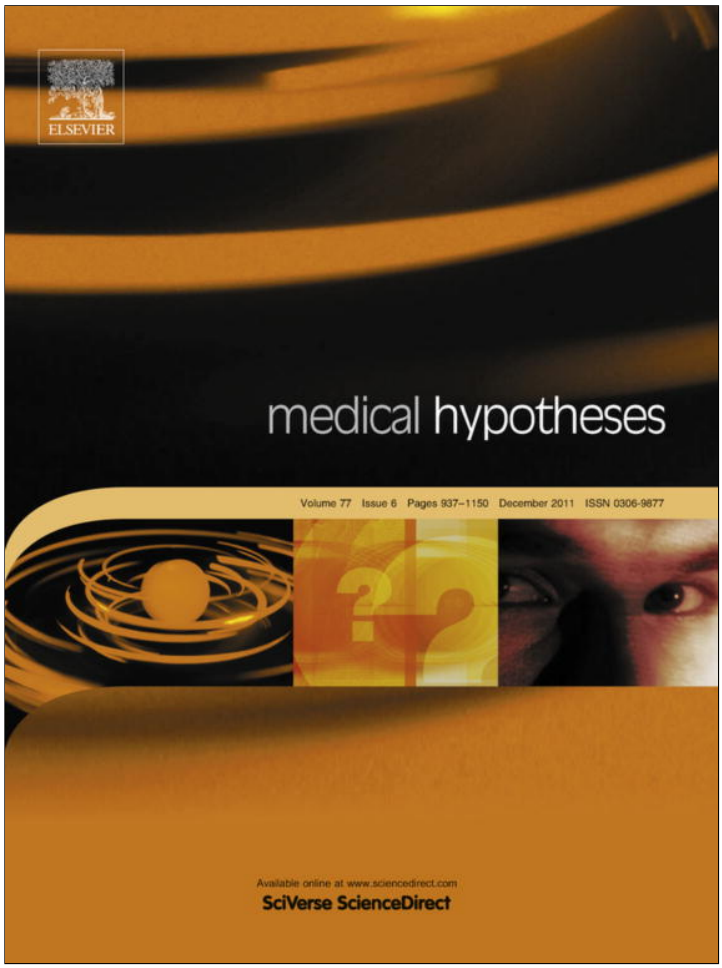

Medical Hypotheses 77 (2011) 996–999

Contents lists available at SciVerse ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

# Neuronal Shc: A gene of longevity in the brain?

Nozomu Mori [a,*], Mari Mori [a,b,1]

[a] Department of Anatomy and Neurobiology, Nagasaki University School of Medicine, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan
[b] Department of Bioinformatics, Center for Biotechnology Education, Johns Hopkins University, USA

ARTICLE INFO

*Article history:*
Received 29 July 2011
Accepted 15 August 2011

ABSTRACT

Aging is inevitable to all multi-cellular organisms, and each organism has its own lifespan. The species-specific lifespan seems determined genetically; however little is known about how the lifespan determined. During the last decades accumulative evidence indicates that there is certainly a set of genes that are involved in the lifespan determination. Among those dozens of genes, the *Shc* gene encoding a phosphotyrosine signal adaptor is of potential interests in mammalian aging and/or longevity determination. *Shc* is merely one form of a gene family, and accumulative evidence demonstrates the presence of additional *Shc* homologues that are strongly expressed in the nervous system. We hypothesize that lifespan is regulated primarily by the nervous system and/or brain, and neurally expressed Shc homologues play pivotal roles in relation to the evolution of longevity with quality of life. We discuss herein the recent progress of our understanding of the neuronally expressed *Shc* genes in comparision with p66-*Shc* as a candidate for the evolution of long life with higher quality of life in mammals.



## Introduction

It is well established that there are some genes that affect the aging process. There is certainly a set of genes that control lifespan and assure longevity [1,2]. The existence of genes that directly affects lifespan became evident through the studies of genetic analyses of Werner's syndrome [3], Hutchinson–Gilford syndrome (known as progeria) [4], and centenarians [5], as well as from studies on genetic variants found in lower invertebrates, such as *Drosophila melanogaster* (fruit fly), *Caenorhabditis elegans* (nematode), and *Saccharomyces cerevisiae* (budding yeast) [1,2]. While a large number of genetic variants affecting lifespan have been identified in those lower organisms, only a limited set of longevity mutants have been identified in mammals [6].

## p66-*Shc*: a longevity-assurance gene in mammals

A remarkable finding of longevity mutants in mice was that for p66-*Shc* [7]. The p66-*Shc* gene encodes a long isoform of the conventional phosphotyrosine signal adaptor molecule (Fig. 1). The genetic deletion of the gene surprisingly resulted in about 30% extension of the mean and maximum lifespan of the mouse [3,4]. The mechanism of this extended life is now explained by enhanced tolerance against mitochondrial oxidative stress [8]. Interestingly, the p66-*Shc* deficient mice also showed reduced heart diseases [9], enhanced cognition [10], and increased resistance to various environmental stresses [11]. The p66-*Shc* mutant mice thus apparently revealed higher quality of life (QOL) that would directly be related to the extended life of the animal [12]. The p66-Shc protein itself is located in the inner mitochondrial membrane and serves as an oxygen radical generator [8]. Importantly, a serine residue located at the 36th residue from the N-terminus is phosphorylated under oxidative stress, which could trigger the pro-apoptotic reaction cascade signaling. The blockade of p66-Shc serine phosphorylation leads to reduced cell death upon oxidative stress [7]. Reduction of mitochondrial p66-Shc does decrease the oxidative stress, thereby making the cells stress-resistant, which may attain a prolonged lifespan for the organism. What is more remarkable is that the p66-Shc deficient mouse not only has a longer lifespan, but also enjoys higher QOL during its extended lifetime.

Given these results, we can hypothesize that, if some human had a genetic mutation resulting in the reduced expression of p66-Shc and/or reduced serine-36 phosphorylation, the phenotype of that human might resemble that of the p66-*Shc* gene deficient mouse with an extended life and higher QOL. This would be an emergence of a physiological "super man". With this interest in mind, researchers tested potential single nucleotide polymorphisms (SNPs) of the *Shc* loci. So far no strong evidence has been found for such mutations that would result in an extended life [13]. In fact, some SNPs in the p66-*Shc* gene were discovered, but none of them have been found to be associated with a change in p66-Shc protein function or eventual extended lifespan [13,14]. Even so, based on the murine experiments, we can speculate that a p66-Shc inhibitor, if available, could become a potential "anti-aging supplement". Research projects hunting for a p66-Shc

* Corresponding author. Tel./fax: +81 95 819 7017.
*E-mail address:* morinosm@nagasaki-u.ac.jp (N. Mori).
[1] Current address: Department of Biomedical Informatics, University of Pittsburgh School of Medicine.

0306-9877/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mehy.2011.08.030

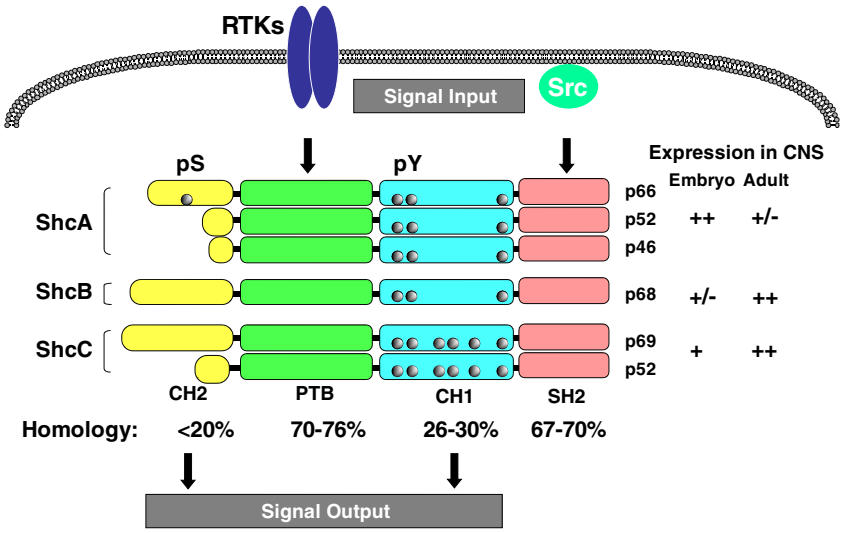


**Fig. 1.** Schematic drawing of the molecular forms of the Shc family members. Shc is a phosphotyrosine signal adaptor, and all the Shc members retain two independent domains for phosphotyrosine – containing peptide-binding: PTB and SH2, which are relatively conserved to compare with the signal output domain (CH1) located in between PTB and SH2. In the CH1 domain, there are several tyrosine residues that are phosphorylated upon binding to receptor tyrosine kinase (RTK) or cytoplasmic kinases such as Src. While all the Shc members, i.e., Shc/ShcA, Sck/ShcB, and N-Shc/ShcC, constituted either a long form and/or short form(s), p66-Shc retains a crucial serine residue (Ser-36) which is a target of the longevity-related signaling. Although both ShcB and ShcC have such long isoforms, signaling mechanisms of these neuron-specific (or enriched) members are less unclear. In the nervous system ShcA is expressed in neuronal progenitors or early in neural development, but ShcA is almost undetectable in neurons in the adult nervous system. Instead, ShcB and ShcC expressions dominate in the adult nervous system. See text for details.

suppressor would be of potential interests in developed countries with aging population.

## Neurons regulating animal lifespan

Now a question arises about where these lifespan genes are expressed to exert their functions. The *C. elegans* nematode, a model organism for longevity research, provides some important clues to this question. In discussing p66-*Shc* as a longevity gene not only in mice but also in other species, we should note that the gene modulates the cascade initiated by the insulin-like growth factor (IGF)-1 signaling, a prominent evolutionally conserved pathway [15–17]. Interestingly, the lifespan phenotype of IGF-1 signaling pathways in *C. elegans* functions only in two types of neurons [18]. They are chemosensory neurons that ensure food sensing, which of course relates to calorie intake in the worm. In mammals, a neuroendocrine network in the hypothalamus should be of primary importance for this kind of nutrient sensing function. Although we still await conclusive evidence, we predict that a certain set of neurons or neural networks through the hypothalamus would play a pivotal role in the longevity of mice and humans.

It should be noted that there is a puzzling phenomenon regarding p66-*Shc*: the expression of this gene in the central nervous system is hardly detectable. *Shc* is expressed in developing neurons; however, the level diminishes as neurons differentiate [19]. In other words, neuronal progenitors do express *Shc* and/or p66-*Shc*, but mature neurons do not [20]. Instead, *Shc* homologues are expressed in mature neurons. We previously isolated a neuron-specific *Shc* in the mid 90's and named it *N-Shc* (see Fig. 1) [21]. The same gene was described and named *Rai* by Pier Giuseppe Pelicci and his colleagues in Italy at around the same time [22]. The gene later was given a yet another name *ShcC* by Tony Pawson and his colleagues [23]. Interestingly, neurons in the central nervous system including the brain express high levels of N-Shc/ShcC, but in contrast, neurons in the peripheral nervous system tend to express another neuronal isoform Sck/ShcB [24] (see Fig. 1). While we know that the *N-Shc/Rai/ShcC* gene gives rise to a gene product with size of 69 kDa, termed p69-N-Shc/ShcC, a p66-Shc equivalent with a longer size, it is still unclear whether p69-N-Shc/ShcC retains a role in neurons equivalent to that of p66-Shc in non-neural cells. It seems possible that p69-N-Shc/ShcC exerts similar but distinct roles in neuronal stress responses in adult and/or aging brains.

## Neuronal Shc: A signal mediator for brain-derived neurotrophic factor (BDNF) and *N*-methyl-D-aspartic acid (NMDA) modulates synaptic transmission and affects cognition

After we initially cloned the human *N-Shc* gene [21], we then isolated rat and mouse cDNAs for the neuronal *Shc* (*N-Shc/ShcC*) [24]. In characterizing the genomic sequences [25] and its gene products, we came to realize that the *N-Shc/ShcC* gene encoded a smaller protein form p52 in addition to p69, similar to the fact that *Shc/ShcA* encodes two isoforms. Biochemical characterization of signal output sequences of N-Shc lead to the identification of novel signal output sequences that are uniquely present in N-Shc but not in the authentic Shc [26]. Another neurally expressed Shc homologue Sck/ShcB turned out to have an interesting character: the *Sck/ShcB* gene encoded only one protein with molecular weight of 68 kDa. The p68-Sck/ShcB responded to calcium related signaling, whereas N-Shc/ShcC preferentially responded to neurotrophin signaling including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) [24,25]. While *Sck/ShcB* and *N-Shc/ShcC* gene expressions have an interesting contrast in that the former is enriched in the peripheral nervous system (PNS) and the latter in the central nervous system (CNS), it should be noted that both are expressed in most neurons in the brain. Therefore, we assume that these two neurally expressed Shc homologues exert distinct signaling properties in a given neuron.

Once we cloned and sequenced all the intron–exon boundaries and mapped the genomic loci on mouse chromosomes [25], we realized the presence of one *Shc*-related locus on mouse chromosome 11. This locus is now considered to correspond to *ShcD*, which is also expressed at certain levels in neurons in the brain [27].

Having mapped both the *Sck/ShcB* and *N-Shc/ShcC* genomes, we tried to generate knockout mice for both genes. We came to the accomplishment rather too late; Sakai and Pawson in Canada had

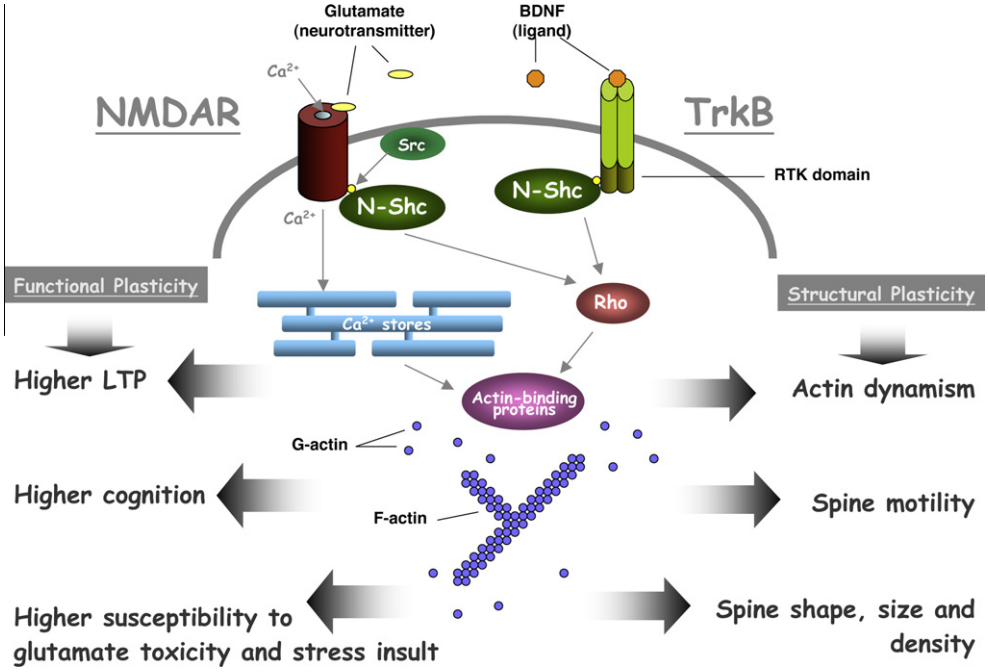


**Fig. 2.** Potential roles of N-Shc in the neural plasticity. N-Shc transmits signals from TrkB and NMDA receptors. Those receptors, one for BDNF and the other for glutamate, are distinct, but N-Shc locates to merge and/or synergize the signaling activation of both receptors, leading to actin modification, which resulted in cognitive modulation in the adult and/or aging animals.

successfully generated both knockouts and analyzed the phenotype of homozygote mice [23]. They found and described precisely the subtle developmental defects of peripheral ganglia. Despite these defects, the two homozygous mutant mice were fertile and survived without drastic abnormality.

In collaboration with Sakai and Pawson, we backcrossed the knockout mice in 129Sv/J with C57BL/6J over 13–15 generations. Then, we carefully examined abnormalities in their behaviors by conducting a series of behavior test paradigms. We found that the *N-Shc/ShcC* gene deficient mice have higher cognition, which was associated with the elevated hippocampal long-term potentiation (LTP) [28]. This was rather a surprising finding. A mouse that lacks *N-Shc/ShcC* was "wiser" or "cleverer" than the control (C57BL/6J) mouse.

How did the mice acquire high cognitive skills? How does the phosphotyrosine signal adaptor molecule N-Shc bring about the high cognitive skills and/or intelligence? The most plausible explanation is that N-Shc protein modulates TrkB and NMDA receptor function, possibly in relation to cytoplasmic tyrosine kinases such as Src or Fyn proteins. We hypothesize that N-Shc functions either independently and/or in connection with the two major neuronal activating receptors, the NMDA receptor and the BDNF-receptor TrkB (see Fig. 2). We assume that N-Shc is activated upon tyrosine phosphorylation of either NMDA-receptor or TrkB, leading to subsequent signaling activation of the Ras-MAPK route, and somehow resulting in modulating actin dynamics in post-synaptic spines. We have some evidence that N-Shc can affect actin dynamics, leading to spine motility (Onga, Shiraishi-Yamaguchi, and Mori, unpublished observations). Though rather a small adaptor molecule, the neuron-specific N-Shc plays an important role in regulating synaptic plasticity in both physiological and morphological bases.

## Neuronal Shc: a longevity-assurance gene in the brain?

As we discussed herein, p66-*Shc* is a longevity determining gene found in mammals, and neuron-specific N-Shc is a longevity-related signal adaptor that affects synaptic plasticity and cognitive function. In the aging brain, cognitive decline is a central issue for the prevention of Alzheimer's disease (AD). Although there is no evidence that N-Shc expression changes in AD or other age-related neurodegenerative conditions, it is worth considering N-Shc as a target for anti-aging research, particularly in relation to the aging brain. Although there are many open questions on the association of N-Shc with the aging process and longevity, we would propose that exploring the molecular mechanisms of N-Shc function in the adult and/or aging brain is crucial. We also propose a search for pharmacological chemicals to suppress N-Shc and p66-Shc functions as a potential candidate of an "anti-aging" supplement for healthy brains with long life.

## Conflicts of interest statement

The authors have no relevant conflict of interest.

## Acknowledgements

The authors thank to our former colleagues who contributed in various ways to elucidate the structure and functions of Shc-related molecules including the neuronal Shc. This work was supported by Grants-in-Aid for Scientific Research, Kiban-B, from MEXT, and also, in part, by the Asian CORE Program from JSPS to N.M.

## References

[1] Guarente L, Kenyon C. Genetic pathways that regulate ageing in model organisms. Nature 2000;408:255–62.
[2] Warner HR. Longevity genes: from primitive organisms to humans. Mech Ageing Dev 2005;126:235–42.
[3] Yu CE, Oshima J, Fu YH, Wijsman EM, Hisama F, Alisch R, et al. Positional cloning of the Werner's syndrome gene. Science 1996;272:258–62.
[4] Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, et al. Recurrent de novo point mutations in lamin A cause Hutchinson–Gilford progeria syndrome. Nature 2003;423:293–8.

[5] Perls T, Kunkel LM, Puca AA. The genetics of exceptional human longevity. J Am Geriatr Soc 2002;50:359–68.
[6] Chen YF, Wu CY, Kao CH, Tsai TF. Longevity and lifespan control in mammals: lessons from the mouse. Ageing Res Rev 2010;9:28–35.
[7] Migliaccio E, Giorgio M, Mele S, Pelicci G, Reboldi P, Pandolfi PP, et al. The p66shc adaptor protein controls oxidative stress response and life span in mammals. Nature 1999;402:309–13.
[8] Giorgio M, Migliaccio E, Orsini F, Paolucci D, Moroni M, Contursi C, et al. Electron transfer between cytochrome c and p66Shc generates reactive oxygen species that trigger mitochondrial apoptosis. Cell 2005;122:221–33.
[9] Graiani G, Lagrasta C, Migliaccio E, Spillmann F, Meloni M, Madeddu P, et al. Genetic deletion of the p66Shc adaptor protein protects from angiotensin II-induced myocardial damage. Hypertension 2005;46:433–40.
[10] Berry A, Greco A, Giorgio M, Pelicci PG, de Kloet R, Alleva E, et al. Deletion of the lifespan determinant p66(Shc) improves performance in a spatial memory task, decreases levels of oxidative stress markers in the hippocampus and increases levels of the neurotrophin BDNF in adult mice. Exp Gerontol 2008;43:200–8.
[11] Berry A, Carnevale D, Giorgio M, Pelicci PG, de Kloet ER, Alleva E, et al. Greater resistance to inflammation at adulthood could contribute to extended life span of p66(Shc-/-) mice. Exp Gerontol 2010;45:343–50.
[12] Purdom S, Chen QM. P66(Shc): at the crossroad of oxidative stress and the genetics of aging. Trends Mol Med 2003;9:206–10.
[13] Kamei H, Adati N, Arai Y, Yamamura K, Takayama M, Nakazawa S, et al. Association analysis of the SHC1 gene locus with longevity in the Japanese population. J Mol Med (Berl) 2003;81:724–8.
[14] Sentinelli F, Romeo S, Barbetti F, Berni A, Filippi E, Fanelli M, et al. Search for genetic variants in the p66Shc longevity gene by PCR-single strand conformational polymorphism in patients with early-onset cardiovascular disease. BMC Genet 2006;7:14.
[15] Katic M, Kahn CR. The role of insulin and IGF-1 signaling in longevity. Cell Mol Life Sci 2005;62:320–43.
[16] Longo VD, Finch CE. Evolutionary medicine: from dwarf model systems to healthy centenarians? Science 2003;299:1342–6.
[17] Fontana L, Partridge L, Longo VD. Extending healthy life span: from yeast to humans. Science 2010;328:21–326.
[18] Bishop NA, Guarente L. Two neurons mediate diet-restriction-induced longevity in *C. elegans*. Nature 2007;447:545–9.
[19] Conti L, Sipione S, Magrassi L, Bonfanti L, Rigamonti D, Pettirossi V, et al. Shc signaling in differentiating neural progenitor cells. Nat Neurosci 2001;4:579–86.
[20] Cataudella T, Conti L, Cattaneo E. Neural stem and progenitor cells: choosing the right Shc. Prog Brain Res 2004;146:127–33.
[21] Nakamura T, Sanokawa R, Sasaki Y, Ayusawa D, Oishi M, Mori N. N-Shc: a neural-specific adapter molecule that mediates signaling from neurotrophin/Trk to Ras/MAPK pathway. Oncogene 1996;13:1111–21.
[22] Pelicci G, Dente L, De Giuseppe A, Verducci-Galletti B, Giuli S, Mele S, et al. CH1 and SH2 regions. Oncogene 1996;13:633–41.
[23] Sakai R, Henderson JT, O'Bryan JP, Elia AJ, Saxton TM, Pawson T. The mammalian ShcB and ShcC phosphotyrosine docking proteins function in the maturation of sensory and sympathetic neurons. Neuron 2000;28:819–33.
[24] Nakamura T, Muraoka S, Sanokawa R, Mori N. N-Shc and Sck, two neuronally expressed Shc adapter homologs. Their differential regional expression in the brain and roles in neurotrophin and Src signaling. J Biol Chem 1998;273:6960–7.
[25] Kojima T, Yoshikawa Y, Takada S, Sato M, Nakamura T, Takahashi N, et al. Genomic organization of the Shc-related phosphotyrosine adapters and characterization of the full-length Sck/ShcB: specific association of p68-Sck/ShcB with pp135. Biochem Biophys Res Commun 2001;284:1039–47.
[26] Nakamura T, Komiya M, Gotoh N, Koizumi S, Shibuya M, Mori N. Discrimination between phosphotyrosine-mediated signaling properties of conventional and neuronal Shc adapter molecules. Oncogene 2002;21:22–31.
[27] Jones N, Hardy WR, Friese MB, Jorgensen C, Smith MJ, Woody NM, et al. Analysis of a Shc family adaptor protein, ShcD/Shc4, that associates with muscle-specific kinase. Mol Cell Biol 2007;27:4759–73.
[28] Miyamoto Y, Chen L, Sato M, Sokabe M, Nabeshima T, Pawson T, et al. Hippocampal synaptic modulation by the phosphotyrosine adapter protein ShcC/N-Shc via interaction with the NMDA Receptor. J Neurosci 2005;25:1826–35.