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Multiple sensory G proteins in the olfactory, gustatory and nociceptive neurons modulate longevity in *Caenorhabditis elegans*

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Abstract

The life span of the nematode *Caenorhabditis elegans* is under control of sensory signals detected by the amphid neurons. In these neurons, *C. elegans* expresses at least 13 Gα subunits and a Gγ subunit, which are involved in the transduction and modulation of sensory signals. Here, we show that loss-of-function mutations in the Gα subunits *odr-3*, *gpa-1* and *gpa-9*, in the Gγ subunit *gpc-1* and the introduction of extra copies of the Gα subunit *gpa-11* extend the life span of *C. elegans*. Loss-of-function of *odr-3* and extra copies of *gpa-11* act synergistically and can together extend life span more than two-fold, indicating that sensory signals play an important role in regulating life span. We show that *gpa-1*, *gpa-11*, *odr-3* and *gpc-1* all signal via the *daf-16* FOXO family transcription factor. In addition, *odr-3* and *gpa-11* might suppress life span extension partially independent of the insulin/IGF-1 like receptor homologue *daf-2*. Our results suggest that the previously unanticipated nociceptive ASH and/or ADL neurons regulate longevity. We expect that the implication of specific G proteins will eventually contribute to the identification of the sensory cues that determine the rate of aging in *C. elegans*.

Keywords: *C. elegans*; G proteins; Sensory signaling; Longevity; Aging; Insulin/IGF-1 signaling; Dauer development

Introduction

Genetic analysis of the life span of the nematode *Caenorhabditis elegans* has greatly aided in understanding the mechanisms that regulate aging. An intriguing finding is that *C. elegans* life span is under control of sensory perception (Apfeld and Kenyon, 1999; Alcedo and Kenyon, 2004). *C. elegans* perceives its environment through 12 bilateral pairs of ciliated amphid neurons. Mutations that disrupt the cilia of these neurons, resulting in the inability to respond to sensory cues, increase the life span of *C. elegans* (Apfeld and Kenyon, 1999). Furthermore, laser ablation of some of the neurons that detect environmental cues, such as the AWA, AWC, ASI and ASG neurons, extends life span (Alcedo and Kenyon, 2004). However, the sensory cues and precise sensory signaling mechanisms that regulate longevity are not yet known.

As in mammals, many sensory cues in *C. elegans* are probably detected by G protein coupled receptors, which, in response, activate multiple G protein mediated signaling cascades (Troemel et al., 1995; Jansen et al., 1999). The genome of *C. elegans* encodes 21 Gα subunits, 2 Gβ subunits and 2 Gγ subunits (Jansen et al., 1999; Cuppen et al., 2003). Of these, 13 Gα subunits and 1 Gγ subunit are specifically expressed in the amphid sensory neurons (Table 1; Zwaal et al., 1997; Roayaie et al., 1998; Jansen et al., 1999, 2002). Thus far, for eight Gα subunits and the Gγ subunit a role in sensory perception has been demonstrated (Zwaal et al., 1997; Roayaie et al., 1998; Jansen et al., 1999, 2002; Chao et al., 2004; Hilliard et al., 2004; Lans et al., 2004; Hukema et al., 2006). For example, the Gα subunit ODR-3 mediates the detection of olfactory and nociceptive stimuli (Roayaie et al., 1998; Hilliard et al., 2004). Furthermore, the Gα subunits ODR-3 and GPA-1 and the Gγ subunit GPC-1 play a role in gustatory plasticity, a behavioral response to NaCl (Jansen et al., 2002; Hukema et al., 2006). The Gα subunit GPA-11 has been shown to regulate octanol sensitivity in response to a food/serotonin signal (Chao et al., 2004).

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Table 1
Mean life spans of G protein mutant and transgenic strains, at 25 °C[a]

Strain[b]	Mean ± SEM (days)	75th perc. (days)[c]	*n*[d]	*p* value[e]	Amphid neuron expression[f]	Sensory function[f]
Amsterdam[g]						
Wild type	13.4±0.2	15	203			
gpa-1	14.4±0.3	16	78	0.007	ADL, ASH, ASI, ASJ	Salt perception
gpa-1XS	12.3±0.4	14	44	0.004		
gpa-2	9.5±0.6	12	40	<0.0001	AWC	Olfaction, dauer pheromone
gpa-2XS	15.1±0.4	17	73	<0.0001		
gpa-3	11.4±0.5	14	40	0.001	AWA, AWC, ADF, ADL, ASE, ASG, ASH, ASI, ASJ, ASK	Nociception, olfaction, dauer pheromone
gpa-3XS	13.1±0.3	15	39	0.144		
gpa-3QL	11.6±1.2	14	28	0.432		
gpa-4	14.1±0.4	16	43	0.053	ASI	
gpa-4XS	12.7±0.6	15	44	0.981		
gpa-5	14.2±0.4	16	43	0.036	AWA, ADL	Olfaction
gpa-5XS	12.1±0.5	14	42	0.052		
gpa-6	12.0±0.5	13	41	0.036	AWA, AWB, ASH, ADL	
gpa-6XS	13.0±0.5	15	46	0.912		
gpa-7	13.4±0.5	15	36	0.976		
gpa-7XS	14.1±0.4	16	22	0.465		
gpa-8	10.7±0.5	13	35	<0.001	None	
gpa-8XS	11.5±0.5	13	42	0.003		
gpa-9	17.5±0.4	19	42	<0.0001	ASJ	
gpa-9XS	11.0±0.6	14	41	0.001		
gpa-10	11.0±0.3	12	50	<0.0001	ADF, ASI, ASJ	
gpa-11	12.8±0.4	18	46	0.278	ADL, ASH	Serotonin/food
gpa-11XS	19.5±0.7	26	65	<0.0001		
gpa-12	13.2±0.5	16	37	0.906	Undetermined	
gpa-13	12.9±0.4	16	38	0.261	ADF, ASH, AWC	Olfaction
gpa-13XS	12.4±0.7	16	46	0.727		
gpa-14	13.7±0.4	16	44	0.668	ASI, ASJ, ASH, ASK	
gpa-14XS	12.9±0.3	13	44	0.118		
gpa-15	13.3±0.4	16	46	0.907	ADL, ASH, ASK	
gpa-15XS	11.1±0.6	13	21	<0.0001		
odr-3	18.0±0.4	19	80	<0.0001	AWA, AWB, AWC, ADF, ASH	Olfaction, salt, nociception
gpc-1	14.7±0.4	17	45	0.002	AWB, ADL, ASH, ASI, ASJ, AFD	Salt perception
gpc-1XS	15.2±0.5	17	33	0.0001		
gpa-11; odr-3	14.3±0.5	17	35	*0.037	**<0.0001	
Rotterdam[b]						
wild type	17.5±0.3	20	89			
gpa-9	19.6±0.3	22	87	<0.0001		
gpa-9XS	19.4±0.4	21	71	0.0001		
gpa-11	17.0±0.6	19	37	0.843		
gpa-11XS	21.1±0.5	24	90	<0.0001		
gpa-11XS(pkIs540)	22.8±0.6	24	93	<0.0001		
odr-3	19.7±0.5	24	84	<0.0001		
gpa-11; odr-3	17.2±0.4	19	69	*0.823	**<0.0001	
odr-3; gpa-11XS	34.7±1.6	42	48	**<0.0001	***<0.0001	
odr-3; gpa-11XS(pkIs540)	25.4±1.1	32	42	**<0.0001	°0.132	

[a] Cumulative results of life span analysis at 25 °C.

[b] All strains carry loss-of-function mutations that represent putative null alleles. This has been verified using antibodies in the case of *odr-3, gpa-2, gpa-3, gpa-5, gpa-6, gpa-13* and *gpc-1* (Lans et al., 2004; S.R. and G.J, personal communication). Strains that have significantly extended life span are indicated in bold. Two independent integrated arrays of *gpa-11XS* were tested, to confirm that additional copies of the *gpa-11* gene caused life span extension. None of the strains, except *gpa-3QL*, shows defective dye filling (Jansen et al., 1999, 2002). XS denotes extra copies of the gene as a transgene, QL a constitutive activating mutation.

[c] The 75th perc. (percentile) is the age when the fraction of animals alive reaches 0.25.

[d] *n* denotes number of animals tested.

[e] *p* values are compared to wild type, except * compared to *gpa-11*, ** compared to *odr-3*, *** compared to *gpa-11XS* and ° compared to *gpa-11XS(pkIs540)*.

[f] Expression patterns and functions were published previously (Zwaal et al., 1997; Roayaie et al., 1998; Jansen et al., 1999, 2002; Yau et al., 2003; Chao et al., 2004; Hilliard et al., 2004; Lans et al., 2004; Hukema et al., 2006).

[g] During the course of our experiments, our lab moved from the city of Amsterdam to Rotterdam. Animals survived significantly longer in Rotterdam, possibly because of different environmental conditions. Results obtained at the same location, however, never showed large variations, emphasizing their significance. Importantly, the outcome of experiments performed at both locations was similar: animals that showed extended life span in Amsterdam showed extended life span in Rotterdam. All assays in Amsterdam were performed once, except assays with *gpa-1, gpa-2XS, gpa-4XS,* which were performed twice and with wild type, which were performed six times. All assays in Rotterdam were performed twice except assays with *gpa-11*, *odr-3; gpa-11XS* and *odr-3; gpa-11XS(pkIs540)*, which were performed once.