Wirotanseng et al. Molecular Pain 2013, 9:54
http://www.molecularpain.com/content/9/1/54

MOLECULAR PAIN

SHORT REPORT Open Access

G_q rather than G_{11} preferentially mediates nociceptor sensitization

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Abstract

Background: The $G_{q/11}$-protein signaling mechanism is essential throughout the nervous system, but little is known about the contribution of the individual G-protein GPCR signaling branches towards nociceptor activation and their specific role on nociceptor sensitization. We aimed to unravel the contribution of the $G_{q/11}$-signaling pathway towards nociceptor activation via a variety of classical inflammatory mediators signalling via different G-protein GPCRs and investigated the specific contribution of the individual G_q and G_{11} G-Proteins in nociceptors.

Findings: Using different transgenic mouse lines, lacking $G\alpha_q$, $G\alpha_{11}$ or both α-subunit of the G-proteins in primary nociceptive neurons, we analyzed the mechanical- and heat-sensitivity upon application of different GPCR-agonists that are known to play an important role under inflammatory conditions (e.g. ATP, Glutamate, Serotonin etc.). We found that the $G_{q/11}$-GPCR signaling branch constitutes a primary role in the manifestation of mechanical allodynia and a minor role in the development of thermal hyperalgesia. Moreover, with respect to the mediators used here, the G_q-protein is the principle G-protein among the $G_{q/11}$-protein family in nociceptive neurons leading to nociceptor sensitization.

Conclusions: Our results demonstrate that the $G_{q/11}$ signaling branch plays a primary role in nociceptor sensitization upon stimulation with classical GPCR ligands, contributing primarily towards the development of mechanically allodynia. Moreover, the deletion of the individual G-proteins led to the finding that the G_q-protein dominates the signalling machinery of the $G_{q/11}$ family of G-proteins in nociceptive neurons.

Findings

Introduction

G-protein coupled receptors (GPCRs) represent the largest family of seven transmembrane receptors and downstream signaling constitutes one of the most important signaling pathways to regulate physiological processes. GPCR family members represent a major primary target for drug development [1,2] and their signaling is a predominant focus in the development of novel analgesic therapeutics [3].

Peripheral sensitization is accompanied by an inflammatory milieu, acting on receptors and channels on the peripheral nerve terminals (reviewed in [4]). Most of these sensitizers are known to bind to GPCRs of the $G_{q/11}$ family, the $G_{i/o}$, G_s and $G_{12/13}$ family of heterotrimeric G-proteins.

We have recently elucidated the specific significance of the $G_{q/11}$ pathway in modulating properties of nociceptors *in vivo* in the context of physiological pain and pathological states [5]. We found that $G_{q/11}$ is involved in sensitization mechanisms in pathological states and tonically modulates basal nociception and acute pain [5].

There are four members of the $G_{q/11}$-protein family, namely G_q, G_{11}, G_{14} and $G_{15/16,}$ which activate Phospholipase C beta isoforms to regulate intracellular calcium. $G_{15/16}$ overall show very low levels of expression whereas G_{14} has been shown to be expressed at high levels selectively in some tissues (e.g. kidney, lung and spleen; reviewed by [6]), and for the first time Han et al. showed that G_{14} is expressed in a subset of DRG neurons [7] but does not compensate for a loss of $G_{q/11}$ [5].

The aim of this study was to investigate the individual role of the G_q or G_{11} signaling branch towards acute nociceptive behavior induced by different GPCR ligands specifically activating $G_{q/11}$-coupled GPCRs or GPCRs that are capable to couple different G-protein classes. This is the first study addressing the distinct roles of G_q and G_{11} towards nociceptor sensitization.

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Table 1 Summary of behavioral results showing main impact of G_q-mediating sensitization processes

Ligand	Receptor	G-protein subclass	Thermal hyperalgesia – paw withdrawal latency (Mean % change over pre-injection)				Mechanical allodynia – paw withdrawal response frequency (Mean Δ increase over pre-injection) 0.4 g von Frey Filament			
			Control	G_{11} $^{-/-}$	SNS-$G_{q/11}$ $^{-/-}$	SNS-$G\alpha_q$ $^{-/-}$	Control	G_{11} $^{-/-}$	SNS-$G_{q/11}$ $^{-/-}$	SNS-$G\alpha_q$ $^{-/-}$
Bradykinin	B	$G_{q/11}$	−51.5 ± 3.3 (n=8)	−37.1 ± 2.5 (n=7)	**−7.4 ± 11.5*** (n=7)	**−8 ± 2.7*** (n=7)	54.1 ± 5.5	**27.8 ± 8***	**14.4 ± 3.6***	**6.7 ± 5.9***
UTP	P2Y	$G_{q/11}$	−44.2 ± 10.4 (n=8)	−23.8 ± 7.2 (n=8)	**−9.7 ± 7.5*** (n=7)	**−9.8 ± 5.1*** (n=8)	32.8 ± 3.2	20 ± 8.9	**4.8 ± 3.5***	**6.7 ± 6.0***
Trypsin	PAR	$G_{q/11}$	−41 ± 5.7 (n=8)	−38.3 ± 5 (n=8)	**−17.7 ± 3.3*** (n=8)	**−14.3 ± 8.1*** (n=6)	−3.3 ± 3.1	4.2 ± 1.8	0.8 ± 0.8	
CGRP	CGRP	$G_{q/11}$, G_s	−31,3 ± 6.9 (n=7)		−29.2 ± 2.3 (n=8)		21.1 ± 8.7		6.7 ± 2.7	
ATP	P2Y	$G_{q/11}$, G_s	−48.4 ± 4.6 (n=8)	−42.2 ± 6.1 (n=7)	**−16.7 ± 5.5*** (n=8)	**−12.3 ± 4.3*** (n=8)	27.5 ± 2	17.1 ± 6.5	**4.8 ± 3.8***	**5 ± 2.4***
ET-1	ET	$G_{q/11}$, G_s, $G_{12/13}$	−39.5 ± 4 (n=8)	−42.3 ± 6.2 (n=7)	**−21.7 ± 3.2*** (n=8)	−25.5 ± 3.9* (n=7)	26.7 ± 8.5	26.7 ± 5.7	**−0.8 ± 4.4***	**4.8 ± 5***
PGE_2	EP	$G_{q/11}$, G_s, $G_{i/o}$	−26.8 ± 5.6 (n=8)	−22.2 ± 8.8 (n=8)	−6.6 ± 8 (n=8)	−8 ± 5.7 (n=7)	15.6 ± 5.8	7.5 ± 4.8	**−0.8 ± 2.9***	**4.8 ± 5***
Serotonin	5-HT	$G_{q/11}$, G_s, $G_{i/o}$	−41.9 ± 3.9 (n=8)	−34.4 ± 4.8 (n=8)	−31.4 ± 3.1 (n=8)	**−24 ± 3.2*** (n=7)	29.2 ± 5.9	**14.2 ± 5.1***	**7.5 ± 2.3***	**2.9 ± 2***
Glutamate	mGluR1,2	$G_{q/11}$, $G_{i/o}$	−45.1 ± 11.8 (n=9)	**−8.2 ± 6.5 *** (n=8)	**−11.2 ± 4.5*** (n=9)	**−12.5 ± 6.7*** (n=9)	19.3 ± 9.7	30.4 ± 8.7	3.3 ± 6.3	6 ± 4.7
mcPAF	PAF	$G_{q/11}$, $G_{i/o}$	−49 ± 1.8 (n=7)	−38.7 ± 4.8 (n=8)	−30.7 ± 5 (n=7)	−26.7 ± 8.3 (n=8)	30.5 ± 5.8	36.7 ± 7.4	**−1 ± 3.1***	**5.8 ± 5.6***
Thrombin	PAR	$G_{q/11}$, $G_{i/o}$, $G_{12/13}$	−27.5 ± 6.2 (n=8)		−30.1 ± 5 (n=8)		20 ± 3.3		16.7 ± 8.2	
S1P	S1P	$G_{q/11}$, $G_{i/o}$, $G_{12/13}$	−51.6 ± 5.7 (n=8)	−50.8 ± 5 (n=8)	**−32.3 ± 4.5*** (n=8)	**−34.2 ± 7.3*** (n=8)	23.3 ± 5	20 ± 7.1	**4.2 ± 2.5***	**0.8 ± 4.1***

Table displays the mean % change of paw withdrawal latency upon thermal stimulation within 90 min upon GPCR-ligand application to the hindpaw and the delta increase of paw withdrawal frequency upon mechanical stimulation with 0.4 g von Frey filament within 75 min upon GPCR-ligand application. *p<0.05 ANOVA, post-hoc Fisher's test and boldface, indicates significant differences towards control mice. n = mice per group for thermal hyperalgesia and mechanical allodynia.

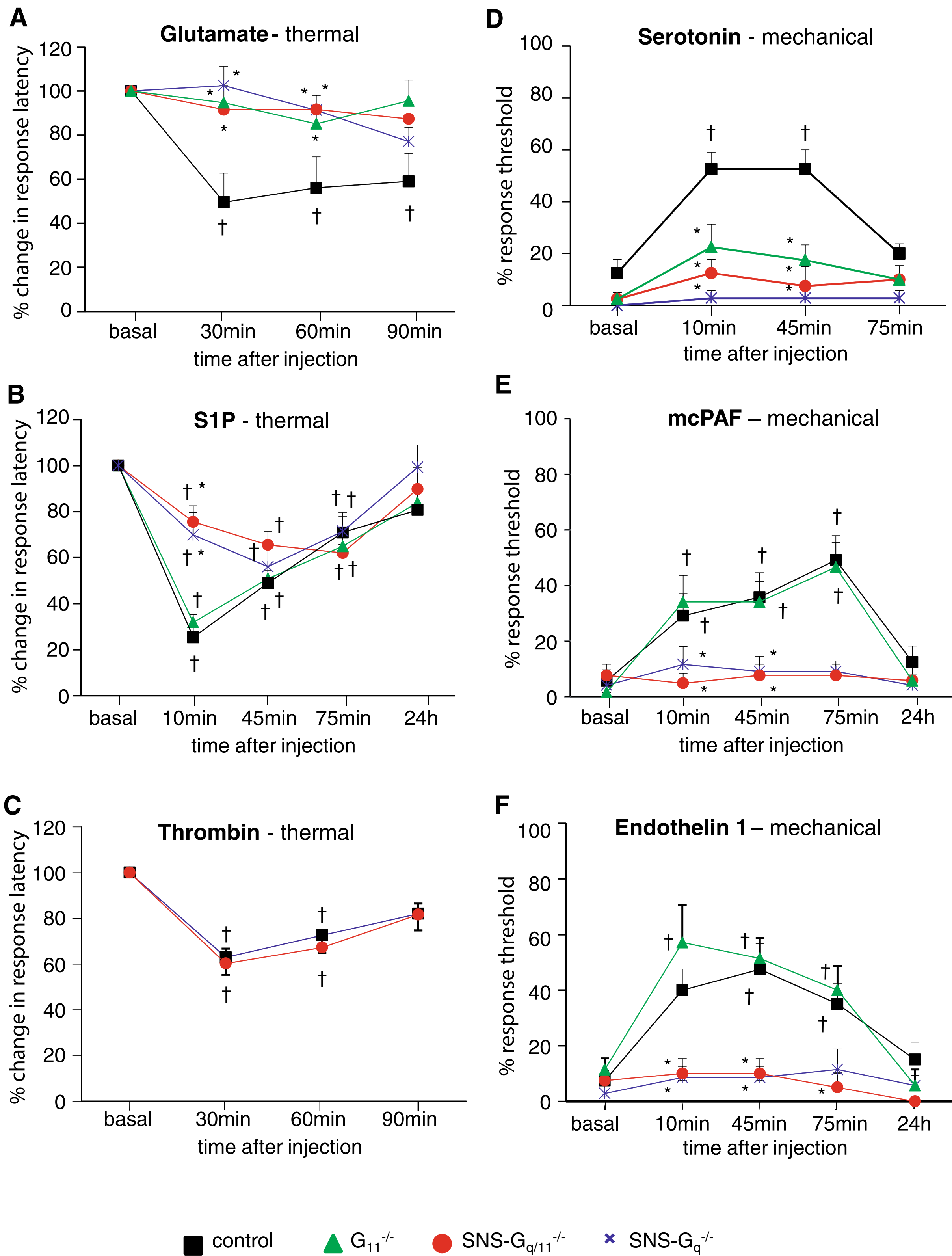

Figure 1 (See legend on next page.)

(See figure on previous page.)
Figure 1 Behavioral responses to intraplantar GPCR-ligands in control mice (black square symbols), $G_{11}^{-/-}$ mice (green triangle symbols), SNS-$G_{q/11}^{-/-}$ mice (red circular symbols) and SNS-$G_q^{-/-}$ mice (blue cross symbols). Magnitude and time course of hyperalgesia to plantar heat following unilateral intraplantar hindpaw injection of Glutamate (**A**; n= 9 for control, SNS-$G_q^{-/-}$ and SNS-$G_{q/11}^{-/-}$ mice and n= 8 for $G_{11}^{-/-}$ mice) S1P (**B**; n= 8 for all groups) and Thrombin (**C**; n= 8 for both groups) and of mechanical allodynia to mechanical von Frey filament stimulation following unilateral injection of Serotonin (**D**; n= 8 for control, $G_{11}^{-/-}$ and SNS-$G_{q/11}^{-/-}$ mice and n= 7 for SNS-$G_q^{-/-}$ mice), mcPAF (**E**; n= 8 for $G_{11}^{-/-}$ and SNS-$G_q^{-/-}$ mice and n= 7 for control and SNS-$G_{q/11}^{-/-}$ mice) Endothelin (**F**; n= 8 for control and SNS-$G_{q/11}^{-/-}$ mice and n= 7 for $G_{11}^{-/-}$ and SNS-$G_q^{-/-}$ mice). * $P<0.05$ as compared to the control group, † as compared to basal values within a group, ANOVA, post hoc Bonferroni's test. All data points represent mean ± SEM.

Methods

All animal use procedures were in accordance with ethical guidelines imposed by the local governing body (Regierungspräsidium Karlsruhe, Germany). All behavioral measurements were done in awake, unrestrained, age-matched mice that were more than 3 months old, by individuals who were blinded to the genotype of the mice being analyzed. Genotypes were identified by genomic tail DNA PCR (as described earlier [5]). Animals were kept on a 12-hour light–dark cycle with constant room temperature and behavioral tests were performed in an appropriate quiet room between 11 am and 4 pm.

We used the following mice, which have been described in detail (except SNS-$G\alpha_q^{-/-}$ mice) before ([5,8]): Homozygous mice deficient for $G\alpha_{11}$ ($G\alpha_{11}^{-/-}$) carrying the floxed allele of the mouse $G\alpha_q$ ($G\alpha_q^{fl/fl}$) gene (SNS-Cre$^-$;$G\alpha_q^{fl/fl}$;$G\alpha_{11}^{-/-}$; referred to as $G\alpha_{11}^{-/-}$ in this manuscript), sensory neuron-specific conditional double deficient mice for $G\alpha_q$ and $G\alpha_{11}$ (SNS-Cre$^+$;$G\alpha_q^{fl/fl}$;$G\alpha_{11}^{-/-}$ mice; referred to as SNS-$G\alpha_{q/11}^{-/-}$ in this manuscript), sensory neuron-specific conditional single deficient mice for $G\alpha_q$ (SNS-Cre$^+$;$G\alpha_q^{fl/fl}$;$G\alpha_{11}^{+/+}$; referred to as SNS-$G\alpha_q^{-/-}$ in this manuscript) and mice carrying the floxed allele of $G\alpha_q$ ($G\alpha_q^{fl/fl}$; referred to as control in this manuscript).

The following classical algogens and agonists were injected into the plantar surface of the hindpaw in a total volume of 20 μl: 5 μg Glutamate (27 nmol), 0.1 μg Bradykinin (94 nmol), 40 μg UTP (83 nmol), 5 μg CGRP (1.3 nmol), 1 μg mcPAF (1.85 nmol), 1 μg S1P (2.64 nmol), 60 μg ATP (0.1 μmol), 10 μg Serotonin (47 nmol), 50 ng PGE2 (142 nmol), 13U Trypsin, 1U Thrombin. Analysis of latency of paw withdrawal in response to heat was done, as previously described in detail ([5]; Plantar test apparatus, Ugo Basile Inc, Comerio, VA, Italy) and mechanical sensitivity was tested in the same cohort of animals via manual application of von Frey hairs to the plantar surface of the hind paw, as previously described in detail [5]. Two different substances were tested per mouse with 1–2 weeks of recovery period between the applications at different hindpaws. We used 6–8 mice per group, the exact numbers per group are given in Table 1 and the Figure legend.

All data are presented as mean ± standard error of the mean (S.E.M.). For multiple comparisons, Analysis of Variance (ANOVA) for random measures was performed followed by post-hoc Bonferroni's test.

Results

The classical deletion of $G\alpha_{11}$ led to a complete abrogation of Glutamate-induced thermal hyperalgesia (Figure 1A, Table 1) whereas mechanical hyperalgesia was entirely preserved (Table 1). We found a minor contribution of G_{11} towards Serotonin- induced mechanical hyperalgesia (Figure 1D, Table 1). Interestingly, thermal and mechanical hyperalgesia elicited by PGE_2, Trypsin, Bradykinin, Endothelin1 (ET1), Sphingosin1 Phosphate (S1P), Platelet-activating factor (PAF), ATP, Thrombin and CGRP were completely preserved in G_{11}-deficient mice (Figure 1B, 1C, 1E, 1F, Table 1).

We analyzed the algogen-induced behavior in $G_{q/11}$ double deficient mice and found a complete loss of thermal hyperalgesia triggered by PGE_2, Bradykinin, Glutamate, UTP and ATP, as well as mechanical hyperalgesia elicit by PGE_2, Trypsin, Glutamate, UTP, Serotonin, ET1, S1P, PAF and ATP (Examples in Figure 1A, 1B, 1D-F, Table 1). There were minor changes with respect to thermal hyperalgesia upon ET1 and S1P application (Example in Figure 1B, Table 1), whereas thermal hyperalgesia towards Thrombin, CGRP and Serotonin and mechanical hyperalgesia towards Thrombin and CGRP was fully preserved in $G_{q/11}$ double deficient mice (Example in Figure 1C, Table 1). Interestingly, the deletion of $G_{q/11}$ in nociceptors had a stronger impact on mechanical allodynia than on thermal hyperalgesia.

Surprisingly, the single deletion of G_q caused the same behavioral phenotype as the double deletion of G_q and $G_{11,}$ (examples in Figure 1, Table 1) indicating a predominant role for G_q- over G_{11}- proteins in nociceptive neurons.

Discussion

We found that a particular G-protein pathway can contribute differentially to the action of diverse algogens and that a particular algogen can employ different G-protein pathways to elicit thermal hyperalgesia and mechanical allodynia. The $G_{q/11}$ G-protein signaling pathway plays an important role for nociceptor sensitization and the transduction of GPCR signaling towards the development of

mechanical allodynia and thermal hyperalgesia with respect to the mediators tested in this manuscript.

To our surprise G_q has a major impact over G_{11} mediated nociceptor sensitization. Although G_q and G_{11} are nearly ubiquitously expressed in overlapping patterns [9], including the dorsal root ganglia and spinal cord [7], it cannot be ruled out that specific, highly localized differences may exist between the expression pattern and subcellular distribution of G_q and G_{11} in central circuits mediating hyperalgesia. Previous studies showing no difference in receptor-coupling with respect to G_q or G_{11} are performed *in vitro* [10-13] and thereby might not reflect the *in vivo* situation. It is more likely that different expression levels as shown for different brain regions [14-17] or membrane compartmentalization might account for the observed phenotypes. With respect to the DRGs it seems that there is a signaling succession for members of the $G_{q/11}$ family. $G_{15/16}$ are not expressed, G_{14}, G_{11} and G_q are expressed, while G_{14} has no specific role, G_{11} plays only a minor role for nociceptor sensitization and G_q is the most prominent G-proteins of this important signaling family. The classical deletion of G_q is known to be lethal [17], indicating essential requirement for this particular G-protein and no possible compensation of other G-proteins from different G-protein classes. Within the $G_{q/11}$ G-protein class, a preferential signaling role of G_q over G_{11} signaling has been demonstrated in various systems [14-16,18-20] and the G_q-protein mediated signaling pathway in DRGs seems to have the major role over all other possible G-protein pathways which are involved in signal transduction upon receptor activation after application of ligands. We used the Cre-lox P system for conditional deletion such that the gene deletion only commences prenatally, thereby excluding early developmental deficits in SNS-$Gq^{-/-}$ mice, but we cannot rule out compensatory mechanisms of G_q in $G_{11}{}^{-/-}$ mice as it has been suggested earlier [21].

Moreover, we were surprised to see the predominant contribution of the $G_{q/11}$ signaling pathway over G_s or $G_{i/o}$ signaling with respect to those substances that are known to activate GPCRs which can bind different classes of G-protein, e.g. ATP, ET1, Glutamate, PAF, PGE_2, Serotonin, S1P or Thrombin. Whereas the inhibitory $G_{i/o}$ proteins contribute to anti-nociceptive signaling pathway, G_s and $G_{q/11}$ protein signaling mediates pro-nociceptive signaling (reviewed in [3]). For example PGE_2, a crucial mediator for inflammatory pain couples to $G_{q/11}$-, $G_{i/o}$- and G_s-GPCRs but does not elicit thermal hyperalgesia or mechanical allodynia in mice lacking G_q, indicating a major contribution of the G_q-GPCR signaling pathway. Similarly, ATP or Serotonin, which can bind $G_{q/11}$- and G_s-GPCRs, do not lead to mechanical allodynia in G_q-deficient mice indicating a dominant role of G_q over the other G-proteins which are known to couple to the same receptors. On the contrary, thermal hyperalgesia and mechanical allodynia induced by CGRP (which can activate $G_{q/11}$- and G_s- coupled GPCRs) or Thrombin (which can bind $G_{q/11}$- $G_{i/o}$- and $G_{12/13}$-GPCRs) are fully preserved, indicating that compensatory mechanisms via other G-proteins are functional.

Interestingly, with respect to thermal hyperalgesia only ATP-mediated heat hyperalgesia is abrogated in G_q-deficient mice whereas Serotonin-induced heat hyperalgesia is preserved in these animals. This predominant role of the G_q-protein in mediating mechanical allodynia over thermal hyperalgesia was also found for Endothelin and to some extend for S1P. It seems that the $G_{q/11}$ signaling pathway contributes significantly to mechanical allodynia elicited via a broad range of inflammatory mediators herein tested and that GPCR agonist-induced heat hyperalgesia is mediated via distinct G-protein GPCRs or other receptors.

Our results constitute a valuable tool to work out *in vivo* conditions of established nociceptive sensitizers. Moreover, this tool can be used for studying the mechanisms of action of new mediators in pain sensitization.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
LNW carried out behavioral experiments and analyzed results. RK provided general support and participated in the design of the study. ATT conceived and designed the study, carried out behavioral experiments, analyzed results and wrote the manuscript. All authors read and approved the final manuscript.

Acknowledgements
The authors thank Stefan Offermanns and Nina Wettschureck for providing $G\alpha_{q/11}$ ($G\alpha_q{}^{fl/fl}$;$G\alpha_{11}{}^{-/-}$) mice. This work was supported by a grant from the Deutsche Forschungsgemeinschaft to A.TT.

Received: 14 June 2013 Accepted: 20 October 2013
Published: 25 October 2013

References
1. Drews J: **Drug discovery: a historical perspective.** *Science* 2000, **287:**1960–1964.
2. Hopkins AL, Groom CR: **The druggable genome.** *Nat Rev Drug Discov* 2002, **1:**727–730.
3. Stone LS, Molliver DC: **In search of analgesia: emerging roles of GPCRs in pain.** *Mol Interv* 2009, **9:**234–251.
4. Julius D, Basbaum AI: **Molecular mechanisms of nociception.** *Nature* 2001, **413:**203–210.
5. Tappe-Theodor A, Constantin CE, Tegeder I, Lechner SG, Langeslag M, Lepcynzsky P, Wirotanseng RI, Kurejova M, Agarwal N, Nagy G, *et al*: **Galpha (q/11) signaling tonically modulates nociceptor function and contributes to activity-dependent sensitization.** *Pain* 2012, **153:**184–196.
6. Wettschureck N, Offermanns S: **Mammalian G proteins and their cell type specific functions.** *Physiol Rev* 2005, **85:**1159–1204.
7. Han SK, Mancino V, Simon MI: **Phospholipase Cbeta 3 mediates the scratching response activated by the histamine H1 receptor on C-fiber nociceptive neurons.** *Neuron* 2006, **52:**691–703.
8. Wettschureck N, Rutten H, Zywietz A, Gehring D, Wilkie TM, Chen J, Chien KR, Offermanns S: **Absence of pressure overload induced myocardial hypertrophy after conditional inactivation of Galphaq/Galpha11 in cardiomyocytes.** *Nat Med* 2001, **7:**1236–1240.
9. Strathmann M, Simon MI: **G protein diversity: a distinct class of alpha subunits is present in vertebrates and invertebrates.** *Proc Natl Acad Sci USA* 1990, **87:**9113–9117.

10. Berstein G, Blank JL, Smrcka AV, Higashijima T, Sternweis PC, Exton JH, Ross EM: **Reconstitution of agonist-stimulated phosphatidylinositol 4,5-bisphosphate hydrolysis using purified m1 muscarinic receptor, Gq/11, and phospholipase C-beta 1.** *J Biol Chem* 1992, **267:**8081–8088.
11. Offermanns S, Heiler E, Spicher K, Schultz G: **Gq and G11 are concurrently activated by bombesin and vasopressin in Swiss 3T3 cells.** *FEBS Lett* 1994, **349:**201–204.
12. Wange RL, Smrcka AV, Sternweis PC, Exton JH: **Photoaffinity labeling of two rat liver plasma membrane proteins with [32P]gamma-azidoanilido GTP in response to vasopressin. Immunologic identification as alpha subunits of the Gq class of G proteins.** *J Biol Chem* 1991, **266:**11409–11412.
13. Wu DQ, Lee CH, Rhee SG, Simon MI: **Activation of phospholipase C by the alpha subunits of the Gq and G11 proteins in transfected Cos-7 cells.** *J Biol Chem* 1992, **267:**1811–1817.
14. Offermanns S, Hashimoto K, Watanabe M, Sun W, Kurihara H, Thompson RF, Inoue Y, Kano M, Simon MI: **Impaired motor coordination and persistent multiple climbing fiber innervation of cerebellar Purkinje cells in mice lacking Galphaq.** *Proc Natl Acad Sci U S A* 1997, **94:**14089–14094.
15. Hartmann J, Blum R, Kovalchuk Y, Adelsberger H, Kuner R, Durand GM, Miyata M, Kano M, Offermanns S, Konnerth A: **Distinct roles of Galpha(q) and Galpha11 for Purkinje cell signaling and motor behavior.** *J Neurosci* 2004, **24:**5119–5130.
16. Kleppisch T, Voigt V, Allmann R, Offermanns S: **G(alpha)q-deficient mice lack metabotropic glutamate receptor-dependent long-term depression but show normal long-term potentiation in the hippocampal CA1 region.** *J Neurosci* 2001, **21:**4943–4948.
17. Offermanns S, Toombs CF, Hu YH, Simon MI: **Defective platelet activation in G alpha(q)-deficient mice.** *Nature* 1997, **389:**183–186.
18. Haley JE, Abogadie FC, Delmas P, Dayrell M, Vallis Y, Milligan G, Caulfield MP, Brown DA, Buckley NJ: **The alpha subunit of Gq contributes to muscarinic inhibition of the M-type potassium current in sympathetic neurons.** *J Neurosci* 1998, **18:**4521–4531.
19. Haley JE, Delmas P, Offermanns S, Abogadie FC, Simon MI, Buckley NJ, Brown DA: **Muscarinic inhibition of calcium current and M current in Galpha q-deficient mice.** *J Neurosci* 2000, **20:**3973–3979.
20. Krause M, Offermanns S, Stocker M, Pedarzani P: **Functional specificity of G alpha q and G alpha 11 in the cholinergic and glutamatergic modulation of potassium currents and excitability in hippocampal neurons.** *J Neurosci* 2002, **22:**666–673.
21. Offermanns S, Zhao LP, Gohla A, Sarosi I, Simon MI, Wilkie TM: **Embryonic cardiomyocyte hypoplasia and craniofacial defects in G alpha q/G alpha 11-mutant mice.** *EMBO J* 1998, **17:**4304–4312.

doi:10.1186/1744-8069-9-54
Cite this article as: Wirotanseng *et al.*: G_q rather than G_{11} preferentially mediates nociceptor sensitization. *Molecular Pain* 2013 **9**:54.

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