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Invited Review

Gastrin-releasing peptide receptor signaling in the integration of stress and memory

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ABSTRACT

Neuropeptides act as signaling molecules that regulate a range of aspects of brain function. Gastrin-releasing peptide (GRP) is a 27-amino acid mammalian neuropeptide, homolog of the amphibian peptide bombesin. GRP acts by binding to the GRP receptor (GRPR, also called BB2), a member of the G-protein coupled receptor (GPCR) superfamily. GRP produced by neurons in the central nervous system (CNS) plays a role in synaptic transmission by activating GRPRs located on postsynaptic membranes, influencing several aspects of brain function. Here we review the role of GRP/GRPR as a system mediating both stress responses and the formation and expression of memories for fearful events. GRPR signaling might integrate the processing of stress and fear with synaptic plasticity and memory, serving as an important component of the set of neurobiological systems underlying the enhancement of memory storage by aversive information.

1. Introduction

Brain processing of aversive information, stress responses, and memory formation are closely intertwined, allowing emotional arousal to enhance memory storage (McGaugh, 2000, 2013). Signaling molecules in the mammalian brain involved in mediating emotional processing, stress, and memory include many types of neuropeptides produced by neurons, which act by activating specific cell membrane receptors that are members of the G protein-coupled receptor (GPCR) superfamily. Neuropeptide receptor activation in turn leads to stimulation of downstream protein kinase signaling pathways and ultimately alters neuronal gene expression (Brain & Cox, 2006; Salio, Lossi, Ferrini, & Merighi, 2006).

Gastrin-releasing peptide (GRP) is a 27-amino acid mammalian neuropeptide, homolog of the 14-amino acid amidated amphibian peptide bombesin originally isolated from the skin of the European frog *Bombina bombina* (Erspamer, Erspamer, & Inselvini, 1970). GRP and bombesin are structurally related, sharing the same seven carboxyl-terminal amino acid sequence, and can display similar biological effects when applied to several mammalian cell and tissue preparations. GRP acts by binding to the GRP receptor (GRPR, also called BB2), located on cell membranes. Over the past three decades accumulating evidence has suggested that the GRP/GRPR system influences a broad spectrum of physiological processes including thermal regulation, glicemia, feeding, gastrin and somatostatin release, gastric acid secretion, pancreatic secretion, gastrointestinal motility, lung development, pain perception, itch responses, memory formation and expression, stress responses, cell proliferation, and chemoattraction in the immune system (Brown, Rivier, & Vale, 1977a, 1977b; Czepielewski et al., 2012; Del Rio & De la Fuente, 1994; Gibbs & Smith, 1988; Gibbs et al., 1979; Gonzalez, Moody, Igarashi, Ito, & Jensen, 2008; Jensen, Battey, Spindel, & Benya, 2008; Niebergall-Roth & Singer, 2001;

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Ohki-Hamazaki, Iwabuchi, & Maekawa, 2005; Pert, Moody, Pert, Dewald, & Rivier, 1980; Roesler & Schwartsmann, 2012; Ruff, Schiffmann, Terranova, & Pert, 1985; Schubert, Hightower, Coy, & Makhlouf, 1991; Sun & Chen, 2007).

In the central nervous system (CNS), GRP may act as a transmitter to activate GRPRs located on postsynaptic neuronal membranes, regulating several aspects of brain function (Moody & Merali, 2004; Roesler & Schwartsmann, 2012; Shumyatsky et al., 2002). In this review, we focus on the role of GRP and GRPR in regulating the formation and expression of memories related to emotional events, as well as stress responses. We propose that GRPR signaling might integrate the processing of stress and fear with synaptic plasticity and memory, being part of the complex neurobiological system underlying the enhancement of memory storage by aversive emotional content.

2. Molecular structure and genomic organization of the GRPR

The GRPR was the first type of bombesin receptor to be cloned, from murine Swiss 3T3 cells (Battey et al., 1991; Spindel, Giladi, Brehm, Goodman, & Segerson, 1990). GRPR binds preferentially to GRP, with lower affinity for another mammalian bombesin-like peptide, neuromedin B (NMB) (Jensen & Gardner, 1981; Ladenheim, Jensen, Mantey, McHugh, & Moran, 1990; Moody, Getz, O'Donohue, & Rosenstein, 1988; Moody, Staley, Zia, Coy, & Jensen, 1992; von Schrenck et al., 1990; Wang et al., 1992). The other types of bombesin receptors described in mammals are the NMB receptor (NMBR), which has higher affinity for NMB than GRP (Wada et al., 1991), and BRS-3, which shows low affinity for all known bombesin-like peptides and is considered an orphan receptor (Fathi et al., 1993; Gorbulev, Akhundova, Buchner, & Fahrenholz, 1992; Jensen et al., 2008; Ohki-Hamazaki, Wada, Matsui, & Wada, 1997; Whitley, Moore, Giraud, & Shulkes, 1999). The current terminology adopted by several receptor classification guides uses the names BB1, BB2, and BB3 for NMBRs, GRPRs, and BRS-3 receptors respectively.

As with the other bombesin receptor types, the GRPR is a member of the G-protein coupled receptor (GPCR) superfamily and exhibits a characteristic 7 transmembrane domain structure. In human, mice, and rats, the GRPR is a 384-amino acid protein (Battey et al., 1991; Jensen et al., 2008; Spindel et al., 1990). The GRPR gene (named *GRPR* in humans and *Grpr* in mice and rats) is located at chromosome Xp22.2-p22.13 (human), X F4 (mouse), and Xq21 (rat) (Jensen, Battey, Benya, & Spindel, IUPHAR database, accessed on July 1st, 2013).

3. Distribution and basic function of GRP/GRPR in the mammalian brain

Experiments in the late 1970s were the first to indicate that bombesin could bind with high affinity to rat brain membranes (Moody, Pert, Rivier, & Brown, 1978). Subsequent autoradiographic studies revealed high densities of GRPRs in areas including the olfactory bulb, nucleus accumbens, caudate putamen, amygdala, dorsal hippocampus, and thalamic nuclei (Wolf & Moody, 1985; Wolf, Moody, O'Donohue, Zarbin, & Kuhar, 1983; Zarbin, Kuhar, O'Donohue, Wolf, & Moody, 1985). GRPR expression in the mouse brain has been characterized in detail by immunohistochemistry, showing high immunoreactivity in the basolateral and central nuclei of the amygdala (BLA and CeA, respectively), hippocampus, hypothalamus, brain stem, nucleus tractus solitarius (NTS), and several cortical sites. Importantly, GRPR expression was restricted to neuronal cell bodies and dendrites, and was not present in axons or glial cells (Kamichi et al., 2005), which is consistent with data from immunohistochemical localization of GRPR in human brain samples (Flores et al., 2010), suggesting that the GRPR in the brain plays a specific role as a postsynaptic receptor mediating neural transmission. At least in some brain areas, GRPR might be preferentially expressed in inhibitory interneurons releasing gamma-aminobutyric acid (GABA) (Kamichi et al., 2005; Shumyatsky et al. (2002).

Studies focusing on the brain distribution of GRP, the receptor endogenous ligand, showed that GRP mRNA has the highest density in forebrain areas and hypothalamus (Wada, Way, Lebacq-Verheyden, & Battey, 1990). It is possible that GRP is released as a co-transmitter from glutamatergic neurons to activate postsynaptic GRPRs (Shumyatsky et al. (2002).

4. GRPR regulation of emotional memory

The role of GRPR in memory formation and expression has been examined by pharmacological and genetic studies in rodents (for a recent review, see Roesler, Kent, Schröder, Schwartsmann, & Merali, 2012). Early experiments reported by Flood and Morley (1988) showed that systemic or intracerebroventricular (i.c.v.) delivery of GRP or bombesin after behavioral training could modulate the retention for a T-maze footshock avoidance task. Subsequent studies found memory-enhancing effects of systemic, intra-NTS, or intrahippocampal posttraining administration of bombesin in rats (Rashidy-Pour & Razvani, 1998; Roesler, Henriques, & Schwartsmann, 2006; Williams & McGaugh, 1994). The evidence for a modulatory role of the GRPR on memory formation was further extended by experiments using selective antagonists. Pretraining systemic injection of [Leu13-(psi-CH(2)NH)-Leu14]BN or RC-3095 impaired retention for the inhibitory avoidance (IA) type of fear conditioning in mice and rats respectively (Roesler, Henriques, & Schwartsmann, 2004; Santo-Yamada, Yamada, Wada, Goto, & Wada, 2003b). Pretraining RC-3095 did not affect memory for a task with less emotional content (a novel object recognition – NOR – task in which rats were habituated to the training environment before learning), suggesting that the GRPR is preferentially involved in regulating memories for events involving more aversive and stressful stimuli (Roesler et al., 2004). Impairing effects of intermediate doses of RC-3095 on inhibitory avoidance memory in rats were also obtained with posttraining injections given systemically (Roesler et al., 2004), pre- or posttraining microinfusions into the dorsal hippocampus (Dantas, Luft, Henriques, Schwartsmann, & Roesler, 2006; Preissler et al., 2007; Roesler et al., 2003; Venturella et al., 2005), or posttraining infusions into the BLA (Roesler, Lessa et al., 2004).

In addition to acquisition and consolidation, GRPRs might influence the expression, extinction, and reconsolidation of memories for fear-motivated tasks. Intrahippocampal administration of RC-3095 impaired the consolidation of extinction memory for inhibitory avoidance (Luft et al., 2006), and produced a transient memory impairment when given after reactivation (Luft, Amaral, Schwartsmann, & Roesler, 2008). GRP infused i.c.v. or into specific amygdaloid nuclei (BLA and CeA) or cortical sites disrupted the expression measured by freezing of contextual and cued fear conditioning (Merali, Mountney, Kent, & Anisman, 2011; Mountney, Anisman, & Merali, 2008; Mountney, Sillberg, Kent, Anisman, & Merali, 2006). Conversely, i.c.v. administration of RC-3095 increased freezing (Merali et al., 2011).

As often observed for peptides and hormones that modulate memory (McGaugh, 1989; Roesler & Schröder, 2011), the effects of GRPR ligands can show an inverted U-shaped dose-response pattern, in which higher doses produce no effect or the opposite effect in comparison to intermediate doses. Thus, memory was enhanced by GRP or bombesin given i.c.v. or systemically at low doses, whereas memory impairment was observed with the use

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