

# Enhancing Synaptic Plasticity and Memory: A Role for Small-Conductance Ca<sup>2+</sup>-Activated K<sup>+</sup> Channels

THANOS TZOUNOPOULOS and ROBERT STACKMAN

Calcium-activated potassium (K<sup>+</sup>) channels are distributed throughout the central nervous system as well as many other peripheral tissues and comprise three distinct classes of K<sup>+</sup> channels: small conductance (SK), intermediate conductance, and large conductance. This update focuses on SK channels. Increases in cytosolic calcium in response to depolarization activate SK channels. Activation of these channels decreases neuronal excitability. In this review, the authors discuss the role of SK channels in the induction of synaptic plasticity and their influence on learning and memory. A testable model that synthesizes the current literature is offered, suggesting that SK channels represent an important regulator of synaptic plasticity and memory. *NEUROSCIENTIST* 9(6):434–439, 2003. DOI: 10.1177/1073858403259282

**KEY WORDS** SK channel, Synaptic plasticity, Memory, Hippocampus, Review

## Small Conductance (SK) Channels

SK channels have six transmembrane domains and assemble as tetramers to form functional channels. Three SK channel subunits (SK1, SK2, SK3) have been cloned so far (Kohler and others 1996). Pharmacological studies of SK channels expressed in *Xenopus* oocytes have revealed that all three SK channel subtypes are specifically blocked by apamin, although there are differences in sensitivity among the channel subtypes (Strobaek and others 2000; Grunnet and others 2001). To date, apamin and transgenic mice (Bond and others 2000) have been the main tools for studying the role of these channels.

The mRNAs for all three SK subtypes are present throughout the mammalian central nervous system, albeit in varying densities. The SK1 and SK2 subunits are found in high densities in limbic forebrain regions such as the hippocampus, entorhinal cortex, septum, and amygdala (Stocker and Pedarzani 2000; Sailer and others 2002). SK3 subunits are expressed in low levels in the hippocampus; higher levels of SK3 subunits are found in the medial habenula, supraoptic nucleus, dorsal

raphe, and the locus coeruleus (Tacconi and others 2001).

SK channels are voltage insensitive, and their activation is dependent on increases in intracellular Ca<sup>2+</sup>. In most neurons, action potentials are followed by an after-hyperpolarization (AHP) with three kinetic components (fast, medium, and slow AHP). The medium AHP (m<sub>AHP</sub>) is blocked by apamin and therefore is attributable to SK channels. Blockade of the m<sub>AHP</sub> of CA1 hippocampal neurons increases the number of action potentials discharged in response to current injection (Stocker and others 1999; Stackman and others 2002) (see Fig. 1). This modulatory influence on neuronal excitability has led to the proposal that SK channels play a role in the induction of synaptic plasticity.

## SK Channels Influence Synaptic Plasticity

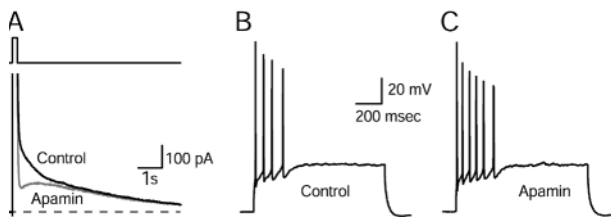
Multiple forms of activity-dependent synaptic plasticity occur at the Schaffer collateral CA1 synapses in the hippocampus, including long-term potentiation (LTP) and long-term depression (LTD) (Malenka and Nicoll 1993). The influx of Ca<sup>2+</sup> through the N-methyl-D-aspartate receptor (NMDAR) and the consequent rise in cytosolic Ca<sup>2+</sup> are essential requirements for LTP and LTD (Malenka and others 1992; Mulkey and Malenka 1992). The magnitude of Ca<sup>2+</sup> influx, as determined by the degree and pattern of NMDAR activation, distinguishes whether a synapse undergoes LTP or LTD: Large Ca<sup>2+</sup> influx leads to LTP, and modest Ca<sup>2+</sup> influx leads to LTD (Artola and Singer 1993; Malenka and Nicoll 1993).

SK channels couple intracellular Ca<sup>2+</sup> levels and membrane potential. Therefore, during repetitive synaptic activation leading to Ca<sup>2+</sup> influx, SK channels may mod-

We thank Rebecca S. Hammond and John P. Adelman for providing helpful comments on this article.

Auditory Neuroscience and Department of Behavioral Neuroscience, Oregon Health and Science University, Portland (TT). Department of Behavioral Neuroscience, Oregon Health and Science University, Portland (RS).

**Address correspondence to:** Dr. Thanos Tzounopoulos, Auditory Neuroscience, L-335A, Oregon Hearing Research Center, Oregon Health and Science University, Portland, OR 97239-3098; e-mail: tzounopo@ohsu.edu; or Dr. Robert W. Stackman, Department of Behavioral Neuroscience, L470, Oregon Health and Science University, Portland, OR 97239-3098; e-mail: stackman@ohsu.edu.



**Fig. 1.** Blockade of the apamin-sensitive afterhyperpolarization ( $m_{\text{AHP}}$ ) increases neuronal excitability. *A*, Medium AHP currents were evoked in voltage clamp by a 200-msec depolarizing pulse to +20 mV followed by a return to the -55 mV holding potential. After application of apamin (100 nM), the  $m_{\text{AHP}}$  of the tail current was selectively inhibited. *B*, Apamin increased the excitability of hippocampal CA1 neurons. Response of a CA1 pyramidal neuron to a 1-s depolarizing current pulse. *C*, Response of the same neuron to the same depolarizing current pulse in the presence of apamin. Under control conditions, cells fired an average  $\pm$  SEM of  $4.7 \pm 1.2$  action potentials/depolarizing pulse, which increased to  $6.7 \pm 1.7$  with apamin.

ulate the induction of synaptic plasticity. Behnisch and Reymann (1998) reported that LTP in the CA1 region was increased by extracellular application of apamin. In a study of age-related alterations in synaptic plasticity, blockade of L-type  $\text{Ca}^{2+}$  channels by nifedipine facilitated synaptic plasticity in Schaffer collateral CA1 synapses in slices from aged rats (Norris and others 1998; Foster 1999). It was concluded that the facilitation of synaptic plasticity was mediated by a reduction in SK channel activity because application of apamin mimicked the effect of nifedipine. The authors suggested that an age-related increase in SK channel activity may underlie impaired plasticity and memory in aging. In addition, application of apamin facilitates the induction of LTP and LTD when induced by different stimulation frequencies (Stackman and others 2002) (see Fig. 2). The smooth transition from LTD to LTP may be demonstrated by systematically varying the frequency of conditioning stimulation for a given number of pulses. The frequency-response relationships for control and apamin-treated slices demonstrate that blockade of SK channels shifts the frequency-response function to the lower frequencies, facilitating the induction of synaptic plasticity. Stimulation frequencies that do not induce synaptic plasticity in control slices (i.e., 5 Hz and 25 Hz) produce LTD and LTP, respectively, in the presence of apamin. This facilitation requires NMDAR activation and appears to involve postsynaptic mechanisms (Stackman and others 2002).

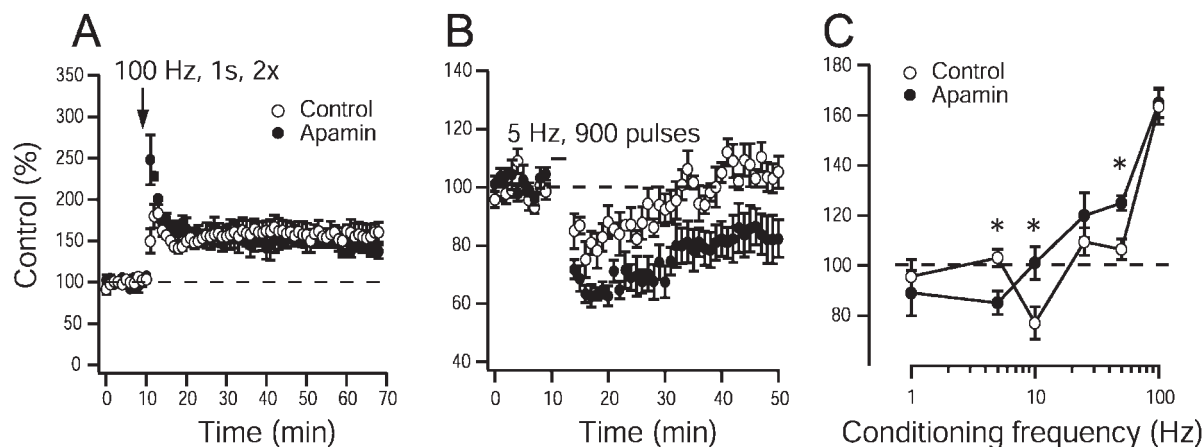
### SK Channels and Memory

Because LTP and LTD represent the most successful experimental models for elucidating the cellular mechanisms of memory, the role of SK channels on both plasticity and memory processes has been extensively studied. Much of the neurobiological study of learning and memory mechanisms has focused on hippocampal-dependent memory. The hippocampal formation is an

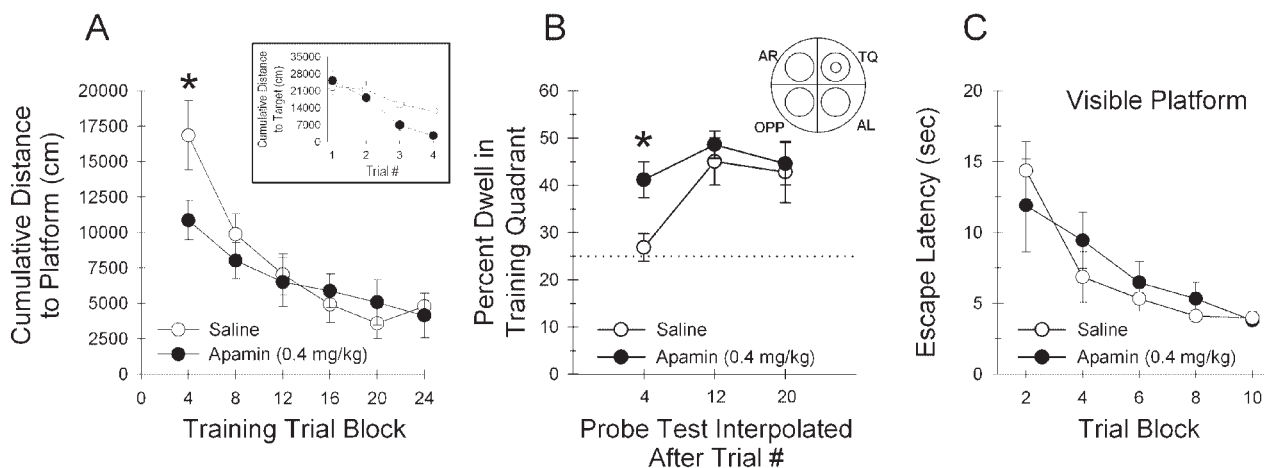
essential neurobiological substrate for declarative or explicit memory—forms of memory that are affected by aging and Alzheimer's disease. Apamin alleviates the memory deficits of mice with compromised hippocampal function when tested in the Morris water maze (Ikonen and others 1998; Ikonen and Riekkinen 1999). The water maze is a hippocampal-dependent spatial task in which mice use extramaze visual cues to learn and remember the location of an escape platform submerged just below the surface of the water (Morris and others 1982). Apamin given by systemic or intracerebroventricular injection attenuates the memory deficits of scopolamine (Ghelardini and others 1998; Inan and others 2000). Scopolamine is a cholinergic antagonist that produces amnesia likely by affecting hippocampal and cortical activity. Collectively, these data indicate that blocking SK channels improves memory retention in experimental models of amnesia.

Mixed results have been reported for apamin's effects on hippocampal-dependent memory in intact rodents. Apamin did not significantly affect memory encoding (i.e., acquisition) in normal rodents in the water maze (van der Staay and others 1999). However, it produced weak influences on spatial memory retention in mice but not in rats. In contrast, apamin facilitates the encoding of memory as assessed by habituation of exploratory activity (Deschaux and Bizot 1997) and facilitates memory encoding in two nonspatial memory tasks (Deschaux and others 1997; Fournier and others 2001). Apamin had no effect on memory retention or retrieval in these studies. The differential effects of apamin on distinct stages of memory may explain the discrepancies between these sets of data.

To address this discrepancy, recent behavioral studies were designed to explicitly test the influence of apamin on the initial stage of spatial memory formation or encoding (Stackman and others 2002). Apamin-treated mice exhibited faster learning of the platform location during the initial training trials in the Morris water maze (see Fig. 3A). Probe tests, in which the platform was removed from the pool, were used to test the spatial search behavior at an early, intermediate, and late stage of memory encoding. Apamin-treated mice exhibited significant spatial memory after minimal training, whereas control mice exhibited chance levels of performance (see Fig. 3B). There were no further differences in performance on subsequent probe tests after more extensive training. These data suggest that blocking SK channels facilitated the encoding of spatial memory. These findings differ from previous water maze studies in which spatial memory was not probed until after extensive training (Ikonen and others 1998; Ikonen and Riekkinen 1999; van der Staay and others 1999). The effects of apamin on spatial memory encoding may be specific to the hippocampus because apamin did not influence memory encoding in a hippocampal-independent water maze task (see Fig. 3C). Together, these data suggest that blockade of SK channels facilitates an early stage of hippocampal-dependent spatial memory.



**Fig. 2.** Apamin block of small conductance channel activity facilitates the induction of synaptic plasticity. *A*, A 100-Hz, 1-s tetanus stimulation protocol in control- and apamin (100 nM)-treated slices. *B*, A 5-Hz, 900-pulse stimulation protocol in control- and apamin (100 nM)-treated slices. *C*, Frequency-response relationship for the induction of long-term potentiation (LTP) and long-term depression (LTD) in controls and experiments from slices in which apamin was applied. The main effect of 900 pulses of conditioning stimulation delivered at various frequencies to the Schaffer collaterals on the synaptic response measured 40 to 50 min after conditioning is shown. \* $P < 0.05$ , versus respective control data point, Student's *t*-test. Dashed line indicates the transition between LTD and LTP. Synaptic strength was measured as the initial slope of the recorded field excitatory postsynaptic potential (EPSP).

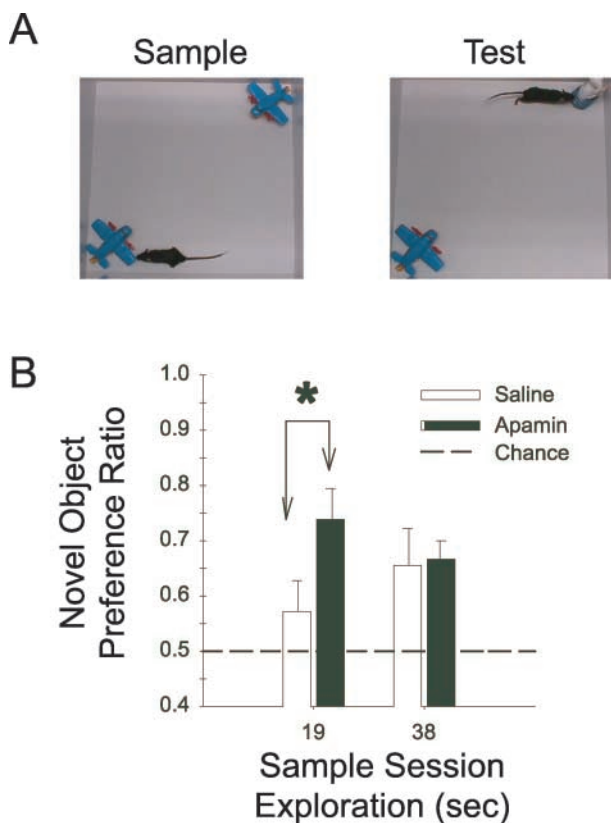


**Fig. 3.** Apamin block of small conductance channels facilitates the encoding of spatial memory. *A*, Apamin-treated mice exhibited accelerated acquisition during the initial training trials of the Morris water maze task. Cumulative distance to platform measures of saline- and apamin-treated mice plotted in blocks of 4 training trials. This plot indicates that apamin-treated mice swam in closer proximity to the platform during the first 4-trial block of training than saline-treated mice (\* $P < 0.04$ , post hoc Tukey multiple comparisons test). Inset figure depicts cumulative distance to platform measures plotted for each of the first 4 trials for both groups of mice, illustrating the improvement in platform search behavior of apamin-treated mice as compared to control mice. *B*, During a 30-s probe test interpolated after the 4th training trial, apamin-treated mice spent significantly more time in the training quadrant during this 1st probe test than control mice (\* vs. saline-treated mice on probe test 1,  $P < 0.009$ , planned comparison Student's *t*-test). The dashed line at 25% represents chance performance. There were no group differences in platform search behavior after more extensive training (i.e., during the 2nd or 3rd probe tests). TQ, training quadrant; AR, adjacent right; OPP, opposite; AL, adjacent left. *C*, Apamin did not facilitate acquisition of a nonhippocampal visible platform water maze task. Escape latency measures of saline- and apamin-treated mice plotted in blocks of 2 training trials.

Systemic apamin produced a similar effect on hippocampal-dependent nonspatial memory as assessed in the spontaneous object recognition task (Stackman and others 2002). In this hippocampal-dependent task (Clark and others 2000), the animal explores two identical novel objects in a familiar arena during a sample session (see Fig. 4A). During a subsequent test session, the animal is returned to the arena that now contains one of the original objects and a novel object. If the animal encod-

ed and retained the memory of the objects explored earlier, then it should now spend more time exploring the novel object.

The spontaneous object recognition task was also modified to explicitly examine the influence of apamin at different stages of object memory encoding (Stackman and others 2002). Apamin- and saline-treated mice were placed into the arena containing two identical novel objects and then removed from the arena after



**Fig. 4.** Apamin block of small conductance channels facilitates the encoding of object memory. *A*, A diagrammatic representation of the sample (left) and test (right) sessions of the spontaneous object recognition task. Object memory is quantified by a novel object preference ratio, computed as the amount of time spent exploring the novel object during the test session divided by the total time spent exploring both the familiar and novel object. *B*, The object recognition task was modified to test the influence of apamin on object memory encoding. During a test session 24 h after the sample session, minimally trained (19 s) apamin-treated mice exhibited significant novel object preference, whereas controls did not (\* vs. saline-treated mice permitted 19 s of object exploration,  $P < 0.04$ , planned comparison Student's *t*-test). There was no difference in novel object preference ratio during the 24-h test session between extensively trained (38 s) apamin- and control-treated mice. The dashed line at 0.5 represents chance performance or a lack of discrimination between the novel and familiar object.

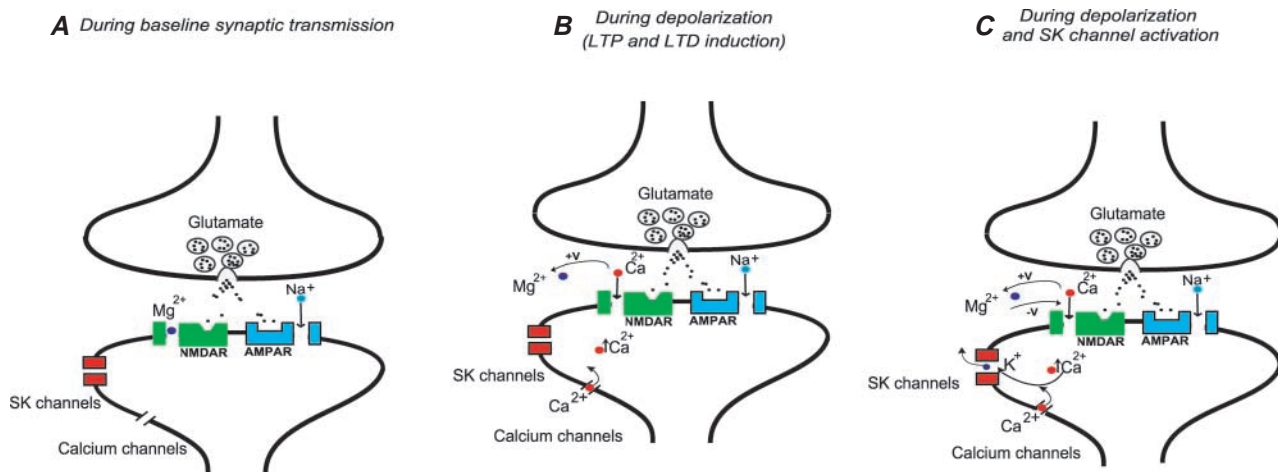
accumulating either 19 s (minimal training) or 38 s (extensive training) of sample object exploration. During the test session, imposed 24 h after the sample session, the minimally trained control mice exhibited poor novel object preference, whereas the apamin-treated mice exhibited significant novel object preference (see Fig. 4B) (Stackman and others 2002). There was no difference in novel object preference ratio between extensively trained control- and apamin-treated mice. In addition, apamin did not affect the retention of object memory at 24- or 48-h delays in extensively trained mice. Collectively, these data suggest that SK channels play a specific role in the early stages of memory encoding. Modification of the water maze and object recognition

tasks was necessary to determine the specificity of apamin's influence on memory encoding.

### A Model for the Role of SK Channels in Synaptic Plasticity and Memory

During SK channel activation, hyperpolarization of the postsynaptic neuron may act to indirectly suppress NMDAR-mediated synaptic plasticity. Postsynaptic depolarization induced by repetitive synaptic stimulation increases intracellular  $Ca^{2+}$  and activates SK channels. By hyperpolarizing the postsynaptic membrane, SK channels decrease excitability and may modulate the activation of NMDARs, which involves voltage-dependent removal of the  $Mg^{2+}$  block (Mayer and others 1988). By affecting the degree of NMDAR activation and the subsequent  $Ca^{2+}$  entry, SK channels modulate the induction of synaptic plasticity (see Fig. 5). This model accounts for recently reported effects of apamin on hippocampal plasticity and memory. However, apamin also facilitates several forms of nonhippocampal memory (Messier and others 1991; van der Staay and others 1999), suggesting that SK channels can exert similar effects in nonhippocampal memory circuits that employ NMDAR-dependent plasticity.

The model predicts that SK channels reside in close proximity to NMDARs in the postsynaptic membrane, forming a local regulatory circuit mediated by  $Ca^{2+}$  entering through NMDARs, but currently there is not experimental support for this hypothesis. Determining the  $Ca^{2+}$  source for synaptic activation of SK channels is an important yet unanswered question. Imaging studies directly measuring  $Ca^{2+}$  influx during repetitive synaptic stimulation in the presence or absence of apamin could provide a better way to test the validity of this model. The influence of apamin on NMDAR-dependent synaptic plasticity can be more easily explained by dendritic localization of SK channels, although direct evidence for this is currently unavailable. However, several studies have indirectly supported dendritic localization of SK channels (Cangiano and others 2002; Womack and Khodakhah 2003). It will be important for future studies to define the subcellular localization of SK channels within hippocampal neurons. The ability of SK channels to modulate the threshold for synaptic plasticity makes them a potential target for physiological modulatory mechanisms such as neurotransmitters, second messenger pathways, and development. It has been suggested that a progressive elevation in SK channel activity during aging may explain age-related increases in the threshold for synaptic plasticity and memory impairments (Norris and others 1998; Foster 1999). Finally, given that current pharmacological agents cannot distinguish between subunits, transgenic mice with selective manipulation of each of the three different subtypes of SK channels will provide useful tools for the elucidation of the differential roles of each SK channel subtype. Understanding the mechanisms through which specific SK subunits regulate hippocampal memory may prove



**Fig. 5.** Model for the role of small conductance (SK) channels on the induction of N-methyl-D-aspartate receptor (NMDAR)-dependent plasticity. *A*, During normal synaptic transmission, glutamate is released from the presynaptic neuron and acts on both AMPA receptors (AMPA) and NMDARs. However, Na<sup>+</sup> flows only through AMPARs but not through NMDARs because Mg<sup>2+</sup> blocks the pore of the NMDAR. *B*, Depolarization of the postsynaptic neuron relieves the voltage-dependent Mg<sup>2+</sup> block of the NMDAR channel, allowing Na<sup>+</sup> and Ca<sup>2+</sup> to flow into the dendritic spine. The resultant increase in Ca<sup>2+</sup> within the spine is the critical trigger for synaptic plasticity. The magnitude and the dynamics of this increase determine whether the synapse will undergo long-term potentiation or long-term depression. *C*, At the same time, increases in intracellular Ca<sup>2+</sup> not only through NMDAR but also through voltage-gated Ca<sup>2+</sup> channels activate SK channels, thus leading to hyperpolarization of the postsynaptic neuron. This hyperpolarization suppresses the opening of NMDARs. Such an SK channel-mediated effect has profound consequences on the induction of synaptic plasticity.

useful for the development of treatment strategies for memory disorders.

## References

Artola A, Singer W. 1993. Long-term depression of excitatory synaptic transmission and its relationship to long-term potentiation. *Trends Neurosci* 16:480–7.

Behnisch T, Reymann KG. 1998. Inhibition of apamin-sensitive calcium dependent potassium channels facilitate the induction of long-term potentiation in the CA1 region of rat hippocampus *in vitro*. *Neurosci Lett* 253:91–4.

Bond CT, Sprengel R, Bissonnette JM, Kaufmann WA, Pribnow D, Neelands T, and others. 2000. Respiration and parturition affected by conditional overexpression of the Ca<sup>2+</sup>-activated K<sup>+</sup> channel subunit, SK3. *Science* 289:1942–6.

Cangiano L, Wallen P, Grillner S. 2002. Role of apamin-sensitive K<sup>+</sup>(ca) channels for reticulospinal synaptic transmission to motoneuron and for the afterhyperpolarization. *J Neurophysiol* 88:289–99.

Clark RE, Zola SM, Squire LR. 2000. Impaired recognition memory in rats after damage to the hippocampus. *J Neurosci* 20:8853–60.

Deschaux O, Bizot JC. 1997. Effect of apamin, a selective blocker of Ca<sup>2+</sup>-activated K<sup>+</sup>-channel, on habituation and passive avoidance responses in rats. *Neurosci Lett* 227:57–60.

Deschaux O, Bizot JC, Goyffon M. 1997. Apamin improves learning in an object recognition task in rats. *Neurosci Lett* 222:159–62.

Foster TC. 1999. Involvement of hippocampal synaptic plasticity in age-related memory decline. *Brain Res Rev* 30:236–49.

Fournier C, Kourrich S, Soumireu-Mourat B, Mourre C. 2001. Apamin improves reference memory but not procedural memory in rats by blocking small conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channels in an olfactory discrimination task. *Behav Brain Res* 121:81–93.

Ghelardini C, Galeotti N, Bartolini A. 1998. Influence of potassium channel modulators on cognitive processes in mice. *Br J Pharmacol* 123:1079–84.

Grunnet M, Jensen BS, Olesen SP, Klaerke DA. 2001. Apamin interacts with all subtypes of cloned small-conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channels. *Pflugers Arch* 441:544–50.

Ikonen S, Riekkinen P, Jr. 1999. Effects of apamin on memory processing of hippocampal-lesioned mice. *Eur J Pharmacol* 382:151–6.

Ikonen S, Schmidt B, Riekkinen P, Jr. 1998. Apamin improves spatial navigation in medial septal-lesioned mice. *Eur J Pharmacol* 347:13–21.

Inan SY, Aksu F, Baysal F. 2000. The effects of some K<sup>(+)</sup> channel blockers on scopolamine- or electroconvulsive shock-induced amnesia in mice. *Eur J Pharmacol* 407:159–64.

Kohler M, Hirschberg B, Bond CT, Kinzie JM, Marrion NV, Maylie J, and others. 1996. Small-conductance, calcium-activated potassium channels from mammalian brain. *Science* 273:1709–14.

Malenka RC, Lancaster B, Zucker RS. 1992. Temporal limits on the rise in postsynaptic calcium required for the induction of long-term potentiation. *Neuron* 9:121–8.

Malenka RC, Nicoll RA. 1993. NMDA-receptor-dependent synaptic plasticity: multiple forms and mechanisms. *Trends Neurosci* 16:521–7.

Mayer ML, Westbrook GL, Vyklicky L, Jr. 1988. Sites of antagonist action on N-methyl-D-aspartic acid receptors studied using fluctuation analysis and a rapid perfusion technique. *J Neurophysiol* 60:645–63.

Messier C, Mourre C, Bontempi B, Sif J, Lazdunski M, Destradre C. 1991. Effect of apamin, a toxin that inhibits Ca<sup>2+</sup>-dependent K<sup>+</sup> channels, on learning and memory processes. *Brain Res* 551:322–6.

Morris RGM, Garrud P, Rawlins JNP, O’Keefe J. 1982. Place navigation impaired in rats with hippocampal lesions. *Nature* 297:681–3.

Mulkey RM, Malenka RC. 1992. Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. *Neuron* 9:967–75.

Norris CM, Halpain S, Foster TC. 1998. Reversal of age-related alterations in synaptic plasticity by blockade of L-type Ca<sup>2+</sup> channels. *J Neurosci* 18:3171–9.

Sailer CA, Hu H, Kaufmann WA, Trieb M, Schwarzer C, Storm JF, and others. 2002. Regional differences in distribution and functional expression of small-conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channels in rat brain. *J Neurosci* 22:9698–707.

Stackman RW, Hammond RS, Linardatos E, Gerlach A, Maylie J, Adelman JP, and others. 2002. Small conductance Ca<sup>2+</sup>-activated

- K<sup>+</sup> channels modulate synaptic plasticity and memory encoding. *J Neurosci* 22:10163–71.
- Stocker M, Krause M, Pedarzani P. 1999. An apamin-sensitive Ca<sup>2+</sup>-activated K<sup>+</sup> current in hippocampal pyramidal neurons. *Proc Natl Acad Sci USA* 96:4662–7.
- Stocker M, Pedarzani P. 2000. Differential distribution of three Ca<sup>2+</sup>-activated K<sup>+</sup> channel subunits, SK1, SK2, and SK3, in the adult rat central nervous system. *Mol Cell Neurosci* 15:476–93.
- Strobaek D, Jorgensen TD, Christophersen P, Ahring PK, Olesen SP. 2000. Pharmacological characterization of small-conductance Ca(2<sup>+</sup>)-activated K(+) channels stably expressed in HEK 293 cells. *Br J Pharmacol* 129:991–9.
- Tacconi S, Carletti R, Bunnemann B, Plumpton C, Merlo Pich E, Terstappen GC. 2001. Distribution of the messenger RNA for the small conductance calcium-activated potassium channel SK3 in the adult rat brain and correlation with immunoreactivity. *Neuroscience* 102:209–15.
- van der Staay FJ, Fanelli RJ, Blokland A, Schmidt BH. 1999. Behavioral effects of apamin, a selective inhibitor of the SK(Ca)-channel, in mice and rats. *Neurosci Biobehav Rev* 23:1087–110.
- Womack MD, Khodakhah K. 2003. Somatic and dendritic small-conductance calcium-activated potassium channels regulate the output of cerebellar Purkinje neurons. *J Neurosci* 23:2600–7.

## **Request Permission or Order Reprints Instantly**

Interested in copying, sharing, or the repurposing of this article? U.S. copyright law, in most cases, directs you to first get permission from the article's rightsholder before using their content.

To lawfully obtain permission to reuse, or to order reprints of this article quickly and efficiently, click on the "Request Permission/ Order Reprints" link below and follow the instructions. For information on Fair Use limitations of U.S. copyright law, please visit [Stamford University Libraries](#), or for guidelines on Fair Use in the Classroom, please refer to [The Association of American Publishers' \(AAP\)](#).

All information and materials related to SAGE Publications are protected by the copyright laws of the United States and other countries. SAGE Publications and the SAGE logo are registered trademarks of SAGE Publications. Copyright © 2003, Sage Publications, all rights reserved. Mention of other publishers, titles or services may be registered trademarks of their respective companies. Please refer to our user help pages for more details: <http://www.sagepub.com/cc/faq/SageFAQ.htm>

**[Request Permissions / Order Reprints](#)**