining challenges in structural biology that need to be addressed in the future to deorphanize oGPCRs and to fully understand the molecular mechanisms underlying the (patho)physiology of GPCRs in the nervous system.

2 | GPCR STRUCTURE AND SIGNALLING PATHWAYS

GPCRs transduce signals across the cell membrane due to their ability to change conformation. The binding of ligands to the extracellular side of the GPCRs promotes conformational changes in the GPCRs, allowing the binding of G proteins, arrestins, and other signalling proteins to the intracellular domain of a given GPCR. GPCRs generally consist of a conserved seven-transmembrane domain (7TMD), an N-terminal extracellular (ECD), and a C-terminal intracellular domain (ICD). 7TM helices span the cell membrane and are connected by alternating three intracellular (ICL1-3) and three extracellular loops (ECL1-3) (Wacker et al., 2017).

GPCRs can be classified into six main families based on their sequence similarities: **class A** (**rhodopsin-like**), class B (**secretin** [**B1**] and **adhesion** [**B2**]), **class C** (**metabotropic glutamate/pheromone**), class D (fungal mating pheromone), class E (cyclic adenosine monophosphate [cAMP]) and **class F** (**frizzled/smoothened**) GPCR families. We will briefly discuss the structural characteristics of classes A, B and C, which are common in the nervous system and to which the GPCRs discussed in this paper belong. They share the same 7TM helix structure but differ in their ECDs, ICDs and activation mechanisms. These structural differences contribute to the recognition of specific ligands and signalling properties of each GPCR class (for details see open-source GPCRdb database: https://gpcrdb.org).

Class A GPCRs (rhodopsin-like receptors) are the most abundant and diverse group, accounting for ~80% of all GPCRs, which include hormone, neurotransmitter, and light receptors. Class A GPCRs exhibit the most typical GPCR structure, characterised by an N-terminal ECD, followed by 7TMDs that form ligand-binding pocket and a C-terminal ICD. Given the broad spectrum of its physiological functions, this GPCR class is the most common drug target among all classes (Yang et al., 2021).

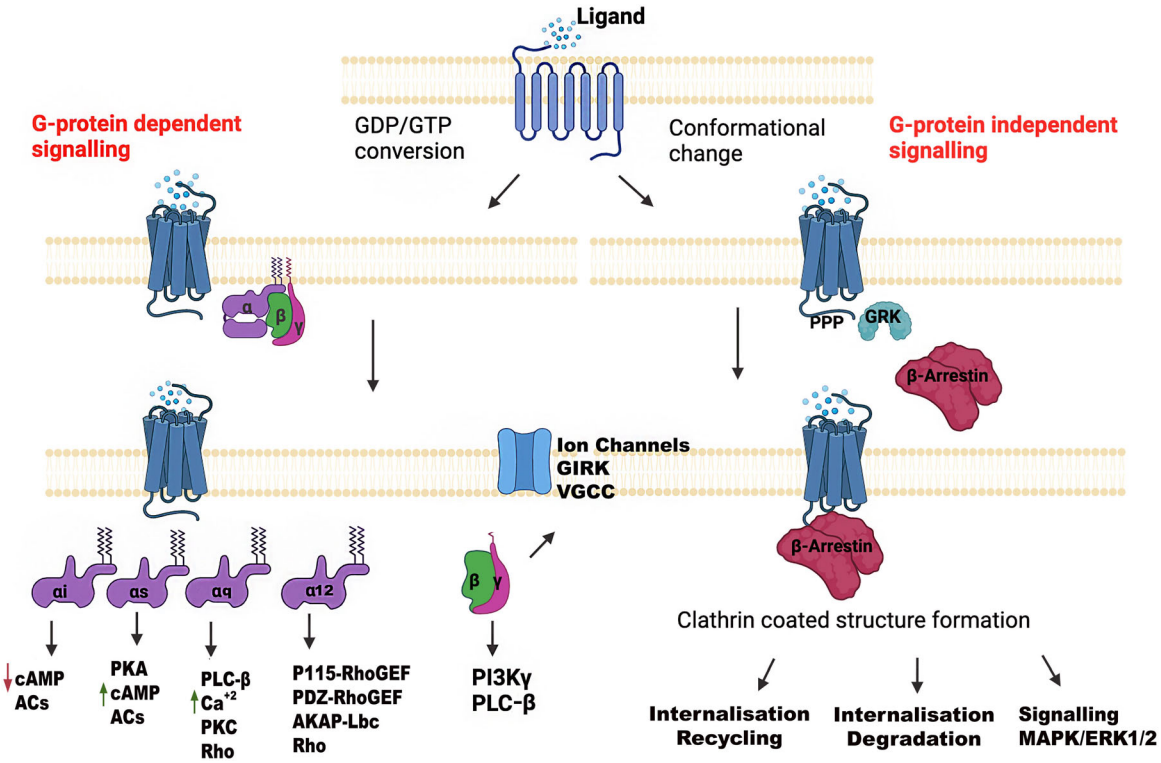

FIGURE 1 Canonical G protein-coupled receptor (GPCR) signalling or G protein-dependent signalling refers to the prototypical pathway activated by ligand binding to the receptor. Ligand binding induces a conformational change in the receptor, that activates the heterotrimeric G protein complex. Upon activation, the Gα subunit undergoes a guanosine diphosphate (GDP)-guanosine triphosphate (GTP) exchange and dissociates from the G$\beta\gamma$ subunit. The activated Gα and G$\beta\gamma$ subunits interact with downstream effectors. A typical Gα_q subunit effector is phospholipase C-β (PLC-β), which cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) into two secondary messengers: inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 binds to IP3 receptors on the intracellular Ca^{2+}-storage organelles, for example, endoplasmic reticulum, releasing a secondary messenger Ca^{2+} into the cytosol, which triggers various cellular responses. Conversely, DAG activates protein kinase C (PKC), which phosphorylates target proteins. Typical effector of excitatory and inhibitory Gα subunits, Gα_s and Gα_i, respectively, is adenylate cyclase (AC), which produces secondary messenger cyclic adenosine monophosphate (cAMP) from ATP. The latter can activate various proteins, such as protein kinase a (PKA). PKA then phosphorylates target proteins. AC is activated by Gα_s and inhibited by Gα_i subunit. Phosphodiesterase (PDE) breaks down cAMP, terminating its signalling effect. Activation of Gα_{12} leads to recruitment of Rho guanine nucleotide exchange factors (Rho-GEFs), PDZ-RhoGEF and p115Rho-GEF, to the plasma membrane. Another Rho-GEF is A-kinase-anchoring protein (AKAP)-Lbc, which acts at the same time as Rho-GEF and A-kinase-anchoring protein (AKAP). Rho-GEF activates Rho GTPases (e.g., RhoA), which regulate cytoskeleton remodelling and cell migration. Effectors of the G$\beta\gamma$ subunit are among others, ion channels (e.g., G protein-coupled inwardly rectifying potassium (GIRK), voltage-gated Ca^{2+} channels (VGCC)), phosphoinositide 3-kinase γ (PI3Kγ), PLC-β. On the other hand, non-canonical GPCR signalling or G protein-independent signalling, encompasses alternative pathways (independent of the canonical G protein pathways). Binding of a ligand to the GPCR activates recruitment of G protein-coupled receptor kinases (GRKs) to the receptor, which phosphorylate the receptor. This phosphorylation signals the recruitment of β-arrestins to the receptor. β-arrestins bind to the phosphorylated GPCR, leading to its desensitisation and internalisation. In addition to desensitisation, β-arrestins can act as signalling scaffolds, interacting with various intracellular proteins and initiating alternative signalling pathways. These pathways can activate downstream signalling molecules, such as mitogen-activated protein kinases (MAPKs), and contribute to cellular responses independent of G protein signalling. Note that not all signalling pathways are included in the scheme.

TABLE 1 G protein coupling, endogenous ligands and distribution of various GPCRs expressed in the nervous system[a].

Class A (rhodopsin-like) GPCR[b]	Receptor subtype	G protein	Endogenous ligand	Main distribution[a]	References
5-hHydroxytryptamine (5-HT) receptors					Celada et al., 2013 Huang & Thathiah, 2015
5-HT_1	5-HT_{1A}	$G_{i/o}$	Serotonin	Cerebral cortex, hippocampus, septum, brainstem	
	5-HT_{1B}	$G_{i/o}$	Serotonin	Hippocampus, basal ganglia	
	5-HT_{1D}	$G_{i/o}$	Serotonin	Basal ganglia, brainstem	
	5-HT_{1E}	$G_{i/o}$	Serotonin	Cerebral cortex, hippocampus, hypothalamus, amygdala	
	5-HT_{1F}	$G_{i/o}$	Serotonin	Cerebral cortex, hippocampus, brainstem	
5-HT_2	5-HT_{2A}	G_q	Serotonin	Cerebral cortex, hippocampus, basal ganglia	
	5-HT_{2B}	G_q	Serotonin	*ND*	
	5-HT_{2C}	G_q	Serotonin	Cerebral cortex, hippocampus, basal ganglia, choroid plexus, amygdala	
5-HT_4	5-HT_4	G_s	Serotonin	Cerebral cortex, olfactory tubercle, hippocampus, basal ganglia, medial habenula, amygdala	
5-HT_5	5-HT_{5A}	$G_{i/o}$	Serotonin	Cerebral cortex, hippocampus, brainstem, hypothalamus	
	$5\text{-HT}_{5B}\text{R}$	$G_{i/o}$	Serotonin	Hippocampus, medial habenula, brainstem	
5-HT_6	5-HT_6	G_s	Serotonin	Cerebral cortex, olfactory tubercle, hippocampus, basal ganglia, hypothalamus	
5-HT_7	5-HT_7	G_s	Serotonin	Hippocampus, septum, brainstem, hypothalamus, thalamus, amygdala	
Dopamine receptors					Beaulieu & Gainetdinov, 2011
D_1-like	D_1	G_s (G_q?)	Dopamine	Striatum, nucleus accumbens, olfactory bulb, substantia nigra, hippocampus, hypotalamus, frontal cortex	Mishra et al., 2018
	D_5		Dopamine	Cortex, substantia nigra, hypothalamus	
D_2-like	D_2	$G_{i/o}$	Dopamine	Striatum, VTA, olfactory bulb, cerebral cortex	Mishra et al., 2018
	D_3	$G_{i/o}$	Dopamine	Striatum, islands of Calleja, cortex	
	D_4	$G_{i/o}$	Dopamine	Frontal cortex, amygdala, hypothalamus, nucleus accumbens	

(Continues)

TABLE 1 (Continued)

Class A (rhodopsin-like) GPCR[b]	Receptor subtype	G protein	Endogenous ligand	Main distribution[a]	References
P2Y receptors					Abbracchio et al., 2009 Burnstock, 2018
$P2Y_1$-like	$P2Y_1$	$G_{q/11}$	ADP	Cerebellum, cerebral cortex, hippocampus, optic nerves, midbrain, cerebellum, etc. (neurons, glia)	Zarrinmayeh & Territo, 2020; Burnstock & Knight, 2004; Weisman et al., 2012
	$P2Y_2$	$G_{q/11}$	ATP, UTP	Brain (neurons, microglia, astrocytes)	
	$P2Y_4$	$G_{q/11}$	UTP	Brain (neurons, microglia, astrocytes)	
	$P2Y_6$	$G_{q/11}$	UDP	Cerebral cortex, cerebellum, hippocampus, basal ganglia, spinal cord, sympathetic ganglia, superior cervical ganglia, dorsal root ganglia, and sciatic nerve (nevrons, microglia)	
	$P2Y_{11}$	$G_{q/11}$, G_s	ATP	Nucleus accumbens, parahippocampal gyrus, putamen, striatum, hippocampus (pyramidal neurons), cerebellum (Purkinje cells)	
$P2Y_{12}$-like	$P2Y_{12}$	$G_{i/o}$	ADP	M2 type microglia, cortex (astrocytes), hippocampus (pyramidal neurons, oligodendrocytes)	Zarrinmayeh & Territo, 2020; Burnstock & Knight, 2004; Weisman et al., 2012
	$P2Y_{13}$	$G_{i/o}$	ADP	Cerebellum (astrocytes, microglia), granule neurons	
	$P2Y_{14}$	$G_{i/o}$	UDP-glucose, UDP-galactose, UDP-glucuronic acid, UDP-N-acetylglucosamine	Cortex and cerebellum (astrocytes, microglia)	
Adenosine receptors					
A_1	-	$G_{i/o}$	Adenosine	Cortex, hippocampus, cerebellum (glutamatergic synapse)	Kofuji & Araque, 2021; Borea et al., 2018
A_2	A_{2A}, A_{2B}	G_s	Adenosine	Striatum, olfactory bulb (glutamatergic synapse)	
A_3	-	$G_{i/o}$	Adenosine	Low levels in the brain, retinal ganglion cells, motor nerve terminals, pial and intracerebral arteries (neurons, microglia, astrocytes)	
Opioid receptors					
δ receptor	-	$G_{i/o}$, G_z, G_{16}	Enkephalins	Cerebral cortex, hippocampus, hypothalamus, cerebellum, striatum, ventral tegmental area, dorsal root ganglion, amygdala	Garzón et al., 1997; Georgoussi et al., 1997; Le Merrer et al., 2009; Han et al., 2023
μ receptor	-	$G_{i/o}$, G_z	*β*-Endorphin		
κ receptor	-	$G_{i/o}$, G_z	Dynorphins		

TABLE 1 (Continued)

Class A (rhodopsin-like) GPCR[b]	Receptor subtype	G protein	Endogenous ligand	Main distribution[a]	References
Acetylcholine receptors (muscarinic)					Felder, 1995
M_1 receptor	-	$G_{q/11}$	Acetylcholine	Cerebral cortex and hippocampus	
M_2 receptor	-	$G_{i/o}$	Acetylcholine	Forebrain, thalamus, and motor neurons	
M_3 receptor	-	$G_{q/11}$	Acetylcholine	Low levels across the brain	
M_4 receptor	-	$G_{i/o}$	Acetylcholine	Striatum	
M_5 receptor	-	$G_{q/11}$	Acetylcholine	Midbrain, hippocampus	
Chemokine receptors					Dorsam & Gutkind, 2007; Berchiche & Sakmar, 2016
CXCR3	CXCR3-a	G_i ($G_{i/2}$, $G_{i/3}$), G_q	CXCL9, CXCL10, CXCL11	Immune cells infiltrating the brain (Th1, CD8 + T, NK and DC cells), glial cells (astrocytes), Purkinje cells of the cerebellum, endothelial cells of the choroid plexus	Van Der Meer et al., 2001; Andrews & Cox, 2016; Groom & Luster, 2011a, 2011b; Lasagni et al., 2003
	CXCR3-b	G_s	CXCL9, CXCL10, CXCL11, CXCL4	Endothelial cells, HMEC-1	
CXCR4	-	G_i (G_q, $G_{12/13}$)	CXCL12	CNS cell types (neurons, astroglia, microglia, oligodendrocyte, NPCs)	Murray et al., 2022
Melatonin receptors					Oishi et al., 2018
MT_1	-	$G_{i/o}$	Melatonin	Suprachiasmatic nucleus, pars tuberalis, cerebellum, third ventricle, aqueduct, lateral ventricle, dorsal third ventricle, medial habenula, habenula commissure, isolated cells in the dentate gyrus of the hippocampus	Klosen et al., 2019; Adamah-Biassi et al., 2014
MT_2	-	$G_{i/o}$	Melatonin	Olfactory bulb, forebrain, hippocampus, amygdala and superior colliculus	
Class B2 (adhesion) GPCR	**Receptor subtype**	**G protein**	**Endogenous ligand**	**Distribution**	**References**
ADGRL/Latrophilin/Cirl	-	$G_{i/o}$	Toll-like receptor 8 (Tollo)	Embryonic ectoderm, nervous tissues	Lavalou et al., 2021; Scholz et al., 2017, 2023; Bormann et al., 2023
ADGRG6 (GPR126)	-	G_s, G_i	Prion protein PrP^c Laminin-211	Nervous system, sensory organs	Küffer et al., 2016; Petersen et al., 2015; Mogha et al., 2013; Paavola et al., 2014
		$G_{i/o}$	Type IV collagen Progesterone 17-Hydroxyprogesterone		

(Continues)

TABLE 1 (Continued)

Class C (metabotropic glutamate/ pheromone) GPCR	Receptor subtype	G protein	Endogenous ligand	Distribution	References
Metabotropic glutamate receptors					Huang & Thathiah, 2015
Group I mGlu	$mGlu_1$, $mGlu_5$	G_q	Glutamate	Cerebral cortex, olfactory bulb, hippocampus, basal ganglia, hypothalamus, thalamus, cerebellum, spinal cord	
Group II mGlu	$mGlu_2$	$G_{i/o}$	Glutamate	Olfactory bulb, cerebellum	
	$mGlu_3$	$G_{i/o}$	Glutamate	Cerebral cortex, olfactory tubercle, hippocampus, basal ganglia, amygdala, cerebellum	
Group III mGlu	$mGlu_4$	$G_{i/o}$	Glutamate	Cerebral cortex, olfactory bulb, hippocampus, brainstem, basal ganglia, cerebellum, spinal cord	
	$mGlu_6$	$G_{i/o}$	Glutamate	Retina	
	$mGlu_7$	$G_{i/o}$	Glutamate	Cerebral cortex, olfactory bulb, hippocampus, brainstem, hypothalamus, thalamus, amygdala, *locus coeruleus*	
	$mGlu_8$	$G_{i/o}$	Glutamate	Cerebral cortex, olfactory bulb, hippocampus, cerebellum	
$GABA_B$ receptors					Huang & Thathiah, 2015
$GABA_B$	$GABA_{B1}$, $GABA_{B2}$	$G_{i/o}$	GABA	Cerebral cortex, hippocampus, basal ganglia, thalamus, cerebellum	

Note: 5-HT, 5-hydroxytryptamine; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CXC, chemokine C-X-C motif; CXCR, CXC receptor; CXCL, CXC ligand; GABA, γ-aminobutyric acid; HMEC-1, human microvascular endothelial cells; MT, melatonin receptor; ND, not determined; NPCs, neuronal progenitor cells; P2Y, purinergic P2Y receptor; Th1, T helper type 1; UDP, uridine diphosphate; UTP, uridine triphosphate.

[a]mRNA and/or protein expression data in the nervous tissue of rodents and human.

[b]Receptors were classified into G protein-coupled receptor (GPCR) families based on data found in the open-source GPCRdb database (https://gpcrdb.org/).

TABLE 2 Phase II, III and phase IV (new agent) active and (not yet) recruiting clinical trials targeting neural cell GPCR function in different neurological disorders.

Target	Disease/indication	Agent clinical trial phase[a]	ID number for a clinical trial (ClinicalTrials.gov)
$GABA_B$ receptors	Charcot–Marie–tooth disease type 1A	**Baclofen** ($GABA_B$ receptor agonist) Phase III	ID NCT04762758
5-Hydroxytriptamine (5-HT) receptors	Major depressive disorder with insomnia	**Mirtazapine** (5-HT_2 and 5-HT_3 receptor antagonist)[b] Phase IV	ID NCT05978219
	Bipolar disorder	**Lurasidone** (5-HT_{2A} and 5-HT_7 receptor antagonist)[c] Phase III	ID NCT02731612
	Migraine	Triptans (5-HT_{1B} and 5-HT_{1D} receptor agonist) Phase III	ID NCT04946734
Dopamine receptors	Tourette's syndrome	**Ecopipam** (D_1 and D_5 receptor antagonist) Phase III **Ecopipam** (D_1 and D_5 receptor antagonist) Phase III	ID NCT06021522 ID NCT05615220
	Tic disorder	**Aripiprazole** (partial D_2 receptor agonist)[d] Phase IV	ID NCT05361993
	Diffuse pontine and midline glioma	**ONC201** (D_2 and D_3 receptor antagonist) Phase II	ID NCT05009992
	Depression, dementia, mild cognitive impairment	**Aripiprazole** (partial D_2 receptor agonist)[d] Phase IV	ID NCT05531591
	Migraine disorders	**Metoclopramide** (D_2 receptor antagonist)[e] Phase III	ID NCT05102591
Adenosine receptors	Parkinson's disease with cognitive impairment	**Istradefylline** (A_{2A} receptor antagonist) Phase II	ID NCT05333549
	Parkinson's disease tremor	**Istradefylline** (A_{2A} receptor antagonist) Phase IV	ID NCT05885360
	Spinal cord injury	**Istradefylline** (A_{2A} receptor antagonist) Phase I/II	ID NCT05217498
	Working memory deficits	**Caffeine** (A_1, A_{2A}, A_{2B}, and A_3 receptor antagonist) Phase II/III	ID NCT05170464
	Postoperative, cognitive dysfunction, mild cognitive impairment	**Caffeine** (A_1, A_{2A}, A_{2B}, and A_3 receptor antagonist) Phase II	ID NCT05574400
	Cognition in Alzheimer's disease	**Caffeine** (A_1, A_{2A}, A_{2B}, and A_3 receptor antagonist) Phase III	ID NCT04570085
Opioid receptors	Major depressive disorder	Aticaprant (κ-receptor antagonist) Phase III	ID NCT05455684
	Sleep disorder	Opioids (opioid receptor agonists) Phase II	ID NCT04299490
	Charcot–Marie–tooth disease type 1A	**Naltrexone** (opioid receptor agonist) Phase III	ID NCT04762758
Melatonin receptors	Ischemic stroke, acute sleep disorders, circadian rhythm	**Melatonin** (melatonin receptor agonist) Phase IV	ID NCT05247125
	Acute ischaemic stroke, depression	**Agomelatine** (MT_1 and MT_2 receptor antagonist)[f] Phase IV	ID NCT05426304

[a]Only G protein-coupled receptor (GPCR) ligands are listed, but may be used in combination with other agents, depending on the clinical trial (for more information check the clinical trial ID).
[b]May also bind to α_2-adrenoceptors, histamine H_1 receptors, with low affinity for 5-HT_1, dopaminergic, muscarinic cholinergic, opioid receptors.
[c]Also a partial agonist of 5-HT_{1A} receptor, an antagonist of dopamine D_2 and D_3 receptors. It also shows a moderate-affinity antagonism at α_{2C}-adrenoceptors and low to very low-affinity antagonism at α_{1A}- and α_{2A}-adrenoceptors.
[d]Also a partial agonist of 5-HT_{1A} receptors and an antagonist of 5-HT_{2A} receptors.
[e]Also an antagonist of 5-HT_3 and an agonist of 5-HT_4 receptors.
[f]Also 5-HT_{2C} receptor antagonist.

In contrast to the class A GPCR family, class B1 GPCRs (secretin-like receptors) are defined by a large, glycosylated N-terminal ECD. The native ligands of class B1 GPCRs are long peptide hormones (e.g., **glucagon-like peptide 1**), with distinct functional roles of the N-and C-termini. The C-terminal part of the peptide ligand forms high-affinity interactions with the ECD of the receptor and drives the binding of the peptide N-terminal to the transmembrane bundle of the receptor ('two-domain/step binding model'), often involving proteolytic cleavage of the receptor's N-terminus (Cong et al., 2022; de Graaf et al., 2017). Class B2 GPCRs (aGPCRs) contain huge ECDs with multiple structural adhesive folds and a characteristic GPCR autoproteolysis-inducing (GAIN) domain (Araç et al., 2012). The GAIN domain harbours a cryptic tethered agonist (Stachel) relevant for receptor activation (Liebscher et al., 2014). It mediates self-cleavage of the maturing protein giving rise to heterodimeric aGPCR with non-covalently associated N- and C-terminal fragments (NTF and CTF) (Hamann et al., 2015; Vizurraga et al., 2020).

Class C GPCRs (metabotropic glutamate/pheromone receptors) have a very large N-terminal ECD that contains the ligand-binding site. It consists of a cysteine-rich region and a 'Venus flytrap' module (VFM) with two lobes (lobe 1 and lobe 2) separated by a cleft as an orthosteric site and undergoes conformational changes upon ligand binding. The other unique characteristic of class C GPCRs is their mandatory dimerization upon activation, either they become homodimers or heterodimers (Chun et al., 2012).

Homo- or heterodimerization of GPCRs refers to the formation of dimeric complexes between one or two types of GPCRs, respectively. The process of dimerization involves the binding of two GPCRs with their specific ligand to form a functional unit. It can occur between different combinations of GPCRs, resulting in the formation of diverse receptor complexes. These complexes may have different signalling properties compared to the individual GPCRs, resulting in altered cellular responses. Dimerization can affect ligand binding, receptor trafficking and downstream signalling pathways. It can also modulate the pharmacological properties of GPCRs, influencing drug efficacy and selectivity (Barnes, 2006; Wnorowski & Jozwiak, 2014).

GPCRs transduce extracellular signals into intracellular signals by coupling to G proteins and arrestins. Depending on the G protein subtype coupling, they either activate or inhibit the downstream signal transduction pathway. G proteins are heterotrimeric proteins composed of α, β and γ subunits bound to the guanine nucleotide (Syrovatkina et al., 2016).

Gα proteins are, based on the sequence and functional similarities, grouped into four families: Gα_s (stimulatory), Gα_i (inhibitory), Gα_q and Gα_{12}. The human genome contains 15 genes for Gα subunits. The Gα_s family has two members; Gα_s, expressed in most cells, and Gα_{olf} (olfactory), expressed in the olfactory sensory neurons. The Gα_i family is the most diverse and expressed ubiquitously, consisting of seven members Gα_{i1}, Gα_{i2}, Gα_{i3}, Gα_o, Gα_t, Gα_g and Gα_z. Gα_o is highly expressed in neurons, Gα_t (*t* stands for transducin) in the rod and cone cells in the eye, Gα_g (gustducin) in taste receptor cells and Gα_z in neuronal tissue and platelets. The Gα_q family in humans consists of four members Gα_q, Gα_{11}, Gα_{14} and Gα_{16} (the mouse equivalent is Gα_{15}). Gα_q and Gα_{11} are ubiquitously expressed, while Gα_{14} and G$\alpha_{15/16}$ expression is more restricted with Gα_{14} mainly found in the kidney, lung and liver, and G$\alpha_{15/16}$ in haematopoietic cells. In the Gα_{12} family, Gα_{12} and Gα_{13} are expressed in most cell types (Syrovatkina et al., 2016).

The human and mouse genomes have five Gβ and 12 Gγ genes. Gβ_1, Gβ_2, Gβ_3 and Gβ_4 show high sequence similarities between each other and are widely expressed. Gβ_5 has a lower sequence and structural similarity with other Gβ subunits and is mainly found in the brain. It does not participate in the formation of heterotrimeric G proteins. Gγ subunits are more diverse than the Gβ subunits (Kankanamge et al., 2022; Syrovatkina et al., 2016).

The activity of G proteins is regulated by **guanosine triphosphate** (**GTP**) and its inactive form, **guanosine diphosphate** (**GDP**). At rest, the Gα subunit, which acts as a weak GTPase, is in the GDP bound state forming a heterotrimeric complex together with Gβ and Gγ subunits. The latter two form a heterodimer G$\beta\gamma$ complex. The ligand binding to the orthosteric site of the receptor stabilises structural conformations that facilitate interaction with G proteins and their activation. The interaction of a G protein with an active receptor stimulates GDP release from the Gα subunit. The GTP concentration in the cytosol is higher than GDP, leading to the replacement of GDP on the Gα subunit with GTP. The active receptor thus acts as a guanine nucleotide exchange factor (GEF). The active Gα subunit with bound GTP dissociates from the receptor and the G$\beta\gamma$ heterodimer. Finally, the dissociated Gα and G$\beta\gamma$ subunits can interact with various downstream effectors, such as **adenylate cyclases** (**ACs**), phospholipase C-β (PLC-β), K^+ and Ca^{2+} channels. The signal is terminated by the GTPase activity of the Gα subunit, which hydrolyses GTP to GDP and returns the Gα subunit to its inactive state. This is followed by a reassociation of the G protein heterotrimer (Calebiro et al., 2021; Sprang, 2016; Tuteja, 2009).

The effectors of stimulatory Gα_s and inhibitory G$\alpha_{i/o}$ are ACs, enzymes that convert ATP into **cyclic adenosine monophosphate** (**cAMP**). Gα_s stimulates, while G$\alpha_{i/o}$ inhibits AC activity, leading to an increase or decrease in intracellular cAMP production, respectively. On the other hand, activation of G$\alpha_{q/11}$ recruits the effector PLC-β from the cytosol to the site of its substrate, that is, membrane-bound **phosphatidylinositol 4,5-bisphosphate** (**PIP2**), which is cleaved by PLC-β to **inositol 1,4,5-trisphosphate** (**IP3**) and diacylglycerol (DAG). IP3 triggers a transient increase in cytosolic Ca^{2+} by stimulating the release of Ca^{2+} from the intracellular stores, which together with DAG activates **protein kinase C** (**PKC**). G$\alpha_{12/13}$ effectors are Rho guanine nucleotide exchange factors (RhoGEFs). Stimulation of RhoGEFs leads to the activation of the Rho family of small GTPases, which are involved in the reorganisation of the cellular cytoskeleton. The targets of G$\beta\gamma$ heterodimers include ion channels, such as **G protein-coupled inwardly rectifying potassium** (GIRK) channels and Ca^{2+} channels, **G protein-coupled receptor kinases** (**GRKs**), **mitogen-activated protein kinases** (**MAPKs**), PLC-β and **phosphatidylinositol 3-kinase γ** (**PI3Kγ**) (Calebiro et al., 2021).

Downregulation of GPCRs and G protein-mediated signalling is coordinated by GRKs and β-arrestins. GRKs phosphorylate serine/threonine residues on the ICLs and C-termini of GPCRs, promoting the recruitment of β-arrestins from the cytosol. β-arrestins are ubiquitously expressed and categorised as visual (arrestin1 and 4) and non-visual (arrestin2 and 3) cytosolic adaptor proteins. Arrestins bind to phosphorylated and ligand-bound GPCRs and sterically prevent G protein binding, mediating receptor desensitisation. Arrestins are also scaffolds for the adaptor protein 2 and clathrin, promoting GPCR accumulation in clathrin-coated pits and their internalisation by clathrin-mediated endocytosis. This leads to the recycling of the receptor or lysosomal degradation. Before this, the receptor needs to be dephosphorylated by phosphatases (Jean-Charles et al., 2017).

While the topic is still subject to ongoing discussion, the interaction between β-arrestins and GPCRs has been suggested to trigger signal transduction pathways independently of G protein signalling. This is achieved through the formation of scaffolds that facilitate the activation of MAPK family members, including extracellular signal-regulated kinases 1/2 (ERK1/2) (Jain et al., 2018). Additionally, activation of β-arrestins by GPCRs allows them to modify signalling events that are typically dependent on G proteins, such as by facilitating the assembly of MAPK/ERK signalling components (Gutkind & Kostenis, 2018; Figure 1).

Another aspect of GPCR modulation is allosteric modulation, which modulates the activity of GPCRs by binding a ligand at a site distinct from the receptor's orthosteric site. Unlike orthosteric ligands that bind directly to the orthosteric (active) site and activate or inhibit the receptor, allosteric modulators bind to allosteric sites on the receptor, leading to conformational changes that can enhance or dampen the receptor's response to its endogenous ligand. Allosteric modulation offers several advantages over orthosteric modulation, including increased selectivity and the potential for fine-tuning receptor activity. By targeting allosteric sites, we can develop drugs that modulate a particular GPCR's signalling without interfering with other GPCRs that may share similar orthosteric ligands (Conn et al., 2014).

The binding of an allosteric modulator can result in positive allosteric modulation (PAM) or negative allosteric modulation (NAM). PAMs enhance the receptor's response to its endogenous ligand, increasing the signalling efficacy. On the other hand, NAMs reduce the receptor's response, effectively inhibiting its signalling. Allosteric modulators can also exhibit allosteric agonism or allosteric antagonism. Allosteric agonists directly activate the receptor in the absence of the endogenous ligand, while allosteric antagonists inhibit the receptor's activity even in the presence of the endogenous ligand. The discovery and development of allosteric modulators have opened up new avenues for drug discovery, as they offer the potential for more precise and targeted therapies. By selectively modulating the activity of specific GPCRs, allosteric modulators hold promise for treating various diseases, including neurological disorders (Wold & Zhou, 2018).

3 | GPCRs IN THE NERVOUS SYSTEM (PATHO)PHYSIOLOGY

3.1 | GPCRs in the modulation of synaptic function

3.1.1 | Physiology of the GPCRs in synaptic function

The synapse is a functional unit in the CNS in which communication between pre- and postsynaptic neurons takes place. Most synapses are 'tripartite synapses'. The tripartite synapse is a concept used to describe a type of synaptic unit that includes three components: the presynaptic neuron, the postsynaptic neuron, and the surrounding astrocytes. In the tripartite unit, the interactions between neurons and astrocytes are bidirectional, which is crucial for the maintenance of synaptic activity (Araque et al., 1999).

To maintain synaptic transmission, a highly energy demanding process involving the release, uptake and recycling of neurotransmitters and the restoration of neuronal ion gradients (Sokoloff, 1960), the supply of nutrients from the bloodstream to the brain and the brain energy metabolism must be tightly controlled. The latter involves the activation of various GPCRs on the surface of neurons, glial and endothelial cells, such as **adrenoceptors** (Fink et al., 2021; Hertz et al., 2010; Horvat, Muhič, et al., 2021) and lactate-sensitive receptors (Horvat, Zorec, & Vardjan, 2021; Vardjan et al., 2018). However, synaptic activity does not depend only on GPCRs regulating metabolic support of the synapse, but also on several GPCRs, which act as modulators, that is, facilitators or inhibitors, of synaptic transmission. GPCRs thus play a crucial role in synaptic plasticity, a mechanism underlying learning and memory in the brain that refers to the ability of synapses to strengthen or weaken over time in response to changes in synaptic activity. How GPCRs, such as mGlu receptors, $GABA_B$ receptors, 5-HT receptors, P2Y receptors and dopamine receptors, contribute to the modulation of synaptic activity, in particular the tripartite synapse activity, will be discussed next.

Metabotropic glutamate receptors (mGlu receptors)

mGlu receptors are class C GPCRs divided into three groups: stimulatory group I (**$mGlu_1$** and **$mGlu_5$**), coupled to $G\alpha_q$ proteins, and inhibitory groups II (**$mGlu_2$** and **$mGlu_3$**) and III (**$mGlu_4$**, **$mGlu_6$**, **$mGlu_7$** and **$mGlu_8$**) coupled to $G\alpha_{i/o}$ proteins. Except for $mGlu_6$ receptor, which is found exclusively in the retina, they are abundantly expressed in neuronal and glial cells throughout the brain (Table 1; Crupi et al., 2019). The endogenous mGlu receptor ligand is **glutamate**, the primary excitatory brain neurotransmitter, whose precursor, **glutamine**, is produced exclusively in astrocytes (Huang & Thathiah, 2015).

During increased brain activity, glutamatergic neurons release glutamate, which binds to and activates astroglial $mGlu_5$ receptors. This causes Ca^{2+} elevations in astrocytes, leading to a Ca^{2+}-dependent glutamate release from astrocytes and feedback regulation of synaptic activity (Araque et al., 1999). For example, astrocyte-derived

glutamate has been shown to activate presynaptic neuronal stimulatory $mGlu_1$ receptors, causing Ca^{2+}-dependent short-term potentiation of neurotransmitter release at hippocampal synapses, increasing synaptic strength. This transient potentiation of glutamate release, coupled with postsynaptic depolarization, can lead to persistent potentiation of glutamate release, causing long-term effects on synaptic transmission (Perea & Araque, 2007). Glutamate released from the individual astrocyte ensheathing multiple synapses can exhibit both excitatory effects on active synapses (described above) and at the same time inhibitory effects on neighbouring inactive synapses. The latter is mediated via presynaptic inhibitory group II and III mGlu receptors causing a transient reduction in glutamate release probability and a negative effect on synaptic strength, that is, heterosynaptic depression (Andersson et al., 2007). At the postsynaptic side, activation of group I mGlu receptors modulates the activity of **ionotropic glutamate N-methyl-D-aspartate (NMDA) receptors**, which was shown to either potentiate or depress synaptic transmission in the hippocampus depending on the type of synapse. This suggests the role of postsynaptic mGlu receptors in the well-studied forms of NMDA-mediated long-term plasticity, long-term potentiation (LTP) and long-term depression (LTD) (Bodzęta et al., 2021). The mGlu receptor-mediated effects of glutamate on synaptic activity are mainly achieved by modulation of ion channels (Reiner & Levitz, 2018).

$GABA_B$ receptors

GABA B receptors ($GABA_B$ receptors) are class C GPCRs. Two subtypes of $GABA_B$ receptors exist in the nervous system: **$GABA_{B1}$** and **$GABA_{B2}$** receptors. They are enriched in cortical, hippocampal and cerebellar brain regions. $GABA_B$ receptors are functional only after heterodimerization of both subtypes (Huang & Thathiah, 2015). They are coupled to $G\alpha_{i/o}$ proteins (Table 1) and exhibit inhibitory effects on neurotransmission. $GABA_B$ receptor signalling is involved, among others, in sleep cycle regulation (Huang & Thathiah, 2015). The endogenous ligand **γ-amino butyric acid** (**GABA**), the principal inhibitory brain neurotransmitter, is synthesised in GABAergic interneurons from astrocyte-derived glutamine or in astrocytes themselves (Yarishkin et al., 2015) as well as in some other groups of neurons, that is, projection neurons from the rostral ventromedial medulla (Aicher et al., 2012) and the subcortical supramammillary nucleus (Hirai et al., 2022).

The GABAergic system allows precise control of the excitatory level of neuronal networks by tuning excitatory and inhibitory synaptic transmission through GABA-mediated signalling at both glutamatergic and GABAergic terminals. At low intensity of perforant path stimulation, astrocyte-derived GABA acting on $GABA_B$ receptors in GABAergic interneurons produces a disinhibitory effect on hippocampal excitatory synapses of dentate granule neurons (Yarishkin et al., 2015). Moreover, stimulation of GABAergic interneurons can trigger $GABA_B$ receptor-dependent Ca^{2+} increase and subsequent glutamate release from astrocytes, resulting in enhanced $mGlu_1$ receptor-dependent excitatory glutamatergic neurotransmission in hippocampal slices (Perea et al., 2016). Alternatively, $GABA_B$ receptor signalling in astrocytes can also cause heterosynaptic depression in the hippocampus (Andersson et al., 2007). The differential effects of $GABA_B$ receptor signalling on synaptic transmission in the context of the tripartite synapse were further supported by the study which showed that depending on the frequency and duration of the stimulation, interneuron-released GABA could cause $GABA_B$ receptor-mediated release of glutamate or **ATP**/**adenosine** from hippocampal astrocytes that either potentiates or depresses neurotransmitter release at CA3-CA1 hippocampal synapses, respectively (Covelo & Araque, 2018). This suggests that astrocytes can decode neuronal activity and even convert inhibitory signals into excitatory ones, especially in the well-studied astrocyte-neuron network in the hippocampal CA1 region, adding another layer of complexity to understanding the physiology of brain excitability. Furthermore, GABAergic medium spiny neurons (MSNs) in the dorsal striatum can by releasing GABA activate $G\alpha_{i/o}$-coupled $GABA_B$ receptors on the surface of neighbouring astrocytes causing intracellular Ca^{2+} signalling in astrocytes. This modifies the neural circuits within the striatum that control behaviour. Specifically, it increases fast synaptic excitation and firing of MSNs, contributing to a state of hyperactivity accompanied by disrupted attention. The latter coincided with an increase in the expression of **thrombospondin-1** (**TSP-1**), an important synaptogenic factor derived from astrocytes, and is reversed by blocking the effects of TSP1, revealing potential new therapeutic targets for addressing hyperactivity, attention deficits, and associated psychiatric disorders (Khakh, 2019; Nagai et al., 2019).

5-Hydroxytryptamine receptors (5-HT receptors)

Most (13 of 14) **serotonin** or **5-hydroxytryptamine** (**5-HT**) receptor subtypes with the exception of the **$5\text{-}HT_3$** receptor subtype, which is a ligand-gated ion channel, belong to class A GPCRs. They are classified into six **5-HT receptor** subtypes: **$5\text{-}HT_1$**, **$5\text{-}HT_2$**, **$5\text{-}HT_4$**, **$5\text{-}HT_5$**, **$5\text{-}HT_6$** and **$5\text{-}HT_7$**. The endogenous ligand serotonin is produced by serotonergic neurons, which mainly originate from the raphe nuclei and innervate practically all brain regions. 5-HT receptors are mostly postsynaptic and have different (even opposing) effects on neurotransmission. They are coupled to $G\alpha_q$, $G\alpha_s$ or $G\alpha_{i/o}$ proteins (Table 1) and modulate various brain processes, including cognition, motor function, sleep–wake behaviour and cortical development (Celada et al., 2013).

The most prevalent and researched are **$5\text{-}HT_{1A}$** and **$5\text{-}HT_{2A}$** receptors, which are coupled to $G\alpha_{i/o}$ and $G\alpha_q$ proteins, exhibiting inhibitory and excitatory effects on brain circuits, respectively. Both subtypes are particularly enriched in the cerebral cortex (especially the prefrontal cortex) and show high co-expression in cortical neurons. At the glutamatergic synapses, activation of neuronal $5\text{-}HT_{1A}$ receptors inhibits ionotropic glutamate NMDA receptor and **α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid** (AMPA) receptor activity. On the other hand, the $5\text{-}HT_{2A}$ receptor is the main excitatory 5-HT receptor whose activation causes neuronal depolarization resulting in an increased discharge rate. $5\text{-}HT_{1A}$ and $5\text{-}HT_{2A}$ receptors also exert homeostatic control over the firing rate of serotonergic neurons and control serotonin efflux (Celada et al., 2013). However, much less is known about the 5-HT effect on synaptic activity mediated by astrocytes. A recent study showed that activation of

astroglial 5-HT_4 receptors triggers a $G\alpha_{13}$-mediated increase in RhoA activity, a small GTPase of the Rho family known to be involved in the regulation of cell cytoskeleton. The resulting accumulation of filamentous actin induces changes in cell morphology, affecting glutamatergic neurotransmission. This represents a novel functional regulation of possibly even multiple excitatory synapses simultaneously (Müller et al., 2021).

Metabotropic purinergic receptors

Purinergic signalling in the nervous system is mediated by two subtypes of purinergic receptors: **P1 purinergic receptors** and P2 purinergic receptors, which bind adenosine or ATP/ADP/**AMP**, respectively. P2 receptors are further subdivided into **ionotropic P2X** and **metabotropic P2Y receptors**. ATP (also adenosine) can be released by neurons and neuroglia. In the extracellular space, ATP is rapidly degraded by extracellular ectonucleotidases to ADP, AMP and adenosine (Abbracchio et al., 2009; Burnstock, 2006, 2018). We will only discuss the role of metabotropic P1 and P2Y GPCRs in synaptic transmission.

Adenosine receptors. P1 purinergic receptors, also named **adenosine receptors** (**ARs**), are class A GPCRs with four subtypes (**A_1**, **A_{2A}**, **A_{2B}** and **A_3**) (Table 1). All subtypes of adenosine receptors are expressed in the nervous tissue, both in neurons and glia (Abbracchio et al., 2009; Verkhratsky & Nedergaard, 2018) and respond to adenosine (Boison, 2007). A_{1A} receptors and A_{2A} receptors are the main brain adenosine receptors, while A_{2B} receptors and A_{3A} receptors are expressed at low levels. A_1 and A_3 receptors are coupled to $G\alpha_{i/o}$ proteins, whereas A_{2A} and A_{2B} receptors are coupled to $G\alpha_s$ proteins. The A_{1A} receptor is abundantly expressed in the cortex, hippocampus, and cerebellum, while the A_{2A} receptor is primarily found in the striatum and olfactory bulb (Table 1). Adenosine receptor subtypes can form heteromers and oligomerize with other GPCRs. Modulation of neurotransmitter release by brain A_1 and A_{2A} receptors has been associated with neuroprotection, sleep–wake cycle regulation, and analgesic effect (Abbracchio et al., 2009; Verkhratsky & Nedergaard, 2018).

A_1 and A_{2A} receptors are located mainly in the excitatory (glutamatergic) synapse. Activation of A_1 receptors by astrocytic adenosine inhibits, while activation of A_{2A} receptors facilitates neuronal excitatory transmission (Kofuji & Araque, 2021). Adenosine via A_1 receptors reduces (i) presynaptic Ca^{2+} influx and glutamate release and (ii) postsynaptic activation of **ionotropic glutamate receptors** and **voltage-gated Ca^{2+} channels** (**VGCCs**). In contrast, the adenosine A_{2A} receptor enhances the evoked presynaptic glutamate release and the function of postsynaptic ionotropic glutamate receptors. A_{2A} receptor activation also decreases the efficiency of presynaptic adenosine A_1-receptor and **cannabinoid CB_1 receptor**-mediated inhibitory systems, switching presynaptic modulation from inhibitory to facilitatory. Adenosine A_{2A} receptors located in astrocytes and microglia regulate glial **Na^+/K^+-ATPase**, glutamate uptake, and proinflammatory cytokine production, which may contribute to the A_{2A} receptor-mediated control of synaptic plasticity (reviewed in Abbracchio et al., 2009; Cunha, 2016; Verkhratsky & Nedergaard, 2018).

P2Y receptors. P2Y receptors belong to the class A GPCRs. They are divided into eight subtypes grouped into $P2Y_1$-like receptors ($P2Y_{1,2,4,6,11}$) and $P2Y_{12}$-like receptors ($P2Y_{12-14}$) with different sensitivity to ATP, ADP, **UTP**/ATP, **UDP**, **UDP-glucose** or other UDP-sugars. $P2Y_1$-like receptors are preferentially coupled to $G\alpha_q$ proteins, while $P2Y_{12}$-like receptors couple to the $G\alpha_i$ proteins (Table 1; Abbracchio et al., 2009). They can form homo- or heterodimers with other P2Y receptors or GPCRs (e.g., A_1 receptor). P2Y receptors are expressed on neurons and glia (Guzman & Gerevich, 2016; Kofuji & Araque, 2021). They inhibit the presynaptic release of neurotransmitters, including GABA, noradrenaline and serotonin and have been linked to the modulation of cognition and stress response. For example, **$P2Y_4$** receptors inhibit GABA release from basket cells, inhibitory interneurons in the cerebellar cortex that innervate Purkinje cells. In the spinal cord, hippocampus, and cortex, noradrenaline release is blocked by activation of **$P2Y_1$**, **$P2Y_{12}$** and **$P2Y_{13}$** receptors. Moreover, in the cortex P2Y receptor activation decreases serotonin release. This inhibitory action of P2Y receptors has been linked to their inhibitory effect on various types of presynaptic VGCCs via the $G\beta\gamma$ subunit (Guzman & Gerevich, 2016).

P2Y receptors can also modulate postsynaptic signalling. Notably, $P2Y_1$ receptor has been found to inhibit the activity of the postsynaptic ionotropic glutamate NMDA receptor, while $P2Y_4$ receptor enhances it. Furthermore, $P2Y_1$ receptor enhances the sensitivity of $GABA_A$ receptors and boosts inhibitory transmission through $GABA_A$ receptors. Moreover, ionotropic P2X receptor activity is reduced by $P2Y_1$ receptors. P2Y receptors were also associated with postsynaptic inhibition of L-type VGCCs, KCNQ2/3 **voltage-gated potassium channels**, and modulation of GIRK1,2,4 channels. The latter can be activated or inhibited by P2Y receptors, depending on the P2Y receptor subtype (Guzman & Gerevich, 2016).

Activation of astrocytic $P2Y_1$ receptors by ATP released from neural cells causes Ca^{2+} elevations in the hippocampal, olfactory bulb and nucleus accumbens (NAc) astrocytes. This can trigger intercellular Ca^{2+} waves in the astrocytic network and Ca^{2+}-dependent glutamate release from astrocytes. Glutamate then postsynaptically activates neuronal extrasynaptic NMDA receptors generating slow inward currents that increase neuronal excitability and/or presynaptic NMDA receptors and NMDA receptor-dependent synaptic potentiation. Astrocytic $P2Y_1$ receptor activation also triggers the activation of neuronal mGlu receptors and P2X receptors, increasing neuronal excitability (Kofuji & Araque, 2021).

Dopamine receptors

Dopamine receptors are class A GPCRs, which are divided into (i) **D_1**-like stimulatory family (**D_1** and **D_5** receptors) coupled to $G\alpha_s$ signalling and (ii) **D_2**-like inhibitory family (**D_2**, **D_3** and **D_4** receptors) coupled to $G\alpha_{i/o}$ signalling (Table 1; Beaulieu & Gainetdinov, 2011). Dopamine receptors are enriched in the striatum, a basal ganglia structure in the brain, but are also found in other regions of the nervous system (Table 1). In the striatum, D_1 and D_2 receptors are preferentially located in the GABAergic MSNs, which represent 90%–95% of the striatal neuronal population. Activation of dopamine receptors on

MSNs in dorsal striatum (caudate nucleus, putamen) has been mainly linked to modulation of motor function (loss of dopaminergic neurons in the substantia nigra with dopamine receptor-mediated signalling in dorsal striatum is a key feature of Parkinson's disease (PD)) and cognitive control, while in ventral striatum (NAc, olfactory tubercle) to modulation of mood, behaviour and reward system (Corkrum et al., 2020).

Aside from the direct influence of **dopamine** on dopamine receptors located on striatal GABAergic MSNs, dopamine released synaptically from midbrain dopaminergic neurons in the NAc can also stimulate astrocytic D_1 receptors. Astrocytes within the NAc establish a tripartite synaptic complex with MSNs that are directly regulated by midbrain dopaminergic neurons and glutamatergic projection neurons originating from corticolimbic brain structures (such as the prefrontal cortex, amygdala, and hippocampus). Dopaminergic activation of astrocytes results in the activation of the IP3 signalling cascade and intracellular Ca^{2+} mobilisation in astrocytes in situ and in vivo. The latter depresses synapse function, most likely by subsequent Ca^{2+}-triggered astrocytic ATP/adenosine release and activation of adenosine A_1 receptors on presynaptic glutamatergic neurons, suggesting that receptors from the D_1-like receptor family are not coupled only to $G\alpha_s$ proteins (Corkrum et al., 2020). Dopamine can trigger intracellular Ca^{2+} elevations in hippocampal astrocytes via D_1 receptor activation in situ (Jennings et al., 2017). In contrast, activation of D_2 receptors in hippocampal and ventral midbrain astrocytes can decrease Ca^{2+} in astrocytes, which has been associated with the inhibition of $\alpha\beta$-crystallin-mediated neuroinflammation in vivo (Kofuji & Araque, 2021). The role of astroglial D_2 receptor activation at the level of neuron–glia communication is not yet clear.

3.1.2 | Pathophysiology and pharmacology of GPCRs modulating synaptic activity

Understanding the role of GPCRs in synaptic plasticity is essential for unravelling the molecular and cellular mechanisms underlying learning and memory processes in the brain. Dysregulation of synaptic GPCR signalling has been implicated in various neurological and psychiatric disorders, emphasising the importance of these receptors in maintaining proper synaptic function. mGlu receptors are critically involved in different forms of synaptic plasticity and also in the pathophysiology of several brain disorders, including Alzheimer's disease (AD), PD and Huntington's disease (HD). Impaired $GABA_B$ receptor function can contribute to the pathophysiology of epilepsy, and sleep disorders and can negatively affect memory formation (Huang & Thathiah, 2015). The serotonergic system is involved in the pathophysiology of different psychiatric disorders (Liu et al., 2019). A recent preprint suggests altered serotonergic neuron-astrocyte communication in depressive-like states. The study shows that in a mouse model of corticosterone-induced depression, astrocytes and neurons in the medial prefrontal cortex exhibit abnormal 5-HT-mediated Ca^{2+} signalling and synaptic plasticity, respectively (https://doi.org/10.21203/rs.3.rs-2361503/v1). The impairment of dopamine's regulation of synaptic plasticity is linked to a range of neuropsychiatric disorders, including attention-deficit/hyperactivity disorder, schizophrenia, PD, and Tourette's syndrome (Madadi Asl et al., 2019). The modulatory effect of A_1 and A_{2A} receptors on synaptic plasticity has been recognised as therapeutic potential across various neuropsychiatric disorders, including depression, anxiety, schizophrenia, autism spectrum disorder, fragile X syndrome, AD, PD, attention-deficit/hyperactivity disorder (Pasquini et al., 2022). Moreover, $P2Y_1$ receptor activation in AD, traumatic brain injury, ischaemia, and schizophrenia has been linked to disease-associated cognitive deficits. Modulating the activity of $P2Y_1$ receptors shows promise as a therapeutic avenue for treating cognitive disorders (Guzman & Gerevich, 2016). Several therapeutic interventions targeting GPCRs that modulate synaptic plasticity (5-HT, dopamine and adenosine receptors) are currently underway or recruiting patients for neurological and neuropsychiatric disorders, for example, dementia, AD, PD, mild cognitive impairment, bipolar disorder, migraine, Tourette's syndrome, tic disorders, Parkinson's tremor, spinal cord injury and gliomas (see Table 2).

3.2 | Opioid receptors

3.2.1 | Physiology of opioid receptors

Opioid receptors are class A rhodopsin-like GPCRs expressed throughout the mammalian nervous system on neurons and glial cells (Table 1). They are divided into three main receptor subtypes: mu (**μ receptor**), delta (**δ receptor**) and kappa (**κ receptor**), which preferentially bind the endogenous opioid peptides (opioids) **β-endorphin**, enkephalins, and dynorphins, respectively (Table 1) (Margolis et al., 2023). The **nociceptin/orphanin FQ (NOP) receptor** is also considered as a member of the opioid receptor family, due to high sequence homology, but, since it does not respond to opioids pharmacologically, will not be further referred to herein (Calo' et al., 2000). Both the opioid receptors and their endogenous peptide ligands have a widespread anatomical distribution in the brain and the central and peripheral nervous systems (Table 1), which associates with specific physiological circuits (Valentino & Volkow, 2018). Specifically, the three opioid receptors are found in the prefrontal/cerebral cortex, amygdala, striatum, NAc, ventral tegmental area and hippocampus (Table 1; Kibaly et al., 2019). Activation of opioid receptors elicits presynaptic and postsynaptic inhibition and their expression pattern and localisation in projection neurons and inhibitory interneurons in these brain regions allow them to be implicated in a wide range of behavioural responses (Benarroch, 2012). Opioid receptors couple to conventional $G\alpha_{i/o}$ and non-conventional $G\alpha_{z/g}$ protein subtypes (Garzón et al., 1997; Georgoussi et al., 1997; Han et al., 2023) to inhibit AC, and regulate PLC, MAPK, and a variety of ion channels (Table 1). Moreover, the recruitment of β-arrestin and opioid receptor interaction with other proteins triggers G protein-independent signalling to regulate processes related to pain perception, tolerance, dependence, stress responses, mood and affect (Georgoussi et al., 2012; Valentino & Volkow, 2018).

3.2.2 | Pathophysiology and pharmacology of opioid receptors

Analgesic effects

Activation of the μ receptors in the midbrain triggers analgesic effects by reducing the transmission of nociceptive signals from peripheral nerves (Pathan & Williams, 2012). However, opioid receptor ligands can also cause severe side effects, including respiratory depression. The potent μ receptor agonist **fentanyl** has high addictive potential but is linked to numerous overdose deaths due to respiratory depression. However, its fluorinated derivative NFEPP (N-[3-fluoro-1-phenetylpiperidin-4-yl]-N-phenylpropionamide) is of therapeutic interest, being less toxic (Spahn et al., 2017) devoid of respiratory depression effects (Jiménez-Vargas et al., 2021). **Fentanyl** and NFEPP have distinct intrinsic dynamics (Giannos et al., 2021), and their binding to the μ receptor associates with distinct responses of the receptor, suggesting that a cytoplasmic interaction partner might encounter agonist-dependent binding interfaces (Lešnik et al., 2023).

Knowing that, under certain conditions, GPCRs can preferentially interact and signal via G proteins or β-arrestins has given rise to efforts to produce so-called signal-biased drugs, that is, drugs that induce receptor conformations that favour G-protein activation over β-arrestin recruitment or vice versa (Kudla & Przewlocki, 2021). Biased agonism is a central topic in μ receptor drug discovery. The adverse effects of **morphine**, another μ receptor agonist, were associated with the β-arrestin2 pathway and not G protein signalling (Raehal et al., 2005). Consequently, significant drug discovery efforts have been made to find biased agonists towards the G protein signalling pathway, which may include evaluations of the various G protein subtypes (Qu et al., 2022). However, the proposal of biased agonism for μ receptor pharmacological therapeutics has been questioned and is currently under debate (Gillis, Kliewer, et al., 2020). Moreover, a new hypothesis has recently emerged proposing that partial agonism and not ligand bias can explain the separation of antinociception from respiratory depression (Gillis, Gondin, et al., 2020). Mathematical models that integrate observations from experiments and computation studies could tackle some of the complexity of the opioid system and can help reconcile the conflicting views on the molecular mechanisms of opioid-associated respiratory depression (Burgueño et al., 2017). The δ receptor is also an attractive therapeutic target for chronic pain with milder adverse effects. However, δ receptor agonists have been linked with proconvulsive activity and the development of analgesic tolerance (Conibear et al., 2020). Recent data reveal that dual-target μ receptor/δ receptor ligands exhibit an improved antinociceptive profile associated with a reduced tolerance-inducing capability (Pasquinucci et al., 2021). On the other hand, activation of the κ receptor elicits antinociceptive effects with low abuse potential. However, κ receptor agonists are not used for pain treatment in humans, due to severe side effects. A possible approach to reduce these effects is the development of biased agonists such as Triazole 1.1, that promotes κ receptor–G protein interaction and not the β-arrestin recruitment responsible for the aversion-related behaviours (Brust et al., 2016; Santino & Gentilucci, 2023). Besides opioid receptors, other membrane proteins are of direct interest as potential targets of drugs against neuropathic pain, for example, the **voltage-gated sodium channels** (Na_V). Still, the role of these channels in neuropathic pain remains under investigation (Finnerup et al., 2021).

Opioids for weight loss and major depressive disorder therapies

Opioid agonists can increase food intake, whereas **naloxone**, a universal opioid antagonist, reduces both food and high-sucrose solutions intake in animal behavioural studies (Cleary et al., 1996; King et al., 1979). The opioid antagonist naltrexone is associated with minimal weight loss compared to placebo (Malcolm et al., 1985). However, a combination of naltrexone with the antidepressant **bupropion**, the latter causing modest weight loss (Anderson et al., 2002), produces a synergistic effect, with 'naltrexone-bupropion therapy' being in phase III clinical trials for long-term weight loss (le Roux et al., 2022). κ receptor antagonists such as the non-peptide **nor-binaltorphimine** (**nor-BNI**) exert anxiolytic effects, possibly through autophagy regulation (Karoussiotis et al., 2022); a major concern regarding its potential clinical usage is drug accumulation arising from long-lasting effects in vivo (Li et al., 2016). Aticaprant, another potent κ receptor antagonist, is of interest as an adjunctive treatment for major depressive disorders, and is currently in phase III clinical trials (Table 2).

Neuroprotective roles of opioid receptors

Opioid drug usage may increase the risk of cerebrovascular events – as observed in intense morphine therapy for prostate cancer patients, and other chronic opioid therapies (Lee et al., 2013). As cerebral disease is linked to dysregulated energy metabolism (Jiang et al., 2007), one potential link between opioid usage and cerebrovascular events might involve energy metabolism: chronic morphine treatment associates with altered expression levels of three metabolic enzymes in rat hippocampus; with cerebral ischaemia/reperfusion injury (Chen et al., 2007). In contrast, naloxone reduced the infarct volume and increased the activity of antioxidant enzymes (Chen et al., 2000). The density of the δ receptor decreased rapidly during the acute phase of focal cerebral ischaemia (Boutin et al., 1999). Activation of the δ receptor exerts a neuroprotective role, as it associates with a reversal of ischaemia-induced reduction of the brain-derived neurotrophic factor (**BDNF**)-**TrkB** cell signalling pathway (Sheng et al., 2018), and it enhances neuronal cell survival by limiting apoptosis due to cellular ischaemic death. Intracerebroventricular administration of δ receptor agonists increases cell proliferation and neural differentiation in the hippocampus leading to memory-enhancing changes in ischaemic animal models (Wang et al., 2016).

Besides ischaemia, δ receptor activation provides retinal neuroprotection (Husain, 2018); in cell models for AD injury, δ receptor activation decreases the expression and catalytic activity of **beta-secretase 1** (**BACE1**), with the μ receptor displaying an opposite effect (Xu et al., 2020). δ Receptor agonists also exert a neuroprotective role via a signalling complex composed of $G\alpha_{i/o}$, **signal transducers and**

activators of transcription 5B (STAT5B) and the regulator of G protein signalling 4 (RGS4) protein (Georganta et al., 2013; Pallaki et al., 2017). The neuroprotective role of the κ receptor is underlined by the findings that its activation reduces dyskinesia caused by levodopa, a drug against PD (Dalefield et al., 2022). The present knowledge could help verify specific hypotheses as to which signal supports desired or undesired side effects on the action mechanisms and could contribute to the rational design of new therapeutics.

3.3 | Acetylcholine receptors (muscarinic)

3.3.1 | Physiology of muscarinic acetylcholine receptors

Acetylcholine receptors (muscarinic) are class A GPCRs comprising five subtypes (M_1–M_5) with different G protein-coupling preferences, which are all expressed throughout the brain (Table 1) (Felder, 1995; Volpicelli & Levey, 2004). The **M_1 receptor** is the most predominant in the CNS, highly expressed in the cerebral cortex and hippocampus. The M_1 receptor is critical for cognition and locomotion control. M_1 receptor signalling exerts neuroprotective effects in mice (Scarpa et al., 2021). **M_2 receptors** are expressed in the forebrain, thalamus, and motor neurons. Compared to other muscarinic subtypes, the **M_3 receptors** are expressed at low levels across the brain. Although its function in the CNS is largely understudied, the M_3 receptor has been implicated in the regulation of cardiovascular sympathetic activity by orexin neurons in the brainstem (Dai et al., 2016). The **M_4** receptor is abundant in the striatum and is involved in emotional and social behaviour (Koshimizu et al., 2012). The **M_5** receptor, found in midbrain projection neurons and hippocampus, is linked to alcohol and morphine-induced addiction (Basile et al., 2002).

3.3.2 | Pathophysiology and pharmacology of muscarinic acetylcholine receptor

M_1 receptor-selective PAMs were shown to reduce pathology in AD animal models (Dwomoh et al., 2022; Lebois et al., 2017). M_1 receptors are a validated drug target for treating cognitive dysfunction, especially in AD (Scarpa et al., 2020). M_2 receptors are reduced in the anterior cingulate cortex of patients with bipolar and major depressive disorders, suggesting the M_2 receptor is a potential drug target for the treatment of such psychiatric conditions (Cannon et al., 2006). Clinical trials of the M_1/M_4-preferring agonist **xanomeline** could improve cognitive impairments and psychosis-like behaviour in schizophrenic patients (Shekhar et al., 2008) and, importantly, the antipsychotic effects were driven by the M_4 receptor (Woolley et al., 2009). M_4 receptor-selective PAMs could induce cognitive enhancement and antipsychotic-like effects in rodent models of schizophrenia, highlighting their promising therapeutic potential (Gould et al., 2018). M_5 receptor expression is up-regulated in rat brain following long-term alcohol consumption, and morphine-induced addiction (Basile et al., 2002). M_5 receptor-selective NAMs reduce alcohol self-administration in rats (Walker et al., 2021), supporting the potential of negatively modulating M_5 receptor signalling as a therapeutic avenue for drug abuse.

3.4 | Chemokine receptors

3.4.1 | Physiology of chemokine receptors

Chemokines, also known as chemotactic cytokines, are small signalling proteins (7–12 kDa) that control several processes, such as cell migration, proliferation, and differentiation (Thelen & Stein, 2008). They exert their biological effects by activating chemokine receptors, class A rhodopsin-like GPCRs. Chemokines and their receptors are widely distributed in the CNS and are expressed in neurons, glia (microglia, astrocytes, oligodendrocytes), and endothelial cells. They are involved in many (patho)physiological brain functions, including synaptic transmission, neuron–glia communication, and inflammation (Sowa & Tokarski, 2021).

Chemokine receptors activate several signalling pathways, such as G proteins, β-arrestins or **Janus kinase**/signal transducers and activators of transcription (**JAK**/STAT) pathways except for some atypical ones. Although some chemokine receptors bind only a unique chemokine, it is common that several chemokines can interact with a particular receptor (Luster et al., 1995) and vice versa. Many chemokines also bind to the atypical chemokine receptors (ACKR), which act mainly as scavenger receptors. Chemokine receptors can form homodimers and heterodimers with other chemokine receptors or GPCRs (e.g., opioid receptors; Dorsam & Gutkind, 2007). Opposite to classical chemokine GPCRs, ACKRs do not promote G protein-mediated signalling upon ligand binding, while they preserve the capability to recruit β-arrestins and internalise bound ligands (Bachelerie et al., 2014). While various chemokine receptors are expressed in the brain, this review will only focus on **CXCR3** and **CXCR4**, which belong to the CXC chemokine receptor (CXCR) family.

CXCR3

CXCR3 is expressed on a wide variety of immune cells infiltrating the brain, such as **interleukin-2** (**IL-2**) activated T helper type 1 (Th1) cells, cytotoxic $CD8^+$ T cells, natural killer (NK) cells and dendritic cells. It is also found in non-immune cells, particularly endothelial, epithelial and smooth muscle cells (Andrews & Cox, 2016; Groom & Luster, 2011a, 2011b). The human CXCR3 has three alternative splice variants: CXCR3-a, CXCR3-b and CXCR3-alt, which differ in their carboxy- or amino-terminal domains (Lasagni et al., 2003). **CXCL9**, **CXCL10**, and **CXCL11** activate CXCR3-a, whereas CXCR3-b interacts with an additional selective ligand, **CXCL4** (Lasagni et al., 2003). In addition to their varying affinities for the ligands, CXCR3-a and CXCR3-b have been proposed to have distinct expressions and functions, leading to opposite cellular effects (Berchiche & Sakmar, 2016). CXCR3-a is present in the fetal and mature brain (especially in glial cells, e.g., astrocytes,

Purkinje cells of the cerebellum, endothelial cells of the choroid plexus) (Van Der Meer et al., 2001). However, CXCR3-b is selectively present in endothelial cells such as the human microvascular endothelial cells (HMEC-1) (Lasagni et al., 2003).

CXCR4. CXCR4 is a critical regulator of cell migration in the context of immune surveillance and development. In humans, there are two variants of CXCR4, CXCR4-A and CXCR4-B, with CXCR4-B being the more highly expressed variant (Kaiser et al., 2021). CXCR4 is one of the few chemokine receptors that bind exclusively to one chemokine, CXCL12, also known as stromal cell-derived factor 1 (Bachelerie et al., 2014). CXCR4 in the CNS is expressed in NPCs, whereas astrocytes express **CXCL12** (Murray et al., 2022). CXCL12 has six functional transcript variants in humans (**CXCL12α**, **CXCL12β**, **CXCL12γ**, **CXCL12ε**, **CXCL12δ** and CXCL12θ), with **CXCL12γ** having the lowest affinity for CXCR4 while CXCL12α has the highest affinity. CXCR4 internalises only after activation by CXCL12, and the internalised receptor subsequently degrades, leading to a negative modulation of CXCR4 expression at the cell membrane. The binding between CXCR4 and CXCL12 is regulated by the scavenger activity of **ACKR3**, which binds CXCL12 more effectively than CXCR4 (Huynh et al., 2020). Thus, ACKR3 actively maintains CXCL12 gradients, critical for target cell migration (Huynh et al., 2020). During CNS development, the CXCR4/ACKR3/CXCL12 axis also directs neuronal migration. CXCR4 signalling induces the survival and migration of NPCs and oligodendrocyte precursor cells (OPCs). In addition, CXCL12 signalling regulates neuroblast migration within the rostral migratory stream. Furthermore, CXCL12 induces the migration of HSCs CXCR4 (Dillenburg-Pilla et al., 2015). Depending on the CXCL12 concentration, CXCL12 can induce different cellular responses (e.g., activation, mobilisation, homing, and retention). In CNS, CXCL12 at low concentrations promotes NPC migration, while, at high concentrations, it favours NPC adhesion (Bianchi & Mezzapelle, 2020).

3.4.2 | Pathophysiology and pharmacology of CXCR3 and CXCR4 chemokine receptors

The CXCR3-a isoform has been associated (with its cognate ligands) with various neurological disorders (Dijkstra et al., 2004; Fife et al., 2001; Hamilton et al., 2002; Huang et al., 2000; Kivisäkk et al., 2002; Pu et al., 2015; Rappert et al., 2004). The CXCR3 and its ligand **CXCL10** were shown to be crucial for microglia activation and migration to the lesion site after brain injury (Rappert et al., 2004). CXCR3 has been implicated in glioma development (Pu et al., 2015) and increased glioma cell migration from the primary tumour site (Boyé et al., 2017). It has also been reported that in glioblastoma, CXCR3 signalling promotes the recruitment of specific brain resident memory T cells to tumour sites (Zhao et al., 2023).

Moreover, the CXCL12/CXCR4 axis in the CNS has therapeutic potential in regeneration processes, inducing homing by regulating cell secretion and adhesion molecules (Bianchi & Mezzapelle, 2020). CXCL12/CXCR4 signalling influences stem cell migration from the bone marrow or niche to repair damaged tissues. CXCL12 in the damaged tissue recruits stem cells and regulates their differentiation to repair injuries in the CNS. In the damaged CNS, CXCR4 in vitro activation promotes the differentiation of human embryonic stem cells into neural stem cells (NSCs). The importance of the CXCL12/CXCR4 signalling axis becomes much more evident in pathological states where signalling is deregulated, including HIV infection and in all major CNS cell types, including neurons, astroglia, microglia, oligodendrocytes (Nash & Meucci, 2014). Consequently, it can be used for regenerative medicine in the future in damaged tissue in patients.

3.5 | Melatonin receptors

3.5.1 | Physiology of melatonin receptors

Melatonin receptors are class A rhodopsin-like GPCRs activated by **melatonin**, a natural neurohormone produced primarily at night by the pineal gland. Melatonin helps regulate circadian rhythms, particularly the sleep–wake cycle. Melatonin is permeable to cell membranes and crosses the BBB to activate two types of melatonin receptors, **MT_1** receptors and **MT_2** receptors, which are found in the brain and preferentially activate inhibitory $G\alpha_{i/o}$ proteins (Table 1).

Although the precise effects and mechanisms of action of melatonin receptors in the brain are still not fully understood, they are gaining interest due to their diverse functions. These receptors are suggested to protect the BBB and may directly or indirectly affect neuronal functions. MT_2 receptor activation has been shown to increase neural stem cell proliferation in vitro and promote neurogenesis in vivo, improving neuronal function in a mouse model of ischaemic stroke (Chern et al., 2012). Additionally, recent intriguing findings reveal that the MT_1 receptor is localised and signals in neuronal mitochondria and may contribute to the neuroprotective effects of melatonin by reducing ischaemic brain damage in mice (Suofu et al., 2017). In addition to their classical signalling functions, these receptors have atypical roles independent of their signalling capacity. MT_1 and MT_2 receptors interact with and retain the dopamine transporter (**DAT**) in its immature, non-glycosylated form within the ER, thereby regulating its availability at the cell membrane. This, in turn, limits the reuptake of striatal dopamine in mice, and melatonin receptor knockout (KO) mice show decreased amphetamine-induced locomotor activity (Benleulmi-Chaachoua et al., 2018).

3.5.2 | Pathophysiology and pharmacology of melatonin receptors

Drugs that target these receptors, such as Ramelteon®, are prescribed for minor conditions like jet lag and insomnia. Agomelatine, a dual

ligand agonist of melatonin receptors and an antagonist of serotonin 5-HT_{2C} receptors, is used for depression treatment. In mice, there is evidence of heteromeric MT_2 receptor/5-HT_{2C} receptor complexes, which may also exist in humans and may contribute to the antidepressant effects of **agomelatine** (Gerbier et al., 2021; Table 2).

Recent advances include the determination of MT_1 and MT_2 receptor structures bound to various ligands (Stauch et al., 2019) or in complex with $G\alpha_{i/o}$ proteins (Wang et al., 2022). These structures are crucial for initiating virtual screens to identify new specific modulating ligands for these receptors (Stein et al., 2020).

3.6 | Adhesion GPCRs

3.6.1 | Physiology of adhesion GPCRs

Adhesion class GPCRs (aGPCRs) are class B2 GPCRs that constitute the second largest GPCR family in mammals. Several aGPCRs are expressed in nervous tissue, shaping fundamental neurobiological processes such as synaptogenesis, axon guidance and myelination (Liebscher et al., 2022).

aGPCRs are metabotropic mechanosensors comprised of non-covalently linked N- and C-terminal fragments (NTF and CTF) (Lin et al., 2022; Scholz et al., 2016). Recent work has shown that NTF-CTF dissociation can be induced by ligands and mechanical force and that the resulting fragments may serve specific neural functions (Hamann et al., 2015; Petersen et al., 2015; Scholz et al., 2023). For example, a critical step during peripheral nervous system development is to choose which axons to myelinate (radial sorting; Feltri et al., 2016). **ADGRG6/GPR126** is expressed in Schwann cells, and its NTF is important to keep them immature and for radial sorting, whereas the CTF promotes axon wrapping by increasing cAMP. The latter is initiated when ADGRG6 'feels' basal lamina stiffening, that is, its ligand Laminin-221 polymerising (Petersen et al., 2015). In the developing *Drosophila* brain, **ADGRL**/Latrophilin/Cirl (calcium-independent receptor of α-latrotoxin) is expressed in the neuroblast lineage and cortex glia. Glia-derived NTF controls the size of the neuroblast pool non-cell autonomously. Strikingly, the **Toll-like receptor** Toll-8/Tollo can promote or prevent this glia-to-neuroblast signalling, depending on its expression in *cis* or *trans* to Cirl (Scholz et al., 2023). Moreover, Cirl modulates the sensitivity of peripheral mechanosensory neurons to touch and sound as well as nociceptive neurons to noxious mechanical stimuli (Dannhäuser et al., 2020; Scholz et al., 2015).

Mounting evidence supports the idea that the mechanical 'signature' of cells and tissues is involved in the modulation of vital neural processes (Barnes et al., 2017). Yet, more often than not, it remains unknown how neural cells sense and transduce mechanical forces and how this impinges on the biochemical and genetic profile. Future investigations are required to gain a more comprehensive understanding of aGPCR biology and to reveal if and how their function intersects with mechanobiological aspects of nervous tissues.

3.6.2 | Pathophysiology and pharmacology of adhesion GPCRs

aGPCR dysfunction was associated with devastating neurological and psychiatric disorders (Liebscher et al., 2022). However, contrary to classical GPCRs, aGPCRs are not yet targets for approved drug therapies to treat or even cure these disorders, a lack which might, at least in part, stem from their unconventional modes of action. Thus, understanding aGPCR function in physiological settings might present a critical step in the development of new and effective strategies to unlock the pharmacological potential of aGPCR.

4 | ORPHAN GPCRs IN THE NERVOUS SYSTEM: (PATHO)PHYSIOLOGY

Orphan GPCRs (oGPCRs), also known as uncharacterized GPCRs, are a group of receptors whose endogenous ligands and functions remain unknown. Deorphanizing these receptors is crucial in understanding their physiological roles and therapeutic applications (Civelli et al., 2006). The three-dimensional (3D) structure of GPCRs is vital in providing insight into their function and potential for drug targeting. In the case of oGPCR, the 3D structure of the ligand binding pocket and conformational changes upon ligand binding are essential for identifying potential ligands and understanding the receptor's signalling mechanisms. Over the years, significant progress has been made in determining the 3D structures of various GPCRs using techniques such as X-ray crystallography and cryo-electron microscopy (Palczewski et al., 2000; van Montfort & Workman, 2017). These studies have revealed that GPCRs consist of 7TMH connected by ICLs and ECLs. The seven-transmembrane helices (7TMH) form a pocket within the cell membrane, where ligands, such as hormones or neurotransmitters, can bind and initiate signalling cascades. Understanding the 3D structure of GPCRs has led to the development of drugs that specifically target these receptors and might help us uncover an unknown disease mechanism we can interfere with through drug therapies (Im, 2002). Yet, it cannot be excluded that some of these receptors do not bind endogenous molecules and regulate physiological conditions exclusively through constitutive initiation of signalling pathways.

In silico analysis using computational methods and algorithms is another essential tool for deorphanizing oGPCRs. By utilising available genomic and proteomic data, in silico studies can predict potential oGPCRs ligands based on sequence similarity, structural homology, and docking simulations (Jaiteh et al., 2020).

Combining 3D structure determination with in silico analysis has proven highly effective in deorphanizing oGPCRs. It resulted in identifying novel ligands, revealing their physiological functions and potential therapeutic applications (Noonan et al., 2022). Additionally, this approach facilitated the development of selective ligands for specific GPCRs, enabling the design of more targeted drugs with reduced side effects. In silico studies also result in cost- and time-effective

research, reducing the time to identify candidate ligands for in vitro validation before advancing to in vivo studies to uncover their therapeutic potential (Agamah et al., 2020). In silico studies include several aspects. If the structure is unknown, the amino acid sequence is needed to model the 3D structure through various online and offline tools and available algorithms (Laschet et al., 2018; Lin & Civelli, 2004). Once the structure is known, virtual screening for extensive compound libraries can be performed (Morris & Lim-Wilby, 2008). Once there is a list of candidate ligands, the in silico studies follow up with molecular dynamics simulations and molecular mechanics – generalised-born surface area analyses to investigate the receptor-ligand interaction stability (Hollingsworth & Dror, 2018; Yoshino et al., 2019; Zhang et al., 2017). This strategy stems from structure-based virtual screening studies (Li & Shah, 2017). Once a list of low-energy scoring compounds is identified as ligand candidates, in vitro screening studies validate them. In vitro, studies generally investigate the GPCR activation and its activity through specific G protein couplings. General methods used to analyse these include colorimetric assays, such as the **transforming growth factor-α** (**TGF-α**) shedding assay (Inoue et al., 2012) and cAMP assay (Vasudevan, 2017), and bioluminescence resonance energy transfer/fluorescence resonance energy transfer (BRET/FRET) assays utilising fluorescent dyes (Salahpour et al., 2012). With TGFα shedding assay, one can determine which G protein is coupling to the oGPCR of interest. The TGFα shedding assay is based on the following principles: activating a GPCR leads to the shedding of the ectodomain of membrane-bound Pro-Alkaline phosphatase-tagged TGFα (pro-AP-TGFα), which serves as a reporter enzyme. The released AP-TGFα is then quantified in the conditioned medium. To perform this assay, cells must be transfected with plasmids encoding AP-TGFα, the oGPCR and each specific G protein (provided in a sequential manner). After applying the candidate ligand, the accumulation of released AP-TGFα in the conditioned medium must be measured (Inoue et al., 2012). Then, after performing these assays, the validated ligand candidates showing GPCR activating activity can be tested in vivo.

Recent research has shed light on these enigmatic receptors, revealing that some can possess endogenous ligands. These ligands may play crucial roles in modulating the activity of oGPCRs. Additionally, oGPCRs can exhibit constitutive activity, meaning they can activate downstream signalling pathways even in the absence of ligand binding (Seifert & Wenzel-Seifert, 2002). This constitutive activity adds another layer of complexity to their functional regulation. Furthermore, oGPCRs can form heteromeric complexes (Barnes, 2006) to form intricate signalling networks. These heteromeric complexes expand the repertoire of potential ligands and provide a means for cross-talk between different signalling pathways (Barnes, 2006). Understanding the characteristics and functions of oGPCRs, including their endogenous ligands, constitutive activity and heteromeric complexes, holds great promise for developing novel therapeutic strategies targeting these intriguing receptors. Overcoming these challenges requires a multifaceted approach. Firstly, identifying endogenous ligands can be achieved through various experimental techniques such as high-throughput screening, ligand fishing, or in silico analysis. Researchers can uncover potential ligands activating oGPCRs by systematically testing multiple compounds. Secondly, addressing constitutive activity can be achieved by employing inverse agonists or biased ligands that selectively inhibit or activate specific signalling pathways. Addressing the constitutive activity of oGPCRs in the absence of known ligands can be challenging. However, several scientific approaches can be employed. One approach uses mutagenesis techniques to introduce specific amino acid substitutions in the GPCR's transmembrane domains. By systematically altering key residues, it is possible to identify mutations that either enhance or diminish the constitutive activity of the receptor. Another approach involves the use of inverse agonists, which are compounds that can inhibit the basal activity of GPCRs. By screening a library of diverse compounds, it is possible to identify inverse agonists that selectively target the oGPCR and reduce its constitutive activity. Additionally, functional assays such as intracellular Ca^{2+} and/or cAMP measurements can be employed to measure the basal activity of the oGPCR and assess the effects of various experimental manipulations. These scientific strategies can provide valuable insights into the constitutive activity of oGPCRs, even without knowledge about their specific ligands. Lastly, the formation of heteromeric complexes can complicate deorphanization. Understanding these complexes' composition and functional consequences is crucial for unravelling the oGPCRs signalling mechanisms. Combining innovative experimental approaches and computational tools, oGPCRs can gradually be deorphanized, shedding light on their physiological roles and potential therapeutic applications. However, identifying the native and candidate ligands by integrating in silico and in vitro analyses poses a challenging task. We will discuss some of the most exciting oGPCRs in the brain, including **GPR3**, **GPR6**, **GPR12**, **GPR17**, **GPR26**, **GPR50** and **GPR160**, which play a role in brain (patho)physiology.

4.1 | GPR3, GPR6 and GPR12

GPR3, GPR6 and GPR12 comprise a cluster of class A oGPCRs that is phylogenetically related to receptors binding **sphingosine-1-phosphate** (**S1P**), **lysophosphatidic acid** (**LPA**), cannabinoids and proopiomelanocortin-derived peptides (George et al., 1997). These three oGPCRs do not only share a high level of sequence similarity (about 60%) but also similar expression patterns across human tissues. Peak expression levels of GPR3/6/12 are found in the CNS, but—in contrast to GPR6 and GPR12—GPR3 can also be detected in several peripheral tissues and cell types, including the reproductive system and adipocytes (Uhlén et al., 2015).

All three oGPCR are associated with the brain's complex physiological and pathological processes. For instance, GPR3, 6, and 12 promote neurite outgrowth and cell survival of isolated rodent neurons (Masuda et al., 2022; Tanaka et al., 2014, 2022). Further studies in mice revealed that GPR3 is associated with the early phases of **cocaine** reinforcement and emotional behaviour during stress, relieving neuropathic pain (Ruiz-Medina et al., 2011; Tourino et al., 2012;

Valverde et al., 2009). GPR6 expressed in murine striatopallidal neurons regulates instrumental conditioning (Lobo et al., 2007), and genetic mapping in outbred mice identified GPR12 as a potent modifier of short-term memory (Hsiao et al., 2020).

Under pathological conditions, GPR12 affects the response to antipsychotic drugs in patients with schizophrenia (Drago & Kure Fischer, 2018; Zhao et al., 2022), while GPR3 and GPR6 play roles in neurodegenerative diseases. Seminal studies in GPR3 deficient mouse models and histological analyses of post-mortem brains of diseased patients found a link between GPR3 and AD. Mechanistically, GPR3 coupling to β-arrestin stimulates **amyloid-β** generation and plaque formation through membrane-bound γ-secretase (Huang et al., 2015; Nelson & Sheng, 2013; Thathiah et al., 2013). Intriguingly, G protein-biased GPR3 mutants ameliorate AD pathology in mouse models, indicating that G protein-biased agonists of this receptor could provide new cues for developing AD drugs (Huang et al., 2022).

GPR6, in contrast, is linked to PD. GPR6 deficient PD model mice show higher basal locomotor activity and reduced dyskinesia—presumably due to increased striatal dopamine concentrations (Oeckl et al., 2014). These observations spurred the development of a selective GPR6 inverse agonist, **CVN424** (Brice et al., 2021; Margolin et al., 2022; Sun et al., 2021). GPR6 inverse agonists like CVN424 normalise activity in basal ganglia circuitry and motor behaviour, and only recently, CVN424 completed clinical trial phase II in PD patients with motor fluctuations (ClinicalTrials.com ID: NCT04191577). This breakthrough raises hopes for developing mechanistically novel drugs for treating motor symptoms in PD.

4.2 | GPR17

GPR17 is expressed in various brain regions, such as the cortical area serving as a source of inhibitory control and decision-making over other brain areas, the NAc controlling motivation and reward, the habenula involved in reward valuation and decision-making, the amygdala associated with fear and negative emotions and the midbrain dopaminergic nuclei which are essential for movement and reward-related behaviours (Ehrlich et al., 2018).

Oligodendrocytes express GPR17 in the brain. GPR17 is a negative regulator of oligodendrocyte transcription factor 1 (Olig1) that promotes oligodendrocyte formation, maturation, and myelination. Thus, GPR17 could be a potential therapeutic target for CNS myelin repair (Chen et al., 2009). Another study also reported that the inhibition of GPR17 signalling pathways in oligodendrocyte precursor cells (OPCs) together with depletion of microglia lead to oligodendrocyte maturation and robust myelination of regenerated axons after optic nerve injury. These findings support the importance of GPR17 in oligodendrocyte maturation and its relevance as a target in the myelination process after CNS injury (Wang et al., 2020).

In 2006, Ciana and colleagues showed that GPR17, which is phylogenetically related to **cysteinyl leukotriene receptors** and P2Y receptors, could be activated by both cysteinyl-leukotriene and uracil nucleotide endogenous ligands (Ciana et al., 2006). However, despite all efforts to deorphanize GPR17, this receptor is still debated in the scientific community due to contradictory findings related to the identity of its endogenous ligand (Benned-Jensen & Rosenkilde, 2010; Ciana et al., 2006; Harden, 2013; Qi et al., 2013). Therefore, determining the GPR17 structure is essential for understanding its physiology and natural ligand prevision. By combining cryo-electron microscopy and directed mutagenesis, it has been shown that the GPR17 receptor is auto-activated by its ECL2, which acts as a 'self-agonist' by coupling the G_i. In GPR17, ECL2 occupies and covers about 40% of the orthosteric binding pocket and forms several interactions with hydrophilic residues suggesting the presence of a hydrophilic environment and, consequently, the hydrophilic nature of GPR17 endogenous ligand (Ye et al., 2022). Other brain-expressed oGPCRs, such as **GPR52** and **GPR21**, follow the general activation pattern by their ECL2, providing them with a high basal activity level (Lin et al., 2023, 2020). ECL2 plays a critical role in many other GPCRs, such as the A_2 receptor, and remains an important drug target structure (Seibt et al., 2013).

4.3 | GPR26

GPR26 was first described in 2000 (Lee et al., 2000) as a class A rhodopsin-like oGPCR (Chung et al., 2008). It contains 317 amino acids with conserved sequence similarity among the orthologues. More than 95% of the sequence identity exists between humans and rodents, indicating high phylogenetic conservation of protein structure and function. GPR26 overexpression demonstrates its stimulatory G protein-releasing constitutive activity, resulting in increased cAMP concentration in target cells. It is predominantly expressed in brain tissues (Jones et al., 2007), for example, amygdala, striatum and hypothalamus, and is related to affective disorders. KO of GPR26 in rodent models shows that they have more anxiety-like behaviours in open field and elevated plus-maze tests and depression-like behaviours in tail suspension and forced swim tests. Also, a two-bottle free-choice paradigm test demonstrated that GPR26-KO mice showed increased alcohol intake, which might be related to addiction (Zhang et al., 2011). Furthermore, GPR26 is involved in glioma and hepatocellular carcinoma. These findings provided evidence for the cancer-promoting effect of miR-188-3p in glioblastoma multiforme (GBM) cells and demonstrated that GPR26 was directly targeted by miR-188-3p, which might contribute to the therapeutic therapy of glioblastoma multiforme (GBM) cells (Meng et al., 2020). Lastly, since targeted inactivation of GPR26 leads to hyperphagia (Chen et al., 2012), this supports the idea that it is involved in appetite. Kichi et al. revealed that GPR26 plays a role in human monocytes in type-2 diabetes patients, potentially activating a defence mechanism against hyperglycaemia. However, chronic and intermittent hyperglycaemic conditions may impair this protective effect, which can be countered by insulin treatment. Additionally, GPR26 was found to independently protect against pro-inflammatory monocyte activation, reactive oxygen species (ROS) production, and apoptosis (Kichi et al., 2022).

4.4 | GPR50

GPR50 is an oGPCR belonging to the melatonin receptor family with around 45% sequence homology within the first 420 residues with MT_1 and MT_2 receptors, with which it heterodimerizes in transfected cells (Levoye et al., 2006). It has lost the ability to bind melatonin during evolution (Clement et al., 2018). Some mechanisms of regulation by heterodimerization with other receptors (Levoye et al., 2006; Wojciech et al., 2018) or involving its C-terminal domain (Ahmad et al., 2020) have been proposed without their physiological implication in the brain. It has been almost 30 years since this GPR50 was found to be expressed in chromosome X, yet the function of this receptor, which is found in the human hippocampus among other brain parts (Hamouda et al., 2007), is not well known. In the neuronal-like neuroscreen-1 cell line, a sub-clone of rat pheochromocytoma (PC12), its expression has been associated with increased neurite outgrowth (Grünewald et al., 2009; Xu et al., 2022). Some sporadic studies suggest that GPR50 regulates energy homeostasis and fasting-induced torpor (Bechtold et al., 2012). In a small number of studies, GPR50 locus has been associated with psychiatric disorders, including schizophrenia and bipolar disorders (Thomson et al., 2005), but these data have not consistently been replicated. A possible association with seasonal affective disorders (Delavest et al., 2012), autism spectrum disorders and depression has been proposed with a sex-dependent susceptibility, but not consistently replicated.

4.5 | GPR160

GPR160 is a class A rhodopsin-like oGPCR. The orthologues of GPR160 exist in diverse vertebrates, including mice, monkeys, cows, and so on, with high sequence coverage. However, GPR160 shares, at most, 18% of sequence identity with the members of the GPCR superfamily, complicating the structural predictions. The highest expression occurs in the small intestine, colon, bone marrow and kidney on a tissue basis. Even though its function has not been fully elucidated, it is been implicated in apoptosis and cell cycle arrest in prostate cancer and associated with traumatic nerve injury and pain (Yosten et al., 2020; C. Zhou et al., 2016).

Recently, Yosten et al. revealed that GPR160 is upregulated in the spinal cord upon traumatic nerve injury. Besides, using monoclonal antibodies (mAb) targeting GPR160 abolishes the neuropathic pain, while normal pain is unaffected. The same group asserted that Cocaine- and amphetamine-regulated transcript peptide (CARTp) is a natural ligand, backed by the inhibition of CARTp formation and the subsequent decrease in ERK1/2 and cAMP response element-binding protein (CREB) phosphorylation. This decrease was also observed when GPR160 was inhibited (Yosten et al., 2020). However, it is essential to recognise that further understanding of this interaction's biochemical and biophysical aspects is necessary. Additionally, Zhou et al. demonstrated a connection between GPR160 and apoptosis and the growth of prostate cancer cells. While normal prostate tissue cells

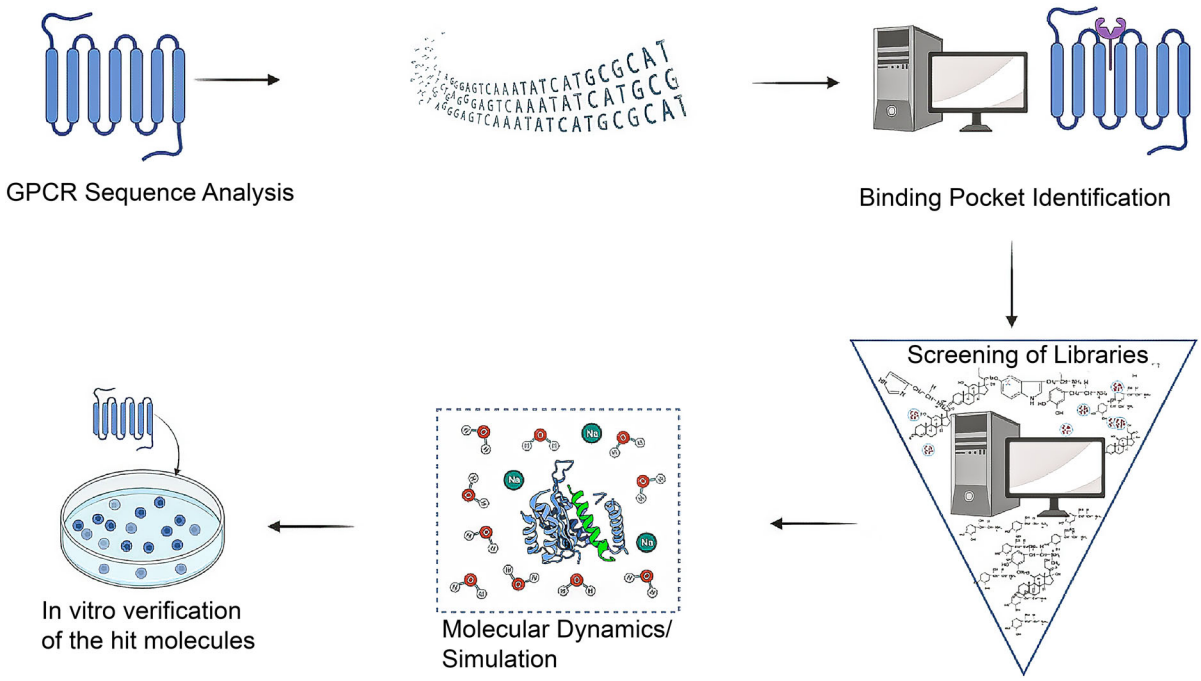

FIGURE 2 In silico strategy for deorphanization of orphan G protein coupled receptor (oGPCRs). The approach for deorphanization involves an in silico strategy. The initial step entails generating a 3D model of the oGPCR using a combination of online and offline tools as well as established algorithms. Subsequently, the orthosteric binding pocket is identified and confirmed through site-directed mutagenesis experiments. Finally, molecular dynamics simulations are employed to screen various in silico libraries, identifying candidate compounds with low-energy scores. These candidates are then validated through in vitro assays.

like RWPE-1 express GPR160 to a small extent, human prostate cancer cell lines such as PC-3, DU145, LNCap and 22Rv1 express GPR160 at a high level. In the same study, the knockdown of GPR160 using two different shRNAs (ShGPR160-A and ShGPR160-D) delivered via lentiviruses hindered colony formation in PC-3 and LNCaP prostate cancer cell lines (Zhou et al., 2016) Furthermore, an independent study suggested that GPR160 could be a prostate cancer biomarker (Guo et al., 2021).

4.6 | How to Deorphanize the orphan GPCRs (reverse physiology, bioinformatics)

In 2000, the X-ray crystal structure of the rhodopsin receptor was revealed for the first time (Palczewski et al., 2000). In 2007, Brian Kobilka and colleagues determined the crystal structure of the β_2-adrenoceptor (Rasmussen et al., 2007). This was followed 4 years later by the structure of the β_2-adrenoceptor-G_s protein complex (Rasmussen et al., 2011). More recently, the structure of GPCRs has been studied more efficiently using bioinformatic analysis. Firstly, the sequence of the targeted GPCR must be identified, and then a homology model using similar models must be constructed. If there are no comparable models and their similarity is less than 30%, creating a shared model by building multiple models and superimposing them is essential. Another alternative is the ab initio, an in silico method used to model a protein given its sequence when there are no similar sequences or crystal structures to use as a template (Alford et al., 2017). The next step is to generate the orthosteric binding pocket. Site-directed mutagenesis is then used to verify the binding pocket (Chan & Zhang, 2020; Jacob et al., 2008). At this point, libraries can be screened, and candidate ligands verified by in vitro assays (Figure 2). Using reverse physiology is another key technique that helps to identify the natural ligands or endogenous compounds that activate the oGPCRs. For the deorphanization process, the receptor has to be cloned and expressed in a suitable cellular system, such as mammalian cells or yeast. The second step is to screen libraries of potential (candidate) ligands, including small molecules, peptides or endogenous compounds, against the expressed oGPCR. If the ligand is identified, the third step is the functional characterisation of the oGPCR (e.g., G protein or β-arrestin coupling identification using TGF-α shedding or β-arrestin recruitment assays, respectively) and the validation process (Im, 2002). Another method for the identification of native ligands involves the isolation of proteins, lipids, or metabolites from tissues that express the oGPCR of interest (Birgül et al., 1999). The first step is to make peptide, lipid, or metabolite extract, and analyse the activity of the oGPCR by activity assay using either in vitro or

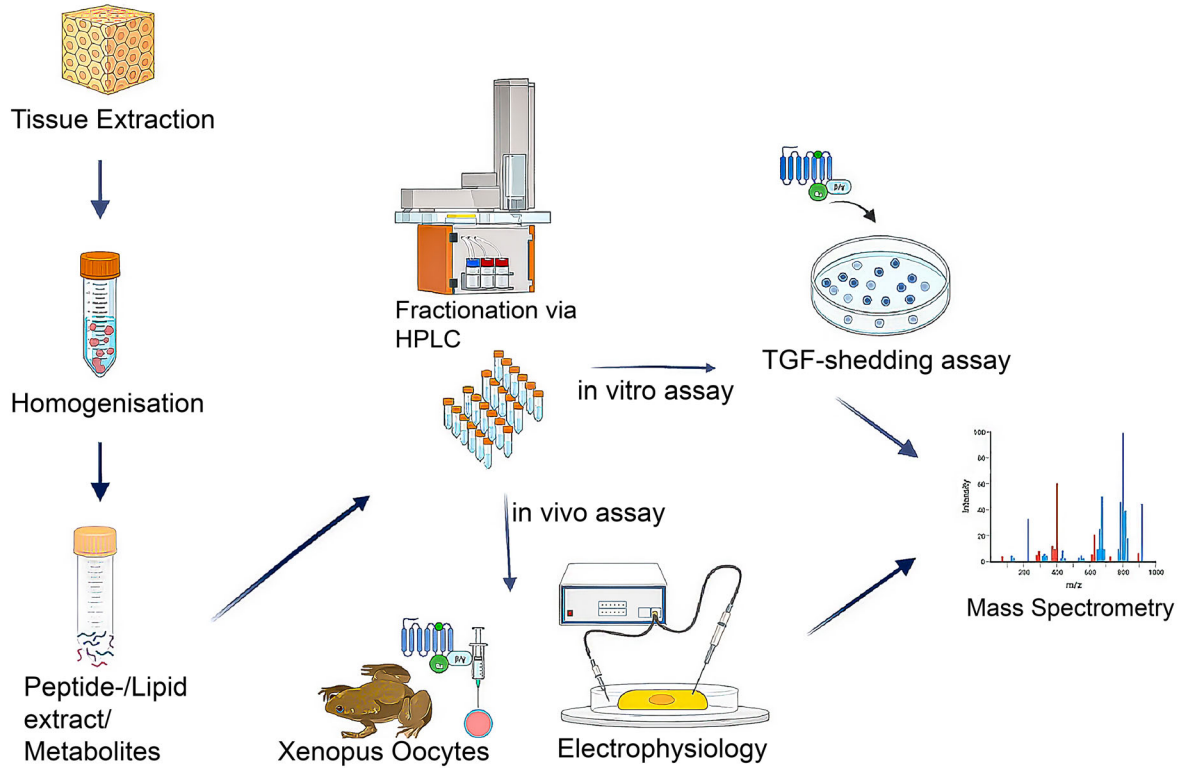

FIGURE 3 Isolation of the native ligand from tissue. The initial step involves extracting the native ligand from the tissue where the orphan G protein coupled receptor (oGPCR) is present. This is achieved by homogenising the tissue and fractionating the resulting homogenate using high-performance liquid chromatography (HPLC). The biological activity of these fractions is subsequently confirmed through in vitro assays, such as the transforming growth factor (TGF) shedding assay or electrophysiology. Fractions exhibiting activity are then concentrated and subjected to repeated rounds of HPLC and in vitro assays for further fractionation. Finally, the identification of the native ligand is accomplished using mass spectrometry.

electrophysiological assays. Those fractions that show activity have to be used for another round of HPLC/ fast protein liquid chromatography (FLPC) to concentrate and fractionate the candidate ligand. This step has to be repeated until the candidate ligand is purified enough to analyse it (Figure 3; Birgül et al., 1999).

There are about 100 oGPCRs whose endogenous ligand and physiological roles are still unknown (Watkins & Orlandi, 2021). Given the importance of GPCRs as primary targets for therapeutic interventions, it is imperative to elucidate the functional properties of oGPCRs extensively.

The deorphanization of oGPCRs is crucial in understanding their physiological functions and potential therapeutic applications, partly achieved by combining 3D structure determination and in silico analysis. However, this process has challenges, particularly concerning heterodimerization and constitutive activity. Heterodimerization can complicate the identification of ligands and the interpretation of signalling pathways. Constitutive activity further complicates the deorphanization process by confounding the determination of ligand-receptor interactions. Overcoming these difficulties by identifying endogenous ligands through various experimental techniques such as high-throughput screening, ligand fishing, or in silico analysis is essential for the successful deorphanization of oGPCRs and for advancing our understanding of their functional roles.

5 | CONCLUSIONS AND FUTURE PERSPECTIVES

Fostering collaboration between neuroscientists, pharmacologists, computational biologists and clinicians promotes a holistic approach to GPCR research in the nervous system. Collaboration under the ERNEST COST Action has shown that the future prospects for GPCRs in the nervous system offer exciting potential for a better understanding of neurobiology and the development of novel therapeutic interventions for a range of neurological and psychiatric disorders.

Advances in our understanding of the intricate signalling pathways involving nervous system GPCRs may pave the way for more targeted therapeutic interventions. Continued advances in structural biology techniques such as cryo-electron microscopy can provide detailed insights into the 3D structures of GPCRs. This information is crucial for designing more specific and efficacious drugs that modulate GPCR activity with high precision. Using computational modelling and artificial intelligence in GPCR research can accelerate the prediction of ligand-receptor interactions and support drug discovery. Virtual screening and deep learning algorithms can facilitate the identification of compounds targeting GPCRs in the future. Moreover, the integration of genomics, transcriptomics and proteomics data will provide a comprehensive overview of the molecular landscape of the nervous system associated with GPCRs in the future. Systems biology approaches can uncover new regulatory networks and potential therapeutic targets. Advanced imaging technologies such as super-resolution microscopy and functional magnetic resonance imaging (MRI) can enable real-time monitoring of GPCR activity in living cells and tissues. This could improve our understanding of the spatio-temporal dynamics of GPCR signalling in the nervous system. Exploration of GPCR modulation in non-neuronal cells within the nervous system, such as glial cells, may uncover additional therapeutic targets. Furthermore, investigation of non-canonical signalling pathways associated with GPCRs may reveal new dimensions of their functional diversity.

This interdisciplinary synergy can lead to innovative breakthroughs and a more comprehensive understanding of GPCR function in health and disease. With all these advances, personalised medicine approaches could emerge in the future that tailor treatments based on individual variations in GPCR function and expression patterns in the nervous system.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/23 (Alexander, Christopoulos, Davenport, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Amarosi, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Annett, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Beuve, et al., 2023; Alexander, Mathie, Peters, Veale, Striessnig, Kelly, Armstrong, Faccenda, Harding, Davies, Aldrich, et al., 2023).

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CONFLICT OF INTEREST STATEMENT

The authors have no multiplicity of interest to disclose.

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