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RECEIVED 25 July 2025

ACCEPTED 15 October 2025

PUBLISHED 30 October 2025

CITATION

Baeken MW, Bekbulat F, Körschgen H,
Clement AM and Behl C (2025) The sigma-1
receptor as a neurohomeostatic decision hub
for GABARAP-mediated receptor trafficking
and macroautophagy.
Front. Mol. Biosci. 12:1673249.
doi: 10.3389/fmolb.2025.1673249

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The sigma-1 receptor as a neurohomeostatic decision hub for GABARAP-mediated receptor trafficking and macroautophagy

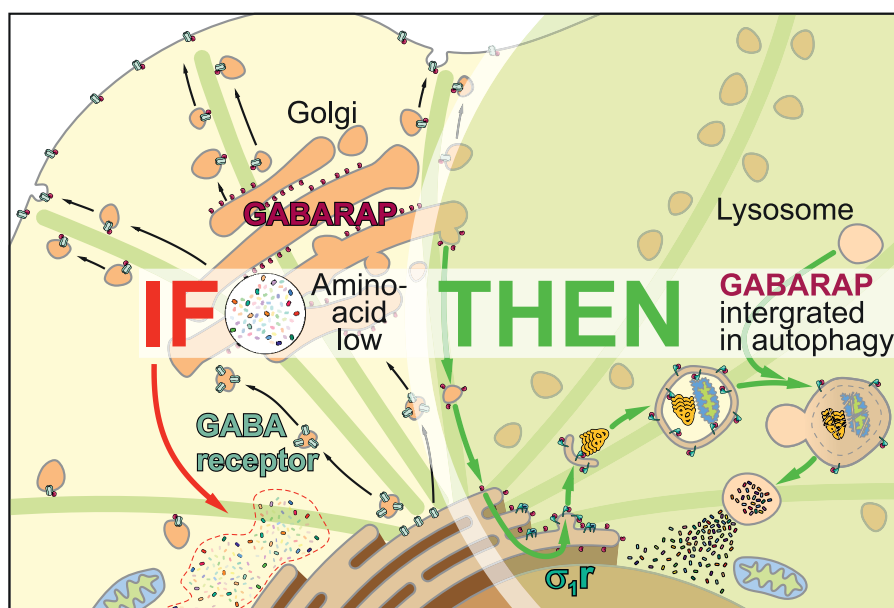
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Gamma-aminobutyric acid receptor-associated protein (GABARAP) is a multifunctional member of the autophagy-related (ATG8) protein family, playing key roles in two distinct cellular pathways: macroautophagy and plasma membrane protein trafficking. In the context of autophagy, GABARAP modulates cargo recognition and supports the maturation and fusion of autophagosomes with lysosomes, a critical step in intracellular clearance and proteostasis. Separately, GABARAP also regulates vesicular receptor protein transport from the Golgi apparatus to the plasma membrane, contributing to proper surface localization and receptor recycling. Both tasks are especially vital for neurons, where protein turnover and receptor localization are tightly linked to synaptic plasticity and neuroprotection. We recently identified a direct interaction between GABARAP and the sigma-1 receptor (σ_1R), an ER-resident receptor involved in diverse cellular stress responses, mitochondrial function, and protein homeostasis. Our findings suggest that σ_1R acts as an upstream regulatory hub, influencing GABARAP's functional commitment to either membrane trafficking or autophagy. Specifically, we hypothesize that ligand-dependent σ_1R activation promotes GABARAP's involvement in macroautophagy at the expense of its role in membrane transport. This regulatory switch may underline part of the neuroprotective effects observed with σ_1R agonists in neurodegenerative disease models, where enhanced autophagy is often beneficial. Overall, we discuss the emerging molecular crosstalk between σ_1R and GABARAP, its potential impact on neuronal homeostasis, and how σ_1R 's pharmacological modulation might be leveraged to bias GABARAP function toward autophagy in diseases such as amyotrophic lateral sclerosis, Huntington's, Parkinson's, and Alzheimer's disease.

KEYWORDS

sigma-1 receptor, GABARAP, autophagy, GABA_A receptor, LIR



GRAPHICAL ABSTRACT

Introduction

Post-mitotic cells, especially neurons, have to co-orchestrate numerous delicate homeostatic systems, such as protein or ion homeostasis, to ensure organismal function. Hence, a cross-talk between these systems is essential.

We recently described the sigma-1 receptor (σ_1R), a protein lacking any close homologs in the human proteome (Moebius et al., 1997), as a regulator that integrates gamma-aminobutyric acid receptor-associated protein (GABARAP) into macroautophagy (Baeken et al., 2025; Christ et al., 2019). In brief, σ_1R -deficient HeLa cells were unable to incorporate GABARAP into autophagosomes, as evidenced by a complete loss of GABARAP-p62 co-localization and a breakdown of the GABARAP-associated autophagic flux (Baeken et al., 2025). However, we noticed that GABARAP's lipidated form still persisted, which suggests an interaction with membranous structures. Interestingly, a previous study has shown that the G¹¹⁶A (amino acids in single letter code) GABARAP mutant, which cannot be C-terminally cleaved, was unable to transport GABA_A receptors to the plasma membrane (Chen et al., 2007). This cleavage is a prerequisite for lipidation, which suggests that lipidation also facilitates the transport of associated vesicles.

Although still circumstantial, this evidence may broaden our understanding of σ_1R 's physiological impact. As its *bona fide* cellular purpose remains elusive, we propose a regulatory role of σ_1R in controlling GABARAP logistics, which affects neurotransmission as well as autophagy. In a broader context, this regulatory function might help explain the neuroprotective properties attributed to σ_1R (Christ et al., 2020).

GABARAP's role in mammalian macroautophagy

Macroautophagy (hereafter autophagy) is a highly conserved cellular degradation pathway, characterized by the formation of double-membraned vesicles – autophagosomes – that engulf cytosolic material and fuse with lysosomes, where contents are degraded by hydrolases and recycled for reuse (He and Klionsky, 2009). Dynamically regulated, autophagy enables cells to deal with changing demands, be it upholding energy homeostasis during nutrient deprivation or selectively removing misfolded proteins and damaged organelles. Thus, autophagy is an essential homeostatic and adaptive process promoting survival and renovation, especially for post-mitotic cells such as neurons (Mizushima and Komatsu, 2011). Autophagic efficiency declines with age and its dysfunction is associated with disease, including neurodegeneration (Aman et al., 2021; Palmer et al., 2025).

Autophagosome formation, maturation, and fusion with lysosomes are coordinated by core autophagy-related (ATG) proteins, including an initiation complex, a membrane expansion complex, and two ubiquitin-like conjugation systems, one being the LC3/GABARAP system (Ariosa and Klionsky, 2016). Microtubule-associated protein 1A/1B-light chain 3 (LC3) and GABARAP, both members of the ATG8-family, form two distinct subfamilies: LC3A, LC3B, and LC3C; and GABARAP, GABARAPL1, and GABARAPL2 (Schaaf et al., 2016).

ATG8 proteins are ubiquitously expressed, though GABARAPs are enriched in the central nervous system and endocrine glands (Lee and Lee, 2016). Although highly homologous, distinct residues mediate selectivity of GABARAP subfamily

members towards interaction partners (Sugawara et al., 2004; Rogov et al., 2014); emerging evidence supports unique and complementary roles for LC3s and GABARAPs in autophagy. During autophagosome formation, LC3B is mainly involved in the elongation of the phagophore, general cargo recognition, and the transport of autophagosomes to lysosomes, while GABARAP has primarily been associated with late events such as autophagosome closure and autophagosome-lysosome fusion (Lee and Lee, 2016; Schaaf et al., 2016). Supporting its function in autophagosome maturation, GABARAP shows a higher affinity to Unc-51 like autophagy activating kinase 1 (ULK1) (Alemu et al., 2012), and mediates autophagosomal targeting of phosphatidylinositol 4-kinase type 2 alpha (PI4KIIa), thereby regulating autophagosome-lysosome fusion (Albanesi et al., 2015).

To function in autophagy, cytosolic ATG8s must undergo lipidation, i.e., a covalent conjugation to phosphatidylethanolamine (PE), enabling incorporation into autophagosomal membranes (Lee and Lee, 2016; Nguyen et al., 2016; Palmer et al., 2025). Initially synthesized as precursors, ATG8s are cleaved by cysteine endopeptidases of the ATG4 family, whereby a C-terminal glycine residue becomes accessible for lipidation (Nguyen et al., 2020). The exposed glycine is then adenylated, sequentially transferred through E1-like and E2-like ATG proteins, and finally conjugated to PE's amino head group via an E3-like ATG conjugation complex (Maruyama and Noda, 2017; Martens and Fracchiolla, 2020).

One hallmark of autophagosome-mediated autophagy is cargo-specific sequestration, in which adaptor proteins bind distinct ubiquitinated cargo and directly interact with inner autophagosomal membrane-bound ATG8 proteins (Khaminets et al., 2016), enabling selective elimination of various cellular components. The latter interaction is assured by distinct binding motifs termed LC3-interacting regions (LIRs), which are recognized by LIR docking sites in ATG8s (Johansen and Lamark, 2020).

The core of the canonical LIR is defined by the hydrophobic consensus sequence [W/F/Y]-X₁-X₂-[L/V/I] (X for variable residue) (Birgisdottir et al., 2013). Its affinity is enhanced by phosphorylated or acidic residues flanking the motif, albeit preferentially on the N-terminus (Johansen and Lamark, 2020). The ubiquitin-binding protein p62, considered a *bona fide* cargo adaptor, directly binds to all ATG8s (Pankiv et al., 2007; Johansen and Lamark, 2020). Specificity of cargo adaptors toward particular ATG8s arises from unique hydrophobic contacts, salt bridges, and hydrogen bonds. Notably, selectivity towards GABARAP is mediated by a restriction of this core motif: [W/F]-[V/I]-X-V (Rogov et al., 2017; Rogov et al., 2023).

GABARAP's role in receptor transport and deployment

Although widely known for its integration into autophagic processes, GABARAP was originally identified as a cellular agent to properly distribute GABA_A receptors to the plasma membrane by interacting with the γ 2 subunit (GABRG2) of the heteropentamer (Wang et al., 1999). Following studies confirmed that GABARAP interacts with γ 1, but not with the γ 3 or δ subunits in yeast hybrid systems (Kneussel et al., 2000). The primary interaction site of GABARAP with GABA_A points to an

intracellular loop between transmembrane regions 3 and 4 within the γ 1/ γ 2 subunits (Nymann-Andersen et al., 2002; Chen et al., 2000). This interaction is facilitated by a classical LIR motif (⁴¹⁴YECL⁴¹⁷) (Ye et al., 2021). This core motif is also present in γ 3 but lacks the favored acidic N-terminal residues (Rogov et al., 2017). Interestingly, Y⁴¹² in γ 2 is phosphorylated by FYN and SRC kinases (Jurd et al., 2010), presumably regulating its affinity (Kittler et al., 2008). While Y⁴¹⁴ can also be phosphorylated, the consequence for GABARAP binding remains unclear (Jurd et al., 2010). However, our *in silico* model suggests that this modification might affect binding negatively, whereas unmodified Y⁴¹⁴ or pY⁴¹² would bind GABARAP (Figure 1A). Here, pY⁴¹² could enable intramolecular interaction with H⁴⁴³, condensing the C-terminal structure of γ 2 and potentially stabilizing GABARAP binding.

Furthermore, GABARAP is involved in maintaining membrane GABA_A localization by several mechanisms. (i) GABARAP can negatively regulate GABA_A receptor reinternalization. This process relies on binding of the adaptor protein complex 2 (AP2) to the γ 2 subunit (Comenencia-Ortiz et al., 2014). Coincidentally, GABARAP and AP2 compete for the same binding sites (Ye et al., 2021; Kittler et al., 2008). (ii) GABARAP partakes in GABA_A receptor recycling by interacting with endosomal receptors, thus rerouting them toward the plasma membrane (Lüscher and Keller, 2001). (iii) GABARAP interacts with gephyrin and ankyrin 3, which facilitate postsynaptic receptor clusters and GABA_A receptor stability (Nelson et al., 2020; Chen and Olsen, 2007). Moreover, lipidated GABARAP could potentially serve as an additional anchor for GABA_A receptors via its PE-tail.

GABARAP-mediated protein trafficking extends beyond GABA_A receptors; it is also involved in depositing angiotensin II receptor type 1 (AGTR1) at the plasma membrane (Cook et al., 2008). Mutagenesis analyses identified F³⁰⁹, L³¹⁶, and L³¹⁷ as critical residues, characterizing the motif as a canonical LIR (³¹³FLQL³¹⁶). This sequence, however, is not flanked by acidic but basic residues, defying the paradigm (Rogov et al., 2017). Notably, AGTR1 is highly expressed in dopaminergic neurons of the *substantia nigra pars compacta* that are highly susceptible to Parkinson's disease (Kamath et al., 2022). Furthermore, GABARAP is responsible for the installation of transient receptor potential vanilloid 1 (TRPV1) at the plasma membrane (Láinez et al., 2010), which is important for microglial function in Alzheimer's disease (AD) (Lu et al., 2021). Here, the cytosolic ⁷⁹¹FALV⁷⁹⁴ sequence might serve as a LIR. GABARAP also couples receptor homeostasis and autophagy by regulating epidermal growth factor receptor degradation via its LIR motif ¹⁰⁸⁶FLPV¹⁰⁸⁹ (Dobner et al., 2020; Üffing et al., 2024).

Dormant GABARAP localizes mainly to the Golgi, where it binds golgin subfamily A member 2 (GOLGA2) (Joachim et al., 2015), and to the ER, suggesting a role at the intersection of autophagy and receptor transport (Nakamura et al., 2008). Upon amino acid starvation, uncleaved GABARAP is displaced from GOLGA2 and rerouted from the Golgi to the ER via the centrosome (Joachim et al., 2015). How GABARAP is ultimately integrated into autophagy, and how these pathways are coordinated, remains unclear, though recent findings suggest a role for σ ₁R (Baeken et al., 2025).

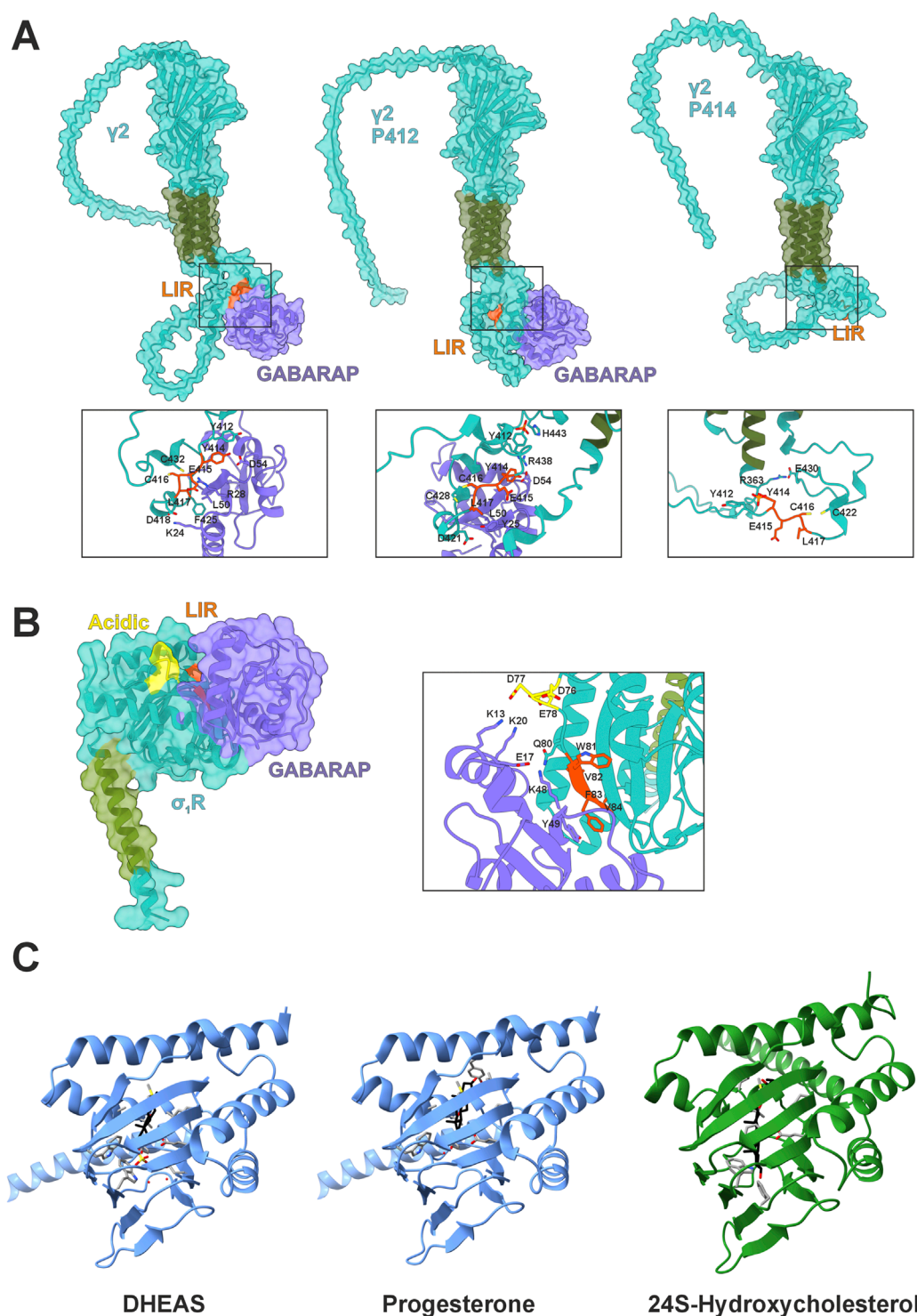


FIGURE 1

GABARAP interactions and $\sigma_1 R$ structural context. **(A)** AlphaFold3 models of GABARAP (purple) in complex with the GABA_A receptor subunit $\gamma 2$ (teal with green transmembrane domain) with highlighted LIR (orange) in their native states including phosphorylated tyrosines $\gamma 412/\gamma 414$. **(B)** AlphaFold3 model of GABARAP (purple) in complex with $\sigma_1 R$ (teal with green transmembrane domain), highlighting the LIR domain (orange) and acidic residues (yellow). **(C)** Crystal structure of *Xenopus laevis* $\sigma_1 R$ (blue) with DHEAS (pdb:8WUE) or progesterone (pdb:8W4C) bound and Boltz-2 predicted interaction of *Homo sapiens* $\sigma_1 R$ (green) with 24S-hydroxycholesterol.

Structure-function relation of σ_1 R

As a modulatory receptor pre-dominantly localized at the mitochondrial associated membrane (MAM) (Aishwarya et al., 2021), the σ_1 R is involved in multiple cell physiological processes such as calcium signaling, NMDA receptor activity, G-protein-mediated signaling pathways, and autophagy (Couly et al., 2023). It thus contributes to neuronal excitability, plasticity, proteostasis, and resilience. Accordingly, σ_1 R agonists have been proposed as therapeutic candidates for neurodegenerative diseases (Couly et al., 2024; Lachance et al., 2023). First identified over four decades ago as a unique opioid receptor class due to its atypical ligand binding properties (Martin et al., 1976; Tam, 1983), the σ_1 R represents an evolutionary orphan, sharing no close homology with any other human protein.

Phylogenetically, σ_1 R shares ~69% structural similarity with yeast sterol isomerases that are involved in ergosterol biosynthesis (Hanner et al., 1996). It is highly conserved among vertebrates, with 80% sequence identity to zebrafish (*Danio rerio*) (Schmidt et al., 2016). X-ray crystallography of purified σ_1 R revealed a homotrimeric organization, where each protomer contains a cupin-like β -barrel ligand-binding domain (LBD) flanked by four α -helices and a deeply buried ligand-binding site (Schmidt et al., 2016). Membrane anchoring likely occurs via a single, poorly conserved N-terminal transmembrane helix linked to E¹⁰² of the LBD by V³⁶ and F³⁷. The protein's topology remains debated – type II (C-terminus in ER-lumen) versus type III (C-terminus cytosolic) – likely due to artifacts from protein tagging (Aydar et al., 2002; Hayashi and Su, 2007). Most structural studies support a type II orientation, placing the C-terminal LBD in the ER-lumen, consistent with its interaction with the luminal chaperone heat shock 70 kDa protein 5 (HSPA5) (Hayashi and Su, 2007; Mavylutov et al., 2018; Sharma et al., 2021). However, this poses questions about the function of the N-terminal di-basic ER retention motif (¹MQWAVGRR⁸) (Seth et al., 1998; Aishwarya et al., 2021). Notably, since most experiments to date have employed tagged proteins, the *in situ* topology of endogenous σ_1 R remains unresolved.

While no specific signal transduction pathway has been defined for σ_1 R, evidence suggests that agonists promote its monomeric, active form, facilitating interactions with client proteins, while antagonists stabilize an inactive oligomeric state. Agonist binding leads to dissociation from HSPA5, allowing σ_1 R to stabilize inositol trisphosphate receptor (IP3R) at the MAM, consequently enhance Ca²⁺ efflux, or modulate NMDA receptor activity (Hayashi and Su, 2007; Balasuriya et al., 2013; Choi et al., 2017). Prolonged activation further drives σ_1 R translocation to nuclear and plasma membranes, expanding its functional repertoire (Tsai et al., 2015).

Agonist treatment features a biphasic dose response, suggesting that high concentrations may suppress σ_1 R activity (Maurice, 2021), this response varies by cell and agonist type and dosage. Overall, σ_1 R activation promotes the unfolded protein response (Alam et al., 2017) and autophagy (Christ et al., 2019; Yang et al., 2019; Wang et al., 2021), reducing ER stress and supporting proteostasis. Several mutations in σ_1 R disrupt this function and are linked to motoneuron diseases; E¹⁰²Q, for instance, is implicated in juvenile-onset ALS (Al-Saif et al., 2011; Vollrath et al., 2014; Dreser et al., 2017) and F⁸³L in an ALS-like condition (Ma et al., 2020). The latter mutation resides in a sequence we have recently identified as

a LIR motif, ⁸¹WVFV⁸⁴ with specificity for GABARAP (Figure 1B) (Baeken et al., 2025). AlphaFold modeling supports experimental data by predicting π -stacking between F⁸³ of σ_1 R and Y⁴⁹ of GABARAP, potentially explaining binding specificity despite F⁸³'s variable motif position (Figure 1B). Notably, the agonist-mediated induction of σ_1 R's monomeric state enables this interaction; we did not observe any interaction in an oligomeric state. This specific interaction between σ_1 R and GABARAP may provide a causal link for the well-established effects of σ_1 R on autophagy (Christ et al., 2019; Yang et al., 2019; Wang et al., 2023).

σ_1 R as pharmaceutical target

The discovery that agonistic compounds such as alazocine [(+)-SKF-10047] and (+)-pentazocine (Martin et al., 1976; Su, 1982) selectively bind σ_1 R sparked its cellular and molecular characterization while highlighting it as a potent druggable target. Its versatile roles as a regulator of Ca²⁺-homeostasis at the MAM, as a modulator of transmembrane receptors, and as an enhancer of the unfolded protein response and autophagy underline the potential neuroprotective properties of σ_1 R activation. Over time, extensive preclinical evidence has demonstrated that σ_1 R agonists confer neuroprotection across a broad spectrum of acute and chronic neurological disorders, including nerve injury, ALS, AD, Parkinson's, and Huntington's disease (Drewes et al., 2025).

Notably, neuroprotective σ_1 R agonists are structurally diverse. Classic benzomorphan-based ligands such as (+)-pentazocine (Li et al., 2021) and (+)-SKF-10047 (Phan et al., 2005), as well as chemically distinct molecules such as blarcamesine (Anavex 2-73), PRE-084 (Lahmy et al., 2013), and pridopidine (Ryskamp et al., 2019; Estévez-Silva et al., 2022), have all demonstrated beneficial behavioral and neuroprotective effects in various pathogenic mouse models. Several of these compounds have progressed to clinical trials. Pridopidine is currently in phase III for Huntington's disease (NCT04556656) and phase II for ALS (NCT04615923); however, the HEALEY-ALS platform trial reported no significant clinical improvement (Shefner et al., 2025). In contrast, a phase IIB/III trial of blarcamesine in early AD has demonstrated significant improvements across multiple clinical outcomes (Macfarlane et al., 2025).

At the molecular level, σ_1 R agonists exhibit distinct modes of action, likely due to subtle differences at the agonist- σ_1 R interface, which may explain divergent cellular responses. Recent findings show that benzomorphan-based compounds – but not phencyclidine-derived compounds such as PRE-084 – induce monomerization of endogenous, untagged σ_1 R *in vitro* and in mouse tissues (Couly et al., 2024), at least under the experimental conditions and compound concentrations used. Moreover, the nature of the cellular stressor influences this response: oxidative stress (H₂O₂), but not ER stress (thapsigargin), promotes σ_1 R monomerization, even though both stressors activate the receptor (Couly et al., 2024). These results suggest that structurally diverse agonists and endogenous ligands regulate the switch between the “open-like” and closed σ_1 R conformation. In line, we recently observed that H₂O₂ and (+)-SKF-10047, but not PRE-084, promote σ_1 R binding to GABARAP (Baeken et al., 2025). An important consideration for the development of novel σ_1 R agonist is whether



σ_1 R-GABARAP interaction in HeLa cells (Baeken et al., 2025), it enhances autophagic flux in both HeLa cells and *C. elegans*, possibly via ULK1 modulation (Christ et al., 2019; Wang et al.,

2021). These findings support the idea that σ_1 R agonists can elicit ligand-specific effects, including differential engagement of the σ_1 R–GABARAP axis.

σ_1 R in GABARAP logistics

A peculiarity concerning σ_1 R and GABARAP is their phylogenetic co-emergence in the *Parahoxozoa*, the earliest metazoan clade with neuronal circuits, suggesting a fundamental role for their interplay in neuronal homeostasis. Intriguingly, choline has been identified as an endogenous σ_1 R agonist (Brailoiu et al., 2019). In neurons, intracellular choline levels rise under oxidative or metabolic stress (e.g., phosphatidylcholine breakdown, hypoxia, or low acetyl-CoA), conditions that typically demand autophagy activation to degrade damaged components or replenish carbon sources. Thus, σ_1 R activation might redirect GABARAP toward autophagic pathways. It remains unclear whether σ_1 R activation sequesters Golgi-resident GABARAP or acts only on newly synthesized protein. The latter could explain σ_1 R's neuroprotective effects, as it would preserve the Golgi's GABARAP pool needed for plasma membrane homeostasis. Testing GABARAP–GOLGA2 interactions after σ_1 R activation may resolve this question.

Another group of molecules that modulate this system are steroid hormones: dehydroepiandrosterone (DHEA) acts as a σ_1 R agonist, while progesterone functions as an antagonist (Moriguchi et al., 2011; Johannessen et al., 2011). This aligns with σ_1 R's evolutionary relationship with ergosterol-synthesizing sterol isomerases in yeast (Hanner et al., 1996). Notably, DHEA also serves as a negative allosteric regulator of GABA_A receptors (Genud et al., 2009), suggesting that simultaneous σ_1 R activation and GABARAP rerouting could alter synaptic tone. Conversely, progesterone acts as a positive GABA_A receptor modulator (Kapur and Joshi, 2021), effectively mirroring DHEA's opposing effects on this dual regulatory axis.

Interestingly, crystal structures of *Xenopus laevis* σ_1 R in complex with DHEA sulfate (DHEAS) or progesterone demonstrate deeper penetration of the antagonist toward the C-terminal, membrane-associated helix (Fu et al., 2024) (Figure 1C). Here, progesterone probably interacts with Y²⁰³, while DHEAS engages W¹⁶¹. Former interaction might tighten the β -barrel, thereby blocking GABARAP interaction. Notably, DHEA levels rise during fasting (Grasfeder et al., 2009), suggesting σ_1 R activation in extrahepatic tissues could promote autophagy and thereby couple cellular energy responses to systemic metabolic status. In this light, σ_1 R may help precondition peripheral tissues for nutrient scarcity. Consequently, σ_1 R agonists might mimic aspects of the fasting response by shifting GABARAP from anabolic trafficking roles toward catabolic autophagy (Figures 2A,B). Mutational analysis of Y²⁰³ and W¹⁶¹ is needed to confirm their roles in agonist vs. antagonist binding. The relevance of this regulatory axis could further be tested *in vivo* by monitoring autophagy and σ_1 R monomerization under altered hormonal conditions.

In cell culture, GABARAP is rerouted toward autophagy during starvation despite the absence of DHEAS, suggesting either σ_1 R bypass of or activation by alternative ligands. In neurons, Cytochrome P450 46A1 (CYP46A1), which is also upregulated during starvation (Shinohara et al., 2022), generates oxysterols

potentially fulfilling this role. The biomolecular foundation model Boltz-2 predicts that 24(S)-hydroxycholesterol, a CYP46A1 product, binds human σ_1 R (Figure 1C), possibly explaining how CYP46A1 enhances autophagy (Nóbrega et al., 2019) and how H₂O₂ induces σ_1 R activity via sterol oxidation. Although further tests with oxysterol treatments and monitoring of σ_1 R and autophagy are required, current evidence highlights σ_1 R as a key regulator of GABARAP-mediated cell functions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MWB: Conceptualization, Visualization, Writing – original draft, Writing – review and editing. FB: Writing – original draft, Writing – review and editing. HK: Writing – original draft, Writing – review and editing. AMC: Writing – original draft, Writing – review and editing. CB: Funding acquisition, Writing – original draft, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the Hanna Bragard-Apfel Foundation, the Peter Beate Heller Foundation of the German Stifterverband, the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) - 530063157, and the COST Action SIGMA-1 EUROPE - CA23156.

Acknowledgments

The authors thank Michael Plenikowski for the graphical illustrations.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that Generative AI was used in the creation of this manuscript. The authors declare that AlphaFold3

(Abramson et al., 2024) and Boltz-2 (Passaro et al., 2025) were used to model molecular structures of proteins.

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References

- Abramson, J., Adler, J., Dunger, J., Evans, R., Green, T., Pritzel, A., et al. (2024). Accurate structure prediction of biomolecular interactions with AlphaFold 3. *Nature* 630 (8016), 493–500. doi:10.1038/s41586-024-07487-w
- Aishwarya, R., Abdullah, C. S., Morshed, M., Remex, N. S., and Bhuiyan, M. S. (2021). Sigmar1's molecular, cellular, and biological functions in regulating cellular pathophysiology. *Front. Physiol.* 12, 705575. doi:10.3389/fphys.2021.705575
- Al-Saif, A., Al-Mohanna, F., and Bohlega, S. (2011). A mutation in sigma-1 receptor causes juvenile amyotrophic lateral sclerosis. *Ann. Neurol.* 70 (6), 913–919. doi:10.1002/ana.22534
- Alam, S., Abdullah, C. S., Aishwarya, R., Orr, A. W., Traylor, J., Miriyala, S., et al. (2017). Sigmar1 regulates endoplasmic reticulum stress-induced C/EBP-homologous protein expression in cardiomyocytes. *Biosci. Rep.* 37 (4), BSR20170898. doi:10.1042/BSR20170898
- Albanesi, J., Wang, H., Sun, H. Q., Levine, B., and Yin, H. (2015). GABARAP-mediated targeting of PI4K2A/PI4KIIa to autophagosomes regulates PtdIns4P-dependent autophagosome-lysosome fusion. *Autophagy* 11 (11), 2127–2129. doi:10.1080/15548627.2015.1093718
- Alemu, E. A., Lamark, T., Torgersen, K. M., Birgisdottir, A. B., Larsen, K. B., Jain, A., et al. (2012). ATG8 family proteins act as scaffolds for assembly of the ULK complex: sequence requirements for LC3-interacting region (LIR) motifs. *J. Biol. Chem.* 287 (47), 39275–39290. doi:10.1074/jbc.M112.378109
- Aman, Y., Schmauck-Medina, T., Hansen, M., Morimoto, R. I., Simon, A. K., Bjedov, I., et al. (2017). Autophagy in healthy aging and disease. *Nat. Aging* 1 (8), 634–650. doi:10.1038/s43587-021-00098-4
- Ariosa, A. R., and Klionsky, D. J. (2016). Autophagy core machinery: overcoming spatial barriers in neurons. *J. Mol. Med. (Berl.)* 94 (11), 1217–1227. doi:10.1007/s00109-016-1461-9
- Aydar, E., Palmer, C. P., Klyachko, V. A., and Jackson, M. B. (2002). The sigma receptor as a ligand-regulated auxiliary potassium channel subunit. *Neuron* 34 (3), 399–410. doi:10.1016/s0896-6273(02)00677-3
- Baeken, M. W., Christ, M., Schmitt, D., Trein, W., Nagel, H., Clement, A. M., et al. (2025). Conserved LIR-specific interaction of Sigma-1 receptor and GABARAP. *iScience* 28, 113287. doi:10.1016/j.isci.2025.113287
- Balasuriya, D., Stewart, A. P., and Edwardson, J. M. (2013). The σ -1 receptor interacts directly with GluN1 but not GluN2A in the GluN1/GluN2A NMDA receptor. *J. Neurosci.* 33 (46), 18219–18224. doi:10.1523/JNEUROSCI.3360-13.2013
- Birgisdottir, Å. B., Lamark, T., and Johansen, T. (2013). The LIR motif - crucial for selective autophagy. *J. Cell Sci.* 126 (Pt 15), 3237–3247. doi:10.1242/jcs.126128
- Brailoiu, E., Chakraborty, S., Brailoiu, G. C., Zhao, P., Barr, J. L., Ilies, M. A., et al. (2019). Choline is an intracellular messenger linking extracellular stimuli to IP3-Evoked Ca²⁺ signals through Sigma-1 receptors. *Cell Rep.* 26 (2), 330–337.e4. doi:10.1016/j.celrep.2018.12.051
- Chen, Z. W., and Olsen, R. W. (2007). GABAA receptor associated proteins: a key factor regulating GABAA receptor function. *J. Neurochem.* 100 (2), 279–294. doi:10.1111/j.1471-4159.2006.04206.x
- Chen, L., Wang, H., Vicini, S., and Olsen, R. W. (2000). The gamma-aminobutyric acid type A (GABAA) receptor-associated protein (GABARAP) promotes GABAA receptor clustering and modulates the channel kinetics. *Proc. Natl. Acad. Sci. U. S. A.* 97 (21), 11557–11562. doi:10.1073/pnas.190133497
- Chen, Z. W., Chang, C. S., Leil, T. A., and Olsen, R. W. (2007). C-terminal modification is required for GABARAP-mediated GABA(A) receptor trafficking. *J. Neurosci.* 27 (25), 6655–6663. doi:10.1523/JNEUROSCI.0919-07.2007
- Choi, S. R., Moon, J. Y., Roh, D. H., Yoon, S. Y., Kwon, S. G., Choi, H. S., et al. (2017). Spinal D-Serine increases PKC-dependent GluN1 phosphorylation contributing to the Sigma-1 receptor-induced development of mechanical allodynia in a mouse model of neuropathic pain. *J. Pain* 18 (4), 415–427. doi:10.1016/j.jpain.2016.12.002
- Christ, M. G., Huesmann, H., Nagel, H., Kern, A., and Behl, C. (2019). Sigma-1 receptor activation induces autophagy and increases proteostasis capacity *in vitro* and *in vivo*. *Cells* 8 (3), 211. doi:10.3390/cells8030211
- Christ, M. G., Clement, A. M., and Behl, C. (2020). The Sigma-1 receptor at the crossroad of proteostasis, neurodegeneration, and autophagy. *Trends Neurosci.* 43 (2), 79–81. doi:10.1016/j.tins.2019.12.002
- Comenencia-Ortiz, E., Moss, S. J., and Davies, P. A. (2014). Phosphorylation of GABAA receptors influences receptor trafficking and neurosteroid actions. *Psychopharmacol. (Berl.)* 231 (17), 3453–3465. doi:10.1007/s00213-014-3617-z
- Cook, J. L., Re, R. N., deHaro, D. L., Abadie, J. M., Peters, M., and Alam, J. (2008). The trafficking protein GABARAP binds to and enhances plasma membrane expression and function of the angiotensin II type 1 receptor. *Circ. Res.* 102 (12), 1539–1547. doi:10.1161/CIRCRESAHA.108.176594
- Couly, S., Yasui, Y., and Su, T. P. (2023). SIGMAR1 confers innate resilience against neurodegeneration. *Int. J. Mol. Sci.* 24 (9), 7767. doi:10.3390/ijms24097767
- Couly, S., Yasui, Y., Foncham, S., Grammatikakis, I., Lal, A., Shi, L., et al. (2024). Benzomorphan and non-benzomorphan agonists differentially alter sigma-1 receptor quaternary structure, as does types of cellular stress. *Cell Mol. Life. Sci.* 81 (1), 14. doi:10.1007/s00018-023-05023-z
- Dobner, J., Simons, I. M., Rufinatscha, K., Hänsch, S., Schwarten, M., Weiergräber, O. H., et al. (2020). Deficiency of GABARAP but not its paralogs causes enhanced EGF-induced EGFR degradation. *Cells* 9 (5), 1296. doi:10.3390/cells9051296
- Dreser, A., Vollrath, J. T., Sechi, A., Johann, S., Roos, A., Yamoah, A., et al. (2017). The ALS-linked E102Q mutation in sigma receptor-1 leads to ER stress-mediated defects in protein homeostasis and dysregulation of RNA-binding proteins. *Cell Death Differ.* 24 (10), 1655–1671. doi:10.1038/cdd.2017.88
- Drewes, N., Fang, X., Gupta, N., and Nie, D. (2025). Pharmacological and pathological implications of Sigma-1 receptor in neurodegenerative diseases. *Biomedicines* 13 (6), 1409. doi:10.3390/biomedicines13061409
- Estévez-Silva, H. M., Cuesto, G., Romero, N., Brito-Armas, J. M., Acevedo-Arozena, A., Acebes, Á., et al. (2022). Pridopidine promotes synaptogenesis and reduces spatial memory deficits in the alzheimer's disease APP/PS1 mouse model. *Neurotherapeutics* 19 (5), 1566–1587. doi:10.1007/s13311-022-01280-1
- Fu, C., Xiao, Y., Zhou, X., and Sun, Z. (2024). Insight into binding of endogenous neurosteroid ligands to the sigma-1 receptor. *Nat. Commun.* 15 (1), 5619. doi:10.1038/s41467-024-49894-7
- Genud, R., Merenlender, A., Gispán-Herman, I., Maayan, R., Weizman, A., and Yadid, G. (2009). DHEA lessens depressive-like behavior via GABA-ergic modulation of the mesolimbic system. *Neuropsychopharmacology* 34 (3), 577–584. doi:10.1038/npp.2008.46
- Grasfeder, L. L., Gaillard, S., Hammes, S. R., Ilkayeva, O., Newgard, C. B., Hochberg, R. B., et al. (2009). Fasting-induced hepatic production of DHEA is regulated by PGC-1alpha, ERRalpha, and HNF4alpha. *Mol. Endocrinol.* 23 (8), 1171–1182. doi:10.1210/me.2009-0024
- Hanner, M., Moebius, F. F., Flandorfer, A., Knaus, H. G., Striessnig, J., Kempner, E., et al. (1996). Purification, molecular cloning, and expression of the mammalian sigma1-binding site. *Proc. Natl. Acad. Sci. U. S. A.* 93 (15), 8072–8077. doi:10.1073/pnas.93.15.8072
- Hayashi, T., and Su, T. P. (2007). Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca²⁺ signaling and cell survival. *Cell* 131 (3), 596–610. doi:10.1016/j.cell.2007.08.036
- He, C., and Klionsky, D. J. (2009). Regulation mechanisms and signaling pathways of autophagy. *Annu. Rev. Genet.* 43, 67–93. doi:10.1146/annurev-genet-102808-114910
- Joachim, J., Jefferies, H. B., Razi, M., Frith, D., Snijders, A. P., Chakravarty, P., et al. (2015). Activation of ULK kinase and autophagy by GABARAP trafficking from the centrosome is regulated by WAC and GM130. *Mol. Cell* 60 (6), 899–913. doi:10.1016/j.molcel.2015.11.018
- Johannessen, M., Fontanilla, D., Mavlyutov, T., Ruoho, A. E., and Jackson, M. B. (2011). Antagonist action of progesterone at σ -receptors in the modulation of voltage-gated sodium channels. *Am. J. Physiol. Cell Physiol.* 300 (2), C328–C337. doi:10.1152/ajpcell.00383.2010

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- Johansen, T., and Lamark, T. (2020). Selective autophagy: ATG8 family proteins, LIR motifs and cargo receptors. *J. Mol. Biol.* 432 (1), 80–103. doi:10.1016/j.jmb.2019.07.016
- Jurd, R., Tretter, V., Walker, J., Brandon, N. J., and Moss, S. J. (2010). Fyn kinase contributes to tyrosine phosphorylation of the GABA(A) receptor gamma2 subunit. *Mol. Cell Neurosci.* 44 (2), 129–134. doi:10.1016/j.mcn.2010.03.002
- Kamath, T., Abdulraouf, A., Burris, S. J., Langlieb, J., Gazestani, V., Nadaf, N. M., et al. (2022). Single-cell genomic profiling of human dopamine neurons identifies a population that selectively degenerates in parkinson's disease. *Nat. Neurosci.* 25 (5), 588–595. doi:10.1038/s41593-022-01061-1
- Kapur, J., and Joshi, S. (2021). Progesterone modulates neuronal excitability bidirectionally. *Neurosci. Lett.* 744, 135619. doi:10.1016/j.neulet.2020.135619
- Khaminets, A., Behl, C., and Dikic, I. (2016). Ubiquitin-dependent and independent signals in selective autophagy. *Trends Cell Biol.* 26 (1), 6–16. doi:10.1016/j.tcb.2015.08.010
- Kittler, J. T., Chen, G., Kukhtina, V., Vahedi-Faridi, A., Gu, Z., Tretter, V., et al. (2008). Regulation of synaptic inhibition by phospho-dependent binding of the AP2 complex to a YECL motif in the GABAA receptor gamma2 subunit. *Proc. Natl. Acad. Sci. U. S. A.* 105 (9), 3616–3621. doi:10.1073/pnas.0707920105
- Kneussel, M., Haverkamp, S., Fuhrmann, J. C., Wang, H., Wässle, H., Olsen, R. W., et al. (2000). The gamma-aminobutyric acid type A receptor (GABAAR)-associated protein GABARAP interacts with gephyrin but is not involved in receptor anchoring at the synapse. *Proc. Natl. Acad. Sci. U. S. A.* 97 (15), 8594–8599. doi:10.1073/pnas.97.15.8594
- Lachance, V., Bélanger, S. M., Hay, C., Le Corvec, V., Banouvang, V., Lapalme, M., et al. (2023). Overview of sigma-1R subcellular specific biological functions and role in neuroprotection. *Int. J. Mol. Sci.* 24 (3), 1971. doi:10.3390/ijms24031971
- Lahmy, V., Meunier, J., Malmström, S., Naert, G., Givalois, L., Kim, S. H., et al. (2013). Blockade of tau hyperphosphorylation and Aβ₁₋₄₂ generation by the aminotetrahydrofuran derivative ANAVEX-73, a mixed muscarinic and σ₁ receptor agonist, in a nontransgenic mouse model of Alzheimer's disease. *Neuropsychopharmacology* 38 (9), 1706–1723. doi:10.1038/npp.2013.70
- Lainez, S., Valente, P., Ontoria-Oviedo, I., Estévez-Herrera, J., Camprubí-Robles, M., Ferrer-Montiel, A., et al. (2010). GABAA receptor associated protein (GABARAP) modulates TRPV1 expression and channel function and desensitization. *FASEB J.* 24 (6), 1958–1970. doi:10.1096/fj.09-151472
- Lee, Y. K., and Lee, J. A. (2016). Role of the mammalian ATG8/LC3 family in autophagy: differential and compensatory roles in the spatiotemporal regulation of autophagy. *BMB Rep.* 49 (8), 424–430. doi:10.5483/bmbrep.2016.49.8.081
- Li, L., He, S., Liu, Y., Yorio, T., and Ellis, D. Z. (2021). Sigma-1R protects retinal ganglion cells in optic nerve crush model for glaucoma. *Invest. Ophthalmol. Vis. Sci.* 62 (10), 17. doi:10.1167/iov.62.10.17
- Lu, J., Zhou, W., Dou, F., Wang, C., and Yu, Z. (2021). TRPV1 sustains microglial metabolic reprogramming in Alzheimer's disease. *EMBO Rep.* 22 (6), e2013. doi:10.15252/embr.202052013
- Lüscher, B., and Keller, C. A. (2001). Ubiquitination, proteasomes and GABA(A) receptors. *Nat. Cell Biol.* 3 (10), E232–E233. doi:10.1038/ncb1001-e232
- Lystad, A. H., Ichimura, Y., Takagi, K., Yang, Y., Pankiv, S., Kanegae, Y., et al. (2014). Structural determinants in GABARAP required for the selective binding and recruitment of ALFY to LC3B-positive structures. *EMBO Rep.* 15 (5), 557–565. doi:10.1002/embr.201338003
- Ma, M. T., Chen, D. H., Raskind, W. H., and Bird, T. D. (2020). Mutations in the SIGMAR1 gene cause a distal hereditary motor neuropathy phenotype mimicking ALS: report of two novel variants. *Neuromuscul. Disord.* 30 (7), 572–575. doi:10.1016/j.nmd.2020.05.005
- Macfarlane, S., Grimmer, T., Teo, K., O'Brien, T. J., Woodward, M., Grunfeld, J., et al. (2025). Blarcamesine for the treatment of early Alzheimer's disease: results from the ANAVEX2-73-AD-004 phase IIB/III trial. *J. Prev. Alzheimers Dis.* 12 (1), 100016. doi:10.1016/j.tjpad.2024.100016
- Martens, S., and Fracchiolla, D. (2020). Activation and targeting of ATG8 protein lipidation. *Cell Discov.* 6, 23. doi:10.1038/s41421-020-0155-1
- Martin, W. R., Eades, C. G., Thompson, J. A., Huppler, R. E., and Gilbert, P. E. (1976). The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J. Pharmacol. Exp. Ther.* 197 (3), 517–532. doi:10.1016/s0022-3565(25)30536-7
- Maruyama, T., and Noda, N. N. (2017). Autophagy-regulating protease Atg4: structure, function, regulation and inhibition. *J. Antibiot. (Tokyo)* 71 (1), 72–78. doi:10.1038/ja.2017.104
- Maurice, T. (2021). Bi-phasic dose response in the preclinical and clinical developments of sigma-1 receptor ligands for the treatment of neurodegenerative disorders. *Expert Opin. Drug Discov.* 16 (4), 373–389. doi:10.1080/17460441.2021.1838483
- Mavlyutov, T., Chen, X., Guo, L., and Yang, J. (2018). APEX2-tagging of sigma 1-receptor indicates subcellular protein topology with cytosolic N-terminus and ER luminal C-terminus. *Protein Cell* 9 (8), 733–737. doi:10.1007/s13238-017-0468-5
- Mizushima, N., and Komatsu, M. (2011). Autophagy: renovation of cells and tissues. *Cell* 147 (4), 728–741. doi:10.1016/j.cell.2011.10.026
- Moebius, F. F., Striessnig, J., and Glossmann, H. (1997). The mysteries of sigma receptors: new family members reveal a role in cholesterol synthesis. *Trends Pharmacol. Sci.* 18 (3), 67–70. doi:10.1016/s0165-6147(96)01037-1
- Moriguchi, S., Yamamoto, Y., Ikuno, T., and Fukunaga, K. (2011). Sigma-1 receptor stimulation by dehydroepiandrosterone ameliorates cognitive impairment through activation of CaM kinase II, protein kinase C and extracellular signal-regulated kinase in olfactory bulbectomized mice. *J. Neurochem.* 117 (5), 879–891. doi:10.1111/j.1471-4159.2011.07256.x
- Nakamura, T., Hayashi, T., Nasu-Nishimura, Y., Sakaue, F., Morishita, Y., Okabe, T., et al. (2008). PX-RICS mediates ER-to-Golgi transport of the N-cadherin/beta-catenin complex. *Genes Dev.* 22 (9), 1244–1256. doi:10.1101/gad.1632308
- Nelson, A. D., Caballero-Florán, R. N., Rodríguez Díaz, J. C., Hull, J. M., Yuan, Y., Li, J., et al. (2020). Ankyrin-G regulates forebrain connectivity and network synchronization via interaction with GABARAP. *Mol. Psychiatry* 25 (11), 2800–2817. doi:10.1038/s41380-018-0308-x
- Nguyen, T. N., Padman, B. S., Usher, J., Oorschot, V., Ramm, G., and Lazarou, M. (2016). Atg8 family LC3/GABARAP proteins are crucial for autophagosome-lysosome fusion but not autophagosome formation during PINK1/Parkin mitophagy and starvation. *J. Cell Biol.* 215 (6), 857–874. doi:10.1083/jcb.201607039
- Nguyen, N., Olivas, T. J., Mires, A., Jin, J., Yu, S., Luan, L., et al. (2020). The insufficiency of ATG4A in macroautophagy. *J. Biol. Chem.* 295 (39), 13584–13600. doi:10.1074/jbc.RA120.013897
- Nóbrega, C., Mendonça, L., Marcelo, A., Lamazière, A., Tomé, S., Despres, G., et al. (2019). Restoring brain cholesterol turnover improves autophagy and has therapeutic potential in mouse models of spinocerebellar ataxia. *Acta neuropathol.* 138 (5), 837–858. doi:10.1007/s00401-019-02019-7
- Nymann-Andersen, J., Wang, H., Chen, L., Kittler, J. T., Moss, S. J., and Olsen, R. W. (2002). Subunit specificity and interaction domain between GABA(A) receptor-associated protein (GABARAP) and GABA(A) receptors. *J. Neurochem.* 80 (5), 815–823. doi:10.1046/j.0022-3042.2002.00762.x
- Palmer, J. E., Wilson, N., Son, S. M., Obrocki, P., Wrobel, L., Rob, M., et al. (2025). Autophagy, aging, and age-related neurodegeneration. *Neuron* 113 (1), 29–48. doi:10.1016/j.neuron.2024.09.015
- Pankiv, S., Clausen, T. H., Lamark, T., Brech, A., Bruun, J. A., Outzen, H., et al. (2007). p62/SQSTM1 binds directly to Atg8/LC3 to facilitate degradation of ubiquitinated protein aggregates by autophagy. *J. Biol. Chem.* 282 (33), 24131–24145. doi:10.1074/jbc.M702824200
- Passaro, S., Corso, G., Wohlwend, J., Reveiz, M., Thaler, S., Somnath, V. R., et al. (2025). Boltz-2: towards accurate and efficient binding affinity prediction. *BioRxiv* 06.14, 2025.06.14.659707. doi:10.1101/2025.06.14.659707
- Phan, V. L., Miyamoto, Y., Nabeshima, T., and Maurice, T. (2005). Age-related expression of sigma1 receptors and antidepressant efficacy of a selective agonist in the senescence-accelerated (SAM) mouse. *J. Neurosci. Res.* 79 (4), 561–572. doi:10.1002/jnr.20390
- Rogov, V., Dötsch, V., Johansen, T., and Kirkin, V. (2014). Interactions between autophagy receptors and ubiquitin-like proteins form the molecular basis for selective autophagy. *Mol. Cell* 53 (2), 167–178. doi:10.1016/j.molcel.2013.12.014
- Rogov, V. V., Stolz, A., Ravichandran, A. C., Rios-Szved, D. O., Suzuki, H., Kniss, A., et al. (2017). Structural and functional analysis of the GABARAP interaction motif (GIM). *EMBO Rep.* 18 (8), 1382–1396. doi:10.15252/embr.201643587
- Rogov, V. V., Nezis, I. P., Tsapras, P., Zhang, H., Dagdas, Y., Noda, N. N., et al. (2023). Atg8 family proteins, LIR/AIM motifs and other interaction modes. *Autophagy Rep.* 2 (1), 2188523. doi:10.1080/27694127.2023.2188523
- Ryskamp, D., Wu, L., Wu, J., Kim, D., Rammes, G., Geva, M., et al. (2019). Pridopidine stabilizes mushroom spines in mouse models of alzheimer's disease by acting on the sigma-1 receptor. *Neurobiol. Dis.* 124, 489–504. doi:10.1016/j.nbd.2018.12.022
- Schaaf, M. B., Keulers, T. G., Vooijs, M. A., and Rouschop, K. M. (2016). LC3/GABARAP family proteins: autophagy-(un)related functions. *FASEB J.* 30 (12), 3961–3978. doi:10.1096/fj.201600698R
- Schmidt, H. R., Zheng, S., Gurpinar, E., Koehl, A., Manglik, A., and Kruse, A. C. (2016). Crystal structure of the human σ1 receptor. *Nature* 532 (7600), 527–530. doi:10.1038/nature17391
- Seth, P., Fei, Y. J., Li, H. W., Huang, W., Leibach, F. H., and Ganapathy, V. (1998). Cloning and functional characterization of a sigma receptor from rat brain. *J. Neurochem.* 70 (3), 922–931. doi:10.1046/j.1471-4159.1998.70030922.x
- Sharma, N., Patel, C., Shenkman, M., Kessel, A., Ben-Tal, N., and Lederkremer, G. Z. (2021). The Sigma-1 receptor is an ER-localized type II membrane protein. *J. Biol. Chem.* 297 (5), 101299. doi:10.1016/j.jbc.2021.101299
- Shefner, J. M., Oskarsson, B., Macklin, E. A., Chibnik, L. B., Quintana, M., Saville, B. R., et al. (2025). Pridopidine in amyotrophic lateral sclerosis: the HEALEY ALS platform trial. *JAMA* 333 (13), 1128–1137. doi:10.1001/jama.2024.26429
- Shinohara, Y., Ando, H., Maekawa, M., Arai, M., Horibata, Y., Satou, M., et al. (2022). Transcription of cytochrome P450 46A1 in NIH3T3 cells is negatively

regulated by FBS. *Biochimica biophysica acta. Mol. cell Biol. lipids* 1867 (6), 159136. doi:10.1016/j.bbalip.2022.159136

Su, T. P. (1982). Evidence for sigma opioid receptor: binding of [3H]SKF-10047 to etorphine-inaccessible sites in guinea-pig brain. *J. Pharmacol. Exp. Ther.* 223 (2), 284–290. doi:10.1016/s0022-3565(25)33330-6

Sugawara, K., Suzuki, N. N., Fujioka, Y., Mizushima, N., Ohsumi, Y., and Inagaki, F. (2004). The crystal structure of microtubule-associated protein light chain 3, a mammalian homologue of *Saccharomyces cerevisiae* Atg8. *Genes cells.* 9 (7), 611–618. doi:10.1111/j.1356-9597.2004.00750.x

Tam, S. W. (1983). Naloxone-inaccessible sigma receptor in rat central nervous system. *Proc. Natl. Acad. Sci. U. S. A.* 80 (21), 6703–6707. doi:10.1073/pnas.80.21.6703

Tsai, S. Y., Chuang, J. Y., Tsai, M. S., Wang, X. F., Xi, Z. X., Hung, J. J., et al. (2015). Sigma-1 receptor mediates cocaine-induced transcriptional regulation by recruiting chromatin-remodeling factors at the nuclear envelope. *Proc. Natl. Acad. Sci. U. S. A.* 112 (47), E6562–E6570. doi:10.1073/pnas.1518894112

Üffing, A., Weiergräber, O. H., Schwarten, M., Hoffmann, S., and Willbold, D. (2024). GABARAP interacts with EGFR - supporting the unique role of this hAtg8 protein during receptor trafficking. *FEBS Lett.* 598 (21), 2656–2669. doi:10.1002/1873-3468.14997

Vollrath, J. T., Sechi, A., Dreser, A., Katona, I., Wiemuth, D., Vervoorts, J., et al. (2014). Loss of function of the ALS protein SigR1 leads to ER pathology associated with defective autophagy and lipid raft disturbances. *Cell death. Dis.* 5 (6), e1290. doi:10.1038/cddis.2014.243

Wang, H., Bedford, F. K., Brandon, N. J., Moss, S. J., and Olsen, R. W. (1999). GABA(A)-receptor-associated protein links GABA(A) receptors and the cytoskeleton. *Nature* 397 (6714), 69–72. doi:10.1038/16264

Wang, M., Wan, C., He, T., Han, C., Zhu, K., Waddington, J. L., et al. (2021). Sigma-1 receptor regulates mitophagy in dopaminergic neurons and contributes to dopaminergic protection. *Neuropharmacology* 196, 108360. doi:10.1016/j.neuropharm.2020.108360

Wang, S. M., Wu, H. E., Yasui, Y., Geva, M., Hayden, M., Maurice, T., et al. (2023). Nucleoporin POM121 signals TFEB-mediated autophagy via activation of SIGMAR1/sigma-1 receptor chaperone by pridopidine. *Autophagy* 19 (1), 126–151. doi:10.1080/15548627.2022.2063003

Yang, H., Shen, H., Li, J., and Guo, L. W. (2019). SIGMAR1/Sigma-1 receptor ablation impairs autophagosome clearance. *Autophagy* 15 (9), 1539–1557. doi:10.1080/15548627.2019.1586248

Ye, J., Zou, G., Zhu, R., Kong, C., Miao, C., Zhang, M., et al. (2021). Structural basis of GABARAP-mediated GABAA receptor trafficking and functions on GABAergic synaptic transmission. *Nat. Commun.* 12 (1), 297. doi:10.1038/s41467-020-20624-z