Gastrin-releasing peptide receptors in the central nervous system: role in brain function and as a drug target

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INTRODUCTION
Neuropeptide signaling regulates a variety of aspects of nervous and neuroendocrine function (Hökfelt et al., 2003; Salio et al., 2006). Neuropeptides act by activating specific cell membrane receptors belonging to the G protein-coupled receptor (GPCR) superfamily, leading to stimulation of downstream signaling processes and ultimately altering gene expression (Oh et al., 2006).

Gastrin-releasing peptide (GRP), a neuropeptide originally isolated from the porcine stomach, is a 27-amino acid peptide synthesized as a 148-amino acid precursor (PreproGRP) and subsequently metabolized posttranslationally (Spindel et al., 1984; Lebacq-Verheyden et al., 1988). GRP is the mammalian homolog of the amphibian 14-amino acid peptide bombesin, isolated from the skin of the European frog Bombina bombina in 1970 (Erspamer et al., 1970). GRP and bombesin display similar biological activities and share the same seven C-terminal amino acid sequence. Early experiments examining the effects of bombesin when administered in the brain showed that intracerebroventricular (i.c.v.) infusions of bombesin induced hypothermia and feeding behavior, especially aspects related to emotional responses, social interaction, memory, and feeding behavior. In addition, some alterations in GRP or GRPR expression or function have been described in patients with neurodegenerative, neurodevelopmental, and psychiatric disorders, as well as in brain tumors. Findings from preclinical models are consistent with the view that the GRPR might play a role in brain disorders, and raise the possibility that GRPR agonists might ameliorate cognitive and social deficits associated with neurodegenerative diseases, while antagonists may reduce anxiety and inhibit the growth of some types of brain cancer. Further preclinical and translational studies evaluating the potential therapeutic effects of GRP ligands are warranted.

Keywords: gastrin-releasing peptide, gastrin-releasing peptide receptor, bombesin receptors, neuropeptide signaling, brain disorders

Neuropeptides acting on specific cell membrane receptors of the G protein-coupled receptor (GPCR) superfamily regulate a range of important aspects of nervous and neuroendocrine function. Gastrin-releasing peptide (GRP) is a mammalian neuropeptide that binds to the GPR receptor (GRPR, BB2). Increasing evidence indicates that GRPR-mediated signaling in the central nervous system (CNS) plays an important role in regulating brain function, including aspects related to emotional responses, social interaction, memory, and feeding behavior. In addition, some alterations in GRP or GRPR expression or function have been described in patients with neurodegenerative, neurodevelopmental, and psychiatric disorders, as well as in brain tumors. Findings from preclinical models are consistent with the view that the GRPR might play a role in brain disorders, and raise the possibility that GRPR agonists might ameliorate cognitive and social deficits associated with neurodegenerative diseases, while antagonists may reduce anxiety and inhibit the growth of some types of brain cancer. Further preclinical and translational studies evaluating the potential therapeutic effects of GRP ligands are warranted.

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MOLECULAR ORGANIZATION OF THE GRPR
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Table 1 | Molecular structure of the gastrin-releasing peptide receptor (GRPR).

| Specie | TM | Chromosomal location | Gene name |
|--------|----|----------------------|-----------|
| Human  | 7  | Xp22.2-p22.13        | GRPR      |
| Rat    | 7  | Xq21                 | Grpr      |
| Mouse  | 7  | X F4                 | Grpr      |

Aminoacid sequence (Homo sapiens)

| Human (1-60) | FENDO-03-00159 | 2 |
|--------------|----------------|---|
| MAINTFLIN | LEVDVHYSNV YIPPRPVSY  | UGLOMNT |
| LIEFCTVVS | MVNSPLAL ISSLGDLTTT TACPADQR | YLADWLVSSR 10QLIQFQ |
| (61-120)    | LTSVGVVSFT  | ITALSADVYK AVPRPQ/GIA SHALMKICLK ARIWVSMAL | LIAPEAVFSD |
| (121-180)   | LHPHHEESTN | DTRCSACYP HSNEMLPHK SSMAFLFVY | IPISUSSVY YHAWKLDS |
| (241-300)   | AQNLWEGNHI | RMXDOESR KLAKTVAVY GIAFQVLIPN | HIYVYRSYH YSEVOMMLH |
| (301-360)   | FVTISCARLL | ATFLNCSNVP ALYLKLKSR KGPNTOILCC | QPGLRPIHS TGSTCCTM TS |
| (361-384)   | LIKTNPSVT | FSLGONICH ERYV |

Structural data are from Spindel et al. (1990), Battey et al. (1991), Wada et al. (1990a, Table 1)

In the rodent spinal cord, GRPR expression is restricted to lamina I of the dorsal spinal cord, and GRP is expressed in a subset of dorsal root ganglion neurons including lumbar spinothalamic neurons (Sun and Chen, 2007; Fleming et al., 2012; Kozyrev et al., 2012). Importantly, the GRP system in the spinal cord is sexually dimorphic. In male rats, neurons in the L3 and L4 levels of the lumbar spinal cord project to the lower lumbar spinal cord (L5-L6 level) and release GRP onto somatic and autonomic centers containing GRPRs, whereas this system is vestigial in females (Sakamoto et al., 2008; Sakamoto, 2011). This has important implications for the control of male sexual reflexes by GRPR signaling (see below).

GRPR regulation of CNS function

Evidence that GRPRs in the brain and spinal cord regulate several physiological functions has come mostly from in vivo studies using pharmacological or genetic manipulation of the GRPR in rats or mice. Below, we summarize relevant findings of selected studies.
focusing on GRPR regulation of memory, stress and anxiety responses, feeding, itching, and sexual behavior.

SYNAPTIC PLASTICITY AND MEMORY

In the late 1980s, Flood and Morley (1988) demonstrated that systemic or i.c.v. injections of GRP or bombesin after learning modulated memory retention for a T-maze footshock avoidance task in mice. When i.c.v. infusions were used, both peptides facilitated memory consolidation, whereas systemic injections produced memory enhancement or impairment depending on the drug dose and training conditions. Consistently with these findings, bombesin given after training through systemic injections (Rashady-Pour and Ravई, 1998) or infusions directly into the NTS (Williams and McGaugh, 1994) enhanced memory retention in rats.

Memory modulation by GRPRs seems to be particularly important for memories involving emotional arousal and fear. Thus, pretraining injections of the GRPR antagonist [Leu13-(psi-CH(2)NH)-Leu14]BN impaired memory for inhibitory avoidance conditioning in mice (Santo-Yamada et al., 2003), and injection of another selective GRPR antagonist, RC-3095, in rats impaired memory for inhibitory avoidance but not for a task with less emotional content, novel object recognition (Roesler et al., 2004b). Similar impairing effects of RC-3095 on inhibitory avoidance memory were obtained with systemic posttraining injections (Roesler et al., 2004c), pre- or posttraining intrahippocampal microinfusions (Roesler et al., 2003; Venturella et al., 2005; Danats et al., 2006; Preissler et al., 2007), or posttraining infusions into the BLA (Roesler et al., 2004c). The effects of the GRPR antagonist followed a typical inverted U-shaped dose–response pattern, in which intermediate doses resulted in memory impairment, whereas higher doses had no effect or produced memory enhancement (Roesler et al., 2003, 2004b; Danats et al., 2006). Conversely, intrahippocampal infusion of bombesin resulted in enhancement of inhibitory avoidance memory at intermediate doses and impairment at higher doses (Roesler et al., 2006b).

In addition to influencing memory formation, pharmacological manipulation GRPRs in specific brain areas has been shown to regulate fear memory expression, extinction, and reconsolidation-like processes (Luft et al., 2006, 2008; Mountney et al., 2006, 2008; Merali et al., 2011). For example, infusion of the GRPR antagonist RC-3095 into the rat dorsal hippocampus after memory reactivation blocks the extinction and reconsolidation of fear memory (Luft et al., 2006, 2008; for a review, see Roesler et al., 2012).

The role of GRPRs in regulating fear memory and synaptic plasticity has also been revealed by genetic studies using GRPR knockout mice. Contextual and cued fear conditioning were enhanced by the genetic deletion of GRPR, whereas spatial in the Morris water maze was unaffected. The enhancement of fear memory in GRPR knockout mice was accompanied by enhanced synaptic plasticity measured by long-term potentiation (LTP) in the amygdala. In wild-type mice, GRPR was preferentially expressed in amygdalar inhibitory interneurons releasing gamma-aminobutyric acid (GABA), and GRP might be released as a co-transmitter from glutamatergic neurons to activate preferentially GRPRs located on GABAergic interneurons to stimulate inhibitory transmission within the amygdala.

We have shown that a number of signal transduction mechanisms downstream of receptor activation are involved in mediating memory regulation by the GRPR. In the CA1 area of the dorsal hippocampus, memory enhancement induced by bombesin was prevented by inhibitors of PKC, MAPK, PKA, and PI3K (Roesler et al., 2006b, 2009, 2012), and potentiated by coinfusion of stimulators of the dopamine D1/D5 receptor (D1R)/(cAMP/PKA pathway, namely the D1R agonist SKF 38393, the adenylyl cyclase activator forskolin, and the cAMP analog 8-Br-cAMP (Roesler et al., 2006b). These findings indicate that the PKC, MAPK, PI3K, and PKA pathways are critical in mediating memory modulation by hippocampal GRPRs, and that GRPR activation can interact with cAMP/PKA signaling in enhancing hippocampal memory formation (Figure 1). GRPRs in the rat brain also show functional interactions with other growth factor systems including basic fibroblast growth factor (bFGF/FGF-2), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF; Kauer-Sant’Anna et al., 2007; Preissler et al., 2007).

EMOTIONAL BEHAVIOR

Gastrin-releasing peptide and GRPR are highly expressed in brain regions, such as the amygdala, activated by stressful stimuli, and, as discussed above, GRPR signaling is likely to be a major regulator of memory associated with fear and emotional arousal. Merali and colleagues have shown that chronic stressor exposure leads to an elevation of GRP levels in the anterior pituitary in rats, and GRP release in the rat amygdala is increased in response to exposure to a shock. GRP may stimulate the release of adrenocorticotropic hormone (ACTH), playing a role in mediating the corticosterone releasing hormone (CRH) stress response, and increasing the activity of the hypothalamic–pituitary–adrenal (HPA) axis. In addition, bombesin administration induces endocrine, autonomic, and behavioral effects associated with stress, and bombesin receptor antagonists attenuate the behavioral and neurochemical effects of stressors (Merali et al., 2002, 2009; Moody and Merali, 2004; Mountney et al., 2011). Moreover, we have shown that systemic administration of a GRPR antagonist can induce an anxiogenic-like effect in the elevated plus maze test in rats.
FIGURE 1 | Proposed molecular mechanisms mediating GRPR regulation of brain function. The stimulation of hippocampal memory consolidation by GRPR activation depends on PKC, MAPK, PKA, and PI3K, and is potentiated by activation of the D1R/cAMP/PKA pathway (Roesler et al., 2006a, 2009, 2012). GRPR activation at the postsynaptic membrane is coupled to Gq protein activity and increases in [Ca\textsuperscript{2+}], leading to stimulation of the PLC/PKC and ERK/MAPK pathways. D1R is coupled to the Gs protein and adenyl cyclase (AC) activation. The D1R-mediated cAMP signal might be potentiated by [Ca\textsuperscript{2+}]-induced stimulation of [Ca\textsuperscript{2+}]-responsive types of AC (Wong et al., 1999; Chan and Wong, 2005; Roesler et al., 2006b, 2012), providing a possible mechanism for the requirement of cAMP/PKA signaling for GRPR influences on memory. Modified from Roesler et al. (2006b, 2012), with permission.

Together, these data suggest that brain GRPRs might regulate emotional behavioral and responses to stress.

FEEDING BEHAVIOR

It has been known for over 30 years that systemic or i.c.v. administration of bombesin or GRP in rats reduces the intake of liquid and solid food (Gibbs et al., 1981). Similar effects on meal size are observed after systemic bombesin injections in mice and intravenous (i.v.) injections in baboons and humans (Gibbs, 1985). In addition, brief vena caval infusions of GRP and NMB in rats, given alone or together at the onset of the first nocturnal meal, significantly reduced meal size and duration (Rushing et al., 1996), and bombesin or GRP given systemically extended the duration of the intermeal interval (Thaw et al., 1998). The suppression of glucose intake induced by systemic administration of GRP or bombesin was blocked by infusion of a GRPR antagonist into the fourth ventricle in rats (Ladenheim et al., 1996), and was absent in GRPR knockout mice (Hampton et al., 1998; Ladenheim et al., 2002), indicating that central GRPRs are critical in mediating the effects of peripheral bombesin and GRP on feeding. In addition, GRPR knockout mice ate significantly more at each meal than wild-type controls (although total 24 h food consumption was equivalent), and elevated elevated body weight compared with wild-type littermates beginning at 45 weeks of age (Ladenheim et al., 2002). The finding that systemic GRP potently reduced independent intake of both sucrose and milk from a bottle but did not affect intraoral intake of either solution indicated that the GRPR regulates the appetitive-related aspects of the feeding process (Rushing and Houpt, 1999). The amygdala is likely a key brain area involved in mediating the regulatory action of GRPRs on feeding: bilateral infusion of GRP into the central amygdala produced a transient inhibition of food intake, an effect that was prevented by the GRPR antagonist \([\text{Leu}(13)-\psi(\text{CH}_2\text{NH})-\text{Leu}(14)]\)BN (Fekete et al., 2002).

These findings provide strong support for a role of GRP/GRPR signaling in regulating feeding. It has been proposed that BLPs may also be released from the gastrointestinal tract in response to food ingestion, acting to bridge the gut and brain to inhibit further food intake. Conversely, the suppression of release of BLPs in the brain may trigger the initiation of a feeding episode (reviewed in Merali et al., 1999).

SEXUAL BEHAVIOR

One of the most exciting recent developments in GRPR research was the identification by Sakamoto et al. (2008) of a sexually dimorphic GRPR system in the spinal cord that is crucial in regulating male sexual function. In male rats, but not in...
females or males with a dysfunctional androgen receptor gene, GRP-containing neurons in the upper lumbar spinal cord inner-
vate lower lumbar regions controlling erection and ejaculation. 
Pharmacological stimulation of spinal GRP receptors restores 
penile reflexes and ejaculation after castration, whereas intrathecal 
administration of the GRPR antagonist RC-3095 inhibits penile 
reflexes and ejaculations. The inhibitory effect of castration on 
GRP expression in this spinal center suggests that androgen sig-
ning plays a major role in regulating GRP expression in the 
male spinal cord (Sakamoto et al., 2009a; Sakamoto, 2010). Thus, 
GRP/GRPR signaling has emerged as a new tar-
tive for the understanding of psychogenic erectile dysfunction 
and the development of potential therapeutic approaches to mas-
culine reproductive dysfunction (Sakamoto et al., 2008, 2009a;3; 
Sakamoto and Kawata, 2009; Sakamoto, 2010, 2011).

ITCHING 

Another function in which GRPRs in the spinal cord have been 
shown to play a major role is itching. GRPR knockout mice show 
normal thermal, mechanical, inflammatory, and pain responses, 
but reduced responses to pruritoceptive stimuli, and GRP-induced 
pruritus in wild-type mice is blocked by intrathecal administration 
of a GRPR antagonist (Sun and Chen, 2007). The selective ablation 
of GRPR-expressing lamina I neurons in the mouse spinal cord of 
mice results in scratching deficits in response to itching stimuli, 
but does not affect pain behaviors (Sun et al., 2009). These findings 
allowed the identification of GRPR as a central molecular mediator 
of the itch sensation in the spinal cord (Sun and Chen, 2007; Sun 
et al., 2009).

A recent seminal study showed that the μ-opioid receptor 
(MOR) isoform MOR1D heterodimerizes with GRPR in the spinal 
cord to relay itch information. Blocking the association between 
MOR1D and GRPR attenuates morphine-induced scratching. 
Morphine triggers internalization of both GRPR and MOR1D, 
whereas GRP specifically triggers both GRPR internalization 
and morphine-independent scratching. These data suggest that 
opioid-induced itch is independent of opioid analgesia and occurs 
via cross-activation of GRPR signaling by MOR1D heterodimer-
ization (Liu et al., 2011).

POSSIBLE ROLE OF ALTERATIONS IN GRPR EXPRESSION 
AND SIGNALING IN THE PATHOGENESIS OF BRAIN 

DISORDERS 

Since GRPRs are highly expressed in neurons in brain areas includ-
ing the hippocampus and BLA, and regulate crucial aspects of 
behavior that can be altered in patients with CNS disorders, it 
is possible that deregulated GRPR signaling contribute to the 
pathogenesis of neurological and psychiatric diseases. Although 
a causative role of GRPR dysfunction in CNS disorders has not 
been directly established, some alterations in the levels of BLPs 
peptides or GRPR density or function have been observed in 
patients with psychiatric, neurodegenerative, and neurodevelop-
mental disorders. In addition, the use of preclinical models has 
provided further evidence indicating a role for the GRPR in some 
CNS pathologies. Based on these findings, we have put forward 
that the GRPR may be a novel molecular target for the develop-
ment of therapeutic strategies for patients with neurological and 
psychiatric disorders (Roesler et al., 2004a, 2006a). Table 2 sum-
maries the findings from studies examining possible alterations 
in GRP and GRPR content or signaling found in patients with 
brain disorders.

NEURODEGENERATIVE DISORDERS 

The concentration of BLPs was found to be significantly reduced in 
the caudate nucleus and globus pallidus of patients with Parkin-
son’s disease (PD) (Bissette et al., 1985). However, Stoddard et al. 
(1991) found no alterations in bombesin-like immunoreactivity in 
the adrenal medullary tissue of patients with PD, although the con-
centration of several other neuropeptides was reduced. A reduc-
tion in bombesin receptor density and altered bombesin-induced 
calcium signaling have been reported in fibroblasts from patients 
with Alzheimer’s disease (AD) (Ito et al., 1994; Gibson et al., 1997).

| CNS disorder          | Main findings                                                                 | Reference               |
|-----------------------|-------------------------------------------------------------------------------|-------------------------|
| Parkinson’s disease   | Reduced levels of BLPs peptides in caudate nucleus and globus pallidus        | Bissette et al. (1985)  |
| Parkinson’s disease   | Normal bombesin-like immunoreactivity in adrenal medullary tissue             | Stoddard et al. (1991)  |
| Alzheimer’s disease   | Reduced bombesin receptor density and enhanced bombesin-induced calcium release in fibroblasts | Ito et al. (1984)       |
| Alzheimer’s disease   | Reduced bombesin-induced calcium mobilization in fibroblasts                  | Gibson et al. (1997)    |
| Autism                | X:8 translocation in the GRPR gene                                           | Ishikawa-Brush et al. (1997) |
| Autism                | No association with two polymorphic sites in the second exon of the GRPR gene | Murai et al. (2004)     |
| Autism                | C6S and L181F mutations in the GRPR gene                                      | Sekita et al. (2008)    |
| Schizophrenia         | Reduced radioimmunoassay-detectable bombesin in the CSF                       | Germer et al. (1985)    |
| Schizophrenia         | Reduced urinary levels of BLPs                                                | Olczynski et al. (1996) |
| Anxiety disorders     | No association between GRP and GRPR genes and panic disorders                 | Hodges et al. (2009)    |
| Eating disorders      | Reduced GRP levels in the CSF of women who were recovered from bulimia nervosa | Frank et al. (2001)     |
| Brain tumors          | GRPR overexpression in gloma                                                  | Flores et al. (2010)    |

Table 2 | Findings from selected studies examining possible alterations in the GRPR system in patients with CNS disorders. Modified from Roesler et al. (2006a), with permission.
Inhibitory avoidance memory (Roesler et al., 2006b) in rat hippocampus as a model of memory dysfunction was assessed by injecting a low dose of beta-amyloid peptide (Abeta; 25–35) into rat CA1 area to induce memory deficits associated with AD. This finding provided preliminary preclinical evidence suggesting GRPR function and ASD was found in two patients (Seidita et al., 2006). In a subsequent study investigating two polymorphic sites in the GRPR gene in patients did not support the association and linkage analyses (Hodges et al., 2009). The possibility that GRPR signaling plays a role in anxiety disorders (Moody and Merlo, 2004; Roesler et al., 2012) is consistent with ASD, and support the possibility that abnormal GRPR expression or function during development might play a role in disease pathogenesis. Also, we have proposed that neonatal GRPR blockade in rats may serve as a novel animal model of ASD (Presti-Torres et al., 2007, 2012).

Other Neuropsychiatric Disorders
The findings from rodent studies discussed above, indicating that normal GRPR function during development might be important for behaviors related to social interaction, attachment, and cognition, and that clozapine rescues social behavior deficits produced by GRPR blockade, are also consistent with the possibility that GRPR signaling is altered in schizophrenia. In addition, we found that GRPR blockade by systemic injections of RC-3095 prevent apomorphine-induced stereotypy in mice and amphetamine-induced hyperlocomotion in rats, which are models of schizophrenia psychoses and mania (Meller et al., 2004; Kauer-Sant’Anna et al., 2007). In patients with schizophrenia, a reduction in the levels of radioligand-detectable bombesin in the cerebrospinal fluid (CSF; Gerner et al., 1985), and reduced urinary levels of BLPs (Olney et al., 1999) have been found. Further studies using samples from patients and animal models are required to examine whether GRPR signaling is involved in schizophrenia.

As reviewed above, data from animal studies also consistently show that GRPRs in brain areas including the amygdala regulate memory related to fear and anxiety responses, raising the possibility that GRPR signaling plays a role in anxiety disorders (Moody and Merlo, 2004; Roesler et al., 2012). For example, pharmacological manipulation of the GRPR in the hippocampus can affect extinction and reconsolidation of fear memory, which are preclinical models used in the investigation and screening of potential therapeutic strategies for post-traumatic stress disorder (PTSD) and other fear-related disorders (Luft et al., 2006, 2008). In postmortem analyses of brains from suicides compared to control subjects, Merlo et al. (2006) reported discrete alterations in the levels of GRP and NMB. More recently, however, the possibility that GRP and GRPR are candidate genes in panic disorders was not confirmed in an association and linkage analysis (Hodges et al., 2009). Anxiety disorders may show comorbidity with eating disorders, anorexia and bulimia nervosa. Given the important role of GRPR in regulating feeding behavior (see above), it is possible that it contributes to eating disorders. One study found significantly reduced GRP levels in the CSF of women who were recovered from bulimia nervosa, compared to women recovered from anorexia or healthy control women. The authors suggested that persistent alterations in GRP levels after recovery indicate that this alteration might be caused by a decrease in GRP expression or an increase in GRPR density.
Roesler and Schwartsmann GRPR function in the central nervous system

FIGURE 3 | GRPR blockade during CNS development in rats results in long-lasting behavioral alterations associated with experimental models of autistic spectrum disorders (ASDs). Rats were given intraperitoneal injections of saline (SAL; control group) or the GRPR antagonist RC-3095 (1 or 10 mg/kg) twice daily from postnatal days (PN) 1 to 10. A social behavior test was carried out at PN 30. (A) Representative photographs of rats given SAL or RC-3095 (1 or 10 mg/kg) during the social interaction test. (B) Mean ± SEM number of social contacts. (C) Mean ± SEM time spent engaged in social interaction (in seconds). The number of animals was 6–7 per group. **P < 0.01 compared to the control group. Reproduced from Presti-Torres et al. (2007), with permission.
trait-related and contribute to episodic hyperphagia in patients with bulimia nervosa (Frank et al., 2001).

**BRAIN TUMORS**

Gastrin-releasing peptide receptor overexpression has been demonstrated in many types of cancer (Cornelio et al., 2007), and we have recently shown widespread expression and a high content of GRPR in human glioma, the most common and lethal type of neurological cancer (Flores et al., 2010; Figure 4). GRPR activation by GRP or bombesin stimulates the growth of glioma cell lines (Moody et al., 1989; Pinski et al., 1994; Sharif et al., 1997; de Farias et al., 2008; Flores et al., 2008). We have recently shown that the stimulatory effect of GRPR activation on proliferation of glioma cells depends on PI3K signaling (Flores et al., 2008) and is potentiated by co-activation of the cAMP/PKA pathway (de Farias et al., 2008; reviewed in Roesler et al., 2010).

Gastrin-releasing peptide receptor antagonists inhibit the growth of human U-87MG and U-373MG gliomas xenografted into nude mice (Pinski et al., 1994; Kiars et al., 1999). In addition, GRPR antagonism by RC-3095, alone or combined with temozolomide, significantly reduced the growth of C6 gliomas both in vitro and in vivo, with the combined administration of TMZ and RC-3095 being the most effective treatment (Figure 5; de Oliveira et al., 2009). These findings strongly suggest that targeting GRPR may be a promising strategy for the development of novel therapies against glioma. The GRPR might also regulate the growth of neuroblastoma (Kim et al., 2002; Qiao et al., 2008; Abujamra et al., 2009), although, in contrast, we could not find a role for GRPR in regulating the in vitro growth of medulloblastoma, the most common brain cancer of childhood (Schmidt et al., 2009).

**GRPR LIGANDS AS CANDIDATE THERAPEUTIC DRUGS IN BRAIN DISORDERS**

The evidence reviewed above indicates that the GRPR might be considered a novel molecular target in different types of CNS disorders, and raise the possibility that GRPR agonists might ameliorate cognitive and social deficits associated with neurological diseases, while antagonists may, for example, reduce anxiety and inhibit the growth of some types of brain cancer. Studies examining the effects of GRP administration on satiety and eating behavior in humans (Gutzwiller et al., 1994), as well as a phase I trial of the GRPR antagonist RC-3095 in patients with solid tumors (Schwartsmann et al., 2006) have suggested that GRP and peptidergic GRPR antagonists can be safely administered intravenously in human subjects. Thus, the potential therapeutic effect of GRPR ligands in preclinical models as well as in patients with CNS disorders warrants further investigation.

**ACKNOWLEDGMENTS**

This work was supported by the National Council for Scientific and Technological Development (CNPq; grant number 303703/2009-1 to Rafael Roesler), the National Institute for Translational Medicine (INCT-TM) and the South American Office for Anticancer Drug Development.
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Conflict of Interest Statement: 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.

Received: 17 October 2012; paper pending published: 04 November 2012; accepted: 23 November 2012; published online: 17 December 2012.

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