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A TRANSIENT INCREASE IN TEMPERATURE INDUCES PERSISTENT POTENTIATION OF SYNAPTIC TRANSMISSION IN RAT HIPPOCAMPAL SLICES

S. A. MASINO*† and T. V. DUNWIDDIE*‡

*Department of Pharmacology and Neuroscience Program, University of Colorado Health Sciences Center, 4200 E. 9th Avenue, Denver, CO 80262, USA

‡Veterans Affairs Medical Research Service, Denver, CO 80220, USA

Abstract—Previous studies have shown that increasing the temperature of rat hippocampal brain slices from 32.5 to 38.5°C initiates a profound, adenosine-mediated decrease in excitatory synaptic transmission in the CA1 region. Here we found that upon lowering the temperature back to 32.5°C, the amplitude of the field excitatory postsynaptic potential often recovers to a level that is significantly potentiated with respect to the initial baseline. This potentiation is rapid in onset (< 5 min following return to 32.5°C) and long lasting (>60 min following the termination of the increase in temperature). Similar effects could not be induced by superfusion with adenosine alone, and adenosine receptor antagonists did not block the potentiation. Therefore, although an adenosine-mediated decrease in excitatory synaptic transmission occurs during the temperature increase, it is unrelated to the potentiation. Likewise, *N*-methyl-D-aspartate receptor activation is not required, as *N*-methyl-D-aspartate receptor antagonists do not influence this form of potentiation.

In summary, we propose that transiently increasing brain slice temperature represents a novel way to induce synaptic plasticity in the hippocampus, and may provide a paradigm to elucidate additional cellular mechanisms involved in functional plasticity.
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Key words: adenosine, CA1, adenosine receptors, synaptic plasticity, long-term potentiation, temperature.

Many studies of synaptic plasticity have focused on the hippocampus as a model system, because many of the glutamatergic pathways within this brain region exhibit long-lasting modifications of synaptic transmission. The first form of synaptic plasticity to be discovered, and still the most commonly studied, is long-term potentiation (LTP).[3] For example, tetanic stimulation of the Schaffer collateral/commissural pathway to the CA1 region of the hippocampus results in a long-lasting enhancement of synaptically evoked responses.[31] In addition to stimulation-induced LTP, other types of physiological or pharmacological treatments can result in long-term changes in synaptic transmission in CA1; these include cAMP-induced LTP[13,27,32] and anoxic LTP.[8,9] In some cases, these types of plasticity share common mechanisms with stimulation-induced LTP, such as *N*-methyl-D-aspartate (NMDA) receptor activation and a rise in intracellular calcium (stimulation-induced LTP[22]; anoxic LTP[7,9,17]). Similarly, the late phase of stimulation-induced LTP,[26] and cAMP-induced LTP both depend upon activation of protein kinase A.[13] However, while some events necessary to the generation of hippocampal LTP have been well established,[22] other aspects of the cellular mechanisms underlying synaptic plasticity in the hippocampus remain unknown.

In a previous study we characterized the effects of changing the incubation temperature on synaptic transmission in the CA1 region.[23] Increasing the temperature from 32.5 to 38.5°C resulted in a profound (> 60%) decrease in synaptic transmission in CA1 of the hippocampus, and this inhibition was largely the consequence of adenosine acting at presynaptic A_1 receptors to depress transmitter release. Upon returning the temperature to the baseline recording temperature, the field excitatory postsynaptic potential (fEPSP) recovered completely. However, we noted that the fEPSP recovered occasionally to an amplitude which was potentiated with respect to the initial baseline, and remained potentiated for the duration of the recording. In the present study we focus on producing this potentiation more reliably, and on characterizing the mechanisms underlying this unusual form of potentiation with respect to the adenosine-mediated inhibition that occurs during the temperature increase. The current results were presented previously in abstract form.[24]

EXPERIMENTAL PROCEDURES

Most of the methods used have been described previously in detail[23] and are outlined briefly here. Housing and treatment of all animals were in accordance with protocols approved by the University of Colorado Animal Care and Use Committee, and were designed to minimize any animal suffering as well as the number of animals used in this study.

Slice preparation

Transverse hippocampal slices (400 μm) were obtained from six- to eight-week-old Sprague–Dawley rats using standard procedures. The artificial cerebrospinal fluid (CSF) contained (in mM): NaCl 126.0, KCl 3.0, $MgSO_4$ 1.5, $CaCl_2$ 2.4, NaH_2PO_4 1.2, $NaHCO_3$ 25.9 and D-glucose 11.0, and was bubbled continuously with a 95%O_2/5%CO_2 mixture. Slices were incubated undisturbed at 32.5°C or 22°C for 90 min before electrophysiological recording.

Electrophysiological recording

All slices were submerged in oxygenated artificial CSF and continuously superfused at 2 ml/min. The extracellular fEPSP was recorded from the CA1 region of the stratum radiatum using glass micropipettes

†To whom correspondence should be addressed. Tel.: +1-303-315-7584; fax: +1-303-315-4814.

E-mail address: susan.masino@uchsc.edu (S. A. Masino).

Abbreviations: ANOVA, analysis of variance; APV, DL-2-amino-5-phosphonovaleric acid; CSF, cerebrospinal fluid; fEPSP, field excitatory postsynaptic potential; LTP, long-term potentiation; NMDA, *N*-methyl-D-aspartate.

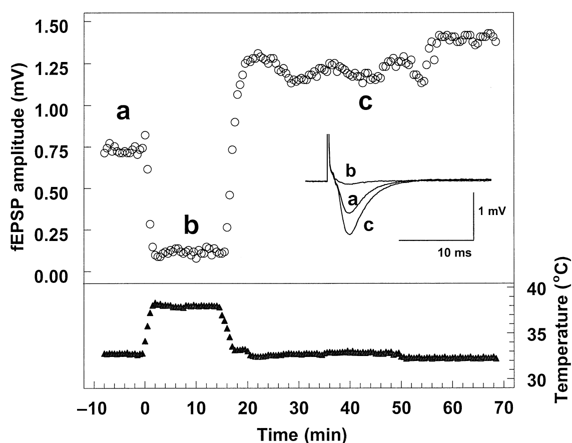

Fig. 1. Temperature-induced potentiation of evoked field excitatory postsynaptic potentials. The effects of a transient increase in the chamber temperature from 32.5 to 38.5°C (bottom; ▲) on fEPSP amplitude (top; ○) in the CA1 region of a hippocampal slice are illustrated. Synaptic responses evoked from this slice at the time points denoted by letters (a, b and c) are displayed in the inset. The chamber temperature was recorded with a small thermistor placed directly in the recording chamber along with the tissue slice. The amplitude of the fEPSP decreased significantly when the temperature was increased, and recovered to a potentiated level when the temperature was returned to the initial recording temperature. The potentiated response persisted for the duration of the recording.

(10–15 MΩ) filled with 3 M NaCl. A concentric bipolar electrode was used to stimulate the Schaffer collaterals in stratum radiatum at 30 s intervals. The pulse duration was 100 μs, and the intensity was set to evoke fEPSP responses that were less than 50% of the maximal fEPSP. All changes in the fEPSP amplitude were calculated with respect to the baseline fEPSP amplitude just prior to the temperature manipulation. Data were digitized and stored in the computer for later analysis. All data are reported as the mean ± S.E.

Temperature manipulation

The initial recording temperature was always the same as the incubation temperature. After establishing a stable baseline recording (less than a 10% change in the fEPSP amplitude over 10 min), the temperature of the superfusion medium was increased quickly (approximately 3.5°C/min; see Fig. 1) from the baseline recording temperature of 32.5 to 38.5°C, or from a baseline recording temperature of 22.0 to 28.0°C. In other experiments the temperature was lowered from 32.5 to 26.5°C. Temperatures were controlled within 0.5°C with an in-line heater and thermostatic controller (Warner Instruments, TC 324B, Hamden, CT). The change in temperature was maintained for 15 min, and the temperature was then returned to the initial recording temperature at the same rate.

Drug application

With the exception of adenosine, all drugs were superfused for a minimum of 12 min before increasing the temperature, and superfused continuously for the remainder of the experiment. Adenosine (60–80 μM) was superfused for 15 min to mimic the depressant effects of endogenous adenosine released as a consequence of increased temperature.

Data analysis

Paired and unpaired Student's *t*-tests were employed as indicated, as well as a one-way repeated measures ANOVA. Significant was set at $P < 0.05$.

Materials

All drugs and artificial CSF constituents were obtained from Sigma (St. Louis, MO).

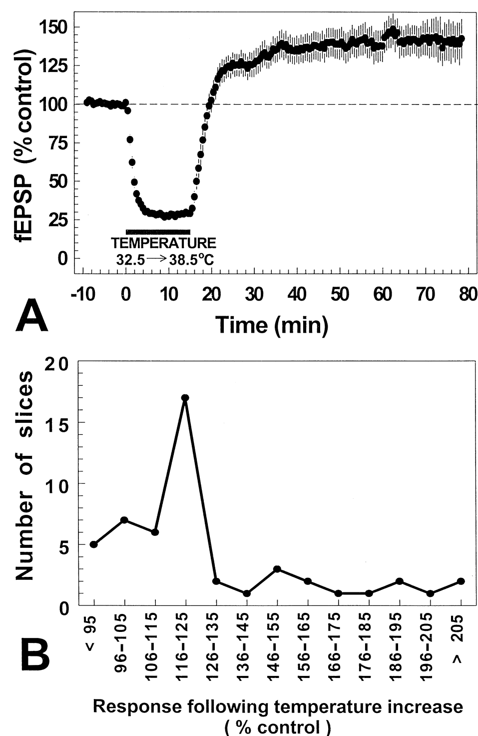

Fig. 2. Average temperature-induced potentiation. (A) On average, the fEPSP amplitude was reduced to 29 ± 2.5% ($n = 50$) of the control value by the temperature increase, and recovered to 130 ± 6.0% when the temperature was returned to baseline. The response remained potentiated for the duration of the recording, and in most slices was followed for at least 1 h. (B) The distribution of the degree of potentiation across the population of slices is illustrated. Within the set of 50 slices averaged in (A), 11 slices (22%) recovered from the temperature-induced depression (to 95 ± 3.8% of the control fEPSP) but did not show any potentiation. The remaining 39 slices (78% of those tested) recovered to an average of 140 ± 6.8% of the control fEPSP. While the majority of slices exhibited a potentiation of approximately 20%, 11 slices potentiated by more than 50%, and three slices potentiated to a level more than 200% above the control fEPSP.

RESULTS

Increasing the temperature from 32.5 to 38.5°C resulted in a significant decrease in the fEPSP evoked by stimulation of the Schaffer collateral and commissural inputs to the CA1 region. On average, the fEPSP was reduced to 29 ± 2.5% of the initial amplitude, an effect that was readily reversible upon decreasing the temperature back to the initial recording temperature. However, as illustrated in Fig. 1, the fEPSP amplitude often recovered to a level that was significantly potentiated with respect to the original baseline (the average response after 15 min of recovery was 130 ± 6.0% of control). This potentiation was apparent immediately, and the potentiated fEPSP was maintained for the duration of the recording, in some cases over 1 h. Similar effects were observed in a majority of the slices tested with this protocol (39/50). The average response of all 50 slices is shown in Fig. 2, and illustrates the persistence of the potentiation with no apparent decrement for at least 60 min following the return to 32.5°C.

To determine whether the potentiation reflected a change in synaptic transmission (as opposed to a change in presynaptic excitability), the change in the slope of the presynaptic fiber spike induced by the temperature increase was compared to the corresponding change in the fEPSP. There was no

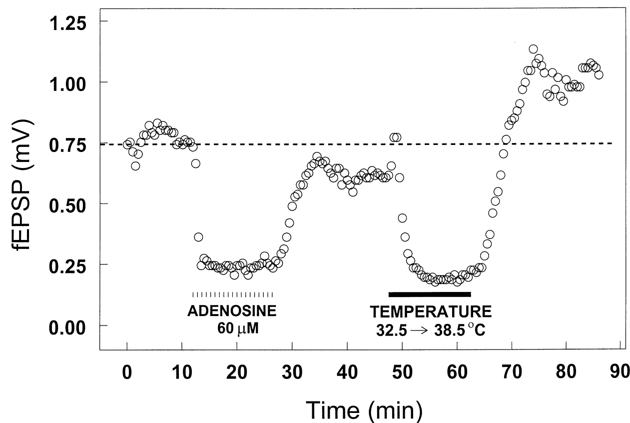

Fig. 3. Adenosine superfusion does not produce potentiation. In this individual example, a slice was superfused with adenosine (60 μM) for 15 min to mimic the inhibition observed during the temperature increase. There was no indication of any potentiation after the adenosine application, but an obvious and immediate potentiation after a subsequent temperature increase in the same slice. In a group of slices, there was no difference in the magnitude of the decrease caused by the temperature increase (reduced to 24 ± 7.3% of control, $n = 8$) vs adenosine application (reduced to 18 ± 7.3% of control, $n = 5$; n.s.), but a significant difference in the amplitude of the fEPSP following recovery (134 ± 12% vs 93 ± 7.3%, respectively; $P < 0.03$).

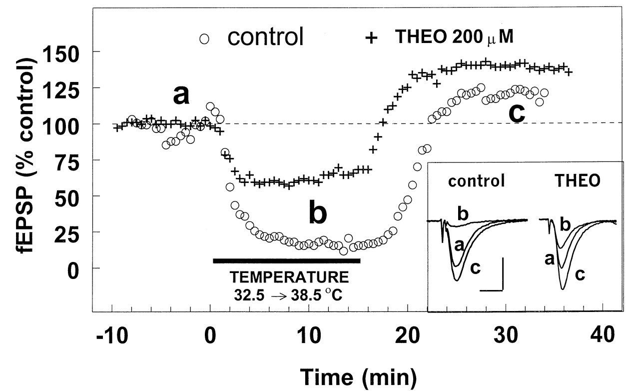

Fig. 4. Adenosine receptor activation is not necessary for temperature-induced potentiation. Because the decrease in fEPSP amplitude in response to the temperature increase is largely mediated by an increase in extracellular adenosine acting on inhibitory presynaptic adenosine receptors,[23] we blocked adenosine receptors with theophylline (THEO), a non-selective adenosine receptor antagonist, to determine whether adenosine receptor activation is critical to the temperature-induced potentiation. This figure shows the effects of a transient temperature increase on the response of a control slice and a slice treated with theophylline (both slices were obtained from the same animal). Both slices exhibited significant temperature-induced potentiation. Synaptic responses recorded from both slices at time-points a, b and c are illustrated in the inset (scale bars = 10 ms and 0.5 mV). As has been shown previously,[14,23] theophylline (200 μM) significantly reduced the temperature-induced decrease in the fEPSP (control: 89 ± 2.1%, $n = 9$; theophylline: 40 ± 4.4%, $n = 6$, $P < 0.0001$). However, theophylline superfusion had no significant effect on the magnitude of the subsequent potentiation (control: +12 ± 2.7%, $n = 9$; theophylline: 21 ± 9.0%, $n = 6$, n.s.).

significant change in the slope of the afferent fiber volley (472 ± 172 mV/ms during control vs 490 ± 166 mV/ms following the temperature change, $n = 3$, n.s., paired t-test) in a subset of slices that exhibited highly significant potentiation of the fEPSP (250 ± 65% of control, $n = 3$, $P < 0.003$, paired t-test). Both the slope of the fiber spike and the magnitude of the fEPSP were measured 30 min after returning the temperature to the baseline value of 32.5°C. Input–output curves demonstrated that there was an increase in fEPSP amplitude across all stimulation voltages ($n = 6$, $P < 0.05$, one-way repeated measures ANOVA at 20%, 50%, 80% and 100% of the stimulation voltage producing the maximal fEPSP).

The decrease in synaptic transmission observed during the temperature increase is primarily mediated by an increase in extracellular adenosine acting on presynaptic A_1 receptors to inhibit glutamate release.[23] To determine whether adenosine by itself was sufficient to induce potentiation under these conditions, we superfused a group of slices with a concentration of adenosine that produced the same magnitude of inhibition as the temperature increase (60–80 μM adenosine). In paired experiments performed on the same group of slices there was no significant difference between the magnitude of the inhibition caused by adenosine (reduced to 18 ± 7.3% of control, $n = 5$) and the temperature increase (reduced to 24 ± 7.3% of control, $n = 8$; n.s., unpaired t-test). However, upon removing the adenosine or decreasing the temperature, there was a significant difference in the recovery of the fEPSP. The response was significantly potentiated after the temperature increase (+34 ± 12%; $n = 8$), but not after the adenosine application (−7.0 ± 7.3%; $n = 5$, $P < 0.03$, unpaired t-test). Although this was demonstrated in different slices, the lack of a persistent effect following adenosine, and potentiation following an increase in temperature could be demonstrated in a single slice (Fig. 3).

The decrease in fEPSP amplitude induced by increasing the temperature is largely due to extracellular adenosine acting at adenosine A_1 receptors[23] (see also Gabriel *et al.*[14]). To determine whether adenosine receptor activation is required for the temperature-induced potentiation, slices were superfused with theophylline (200–250 μM), a non-selective competitive adenosine receptor antagonist. Theophylline significantly reduced the temperature-induced decrease in the fEPSP; in control slices, the fEPSP was reduced by 89 ± 2.1% ($n = 9$), whereas in the presence of theophylline, a 40 ± 4.4% ($n = 6$) reduction was observed ($P < 0.0001$, unpaired t-test). However, theophylline superfusion did not reduce, and if anything increased the magnitude of the subsequent potentiation (21 ± 9.0%) relative to a paired group of control slices (12 ± 2.7%; n.s.; Fig. 4).

Significant potentiation was induced by a transient increase of 6°C (32.5 to 38.5°C; Fig. 2A), but not when slices were incubated at an initial temperature of 22°C and raised transiently to 28°C (fEPSP amplitude 30 min following the return to 22°C was 103.4 ± 1.8% of control, $n = 5$, n.s., paired t-test). Similarly, transiently cooling a separate set of slices by 6°C, from 32.5 to 26.5°C, did not produce any subsequent potentiation upon return to 32.5°C (99.4 ± 1.9% of control, $n = 5$, n.s., paired t-test). Thus, it appears that the temperature-induced potentiation is specific to temperature increases in a range starting above 30°C.

Stimulation-induced LTP in CA1 has been shown to require activation of NMDA receptors.[6] Therefore, we applied the competitive NMDA receptor antagonist DL-2-amino-5-phosphonovaleric acid (APV; 50 μM) before, during and after the temperature change to determine whether activation of NMDA receptors was necessary for the induction of this type of potentiation. This concentration of APV is sufficient to block completely stimulation-induced LTP in the CA1 region.[15] As we have shown previously,[23] antagonizing NMDA receptors during the increased temperature does

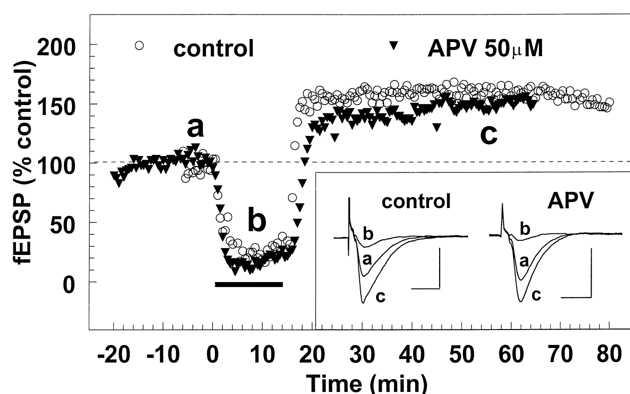

Fig. 5. The role of *N*-methyl-D-aspartate receptor activation in temperature-induced potentiation. Blocking NMDA receptors before, during and after the temperature increase did not alter the temperature-induced potentiation. The slice shown here was superfused throughout the recording period illustrated with 50 µM APV. The temperature increase from 32.5 to 38.5°C is indicated by the bar along the *x*-axis. There was no significant difference in either the magnitude of the inhibition seen during the temperature increase or the magnitude of the subsequent potentiation in control vs NMDA-treated slices (inhibition: 70 ± 6.7% vs 76 ± 11%, respectively, n.s.; potentiation: 34 ± 17% vs 23 ± 11%, respectively, n.s.; $n = 5$ for each group). Synaptic responses are illustrated in the inset from the time points indicated (scale bars = 10 ms and 1.0 mV).

not alter the magnitude of the inhibition seen during the temperature increase (reduced by 70 ± 6.7% in control slices vs 76 ± 11% in APV-treated; $n = 5$, n.s.) but also does not prevent the temperature-induced potentiation (Fig. 5). There was no significant difference in the magnitude of the potentiation observed in control vs APV-treated slices (32 ± 17% vs 23 ± 11%, respectively, $n = 5$ for each group; n.s., unpaired *t*-test).

DISCUSSION

These experiments demonstrate an immediate, robust and persistent potentiation of synaptic transmission in CA1 after a transient temperature increase. Raising the recording temperature from 32.5 to 38.5°C initiates a large adenosine-mediated decrease in synaptic transmission, as has been reported previously.[23] However, upon lowering the temperature back to 32.5°C, the fEPSP recovers to an amplitude that is potentiated with respect to the initial baseline. This temperature protocol represents a novel stimulus for the induction of synaptic plasticity in the hippocampal slice.

Although the adenosine released during the temperature increase produces a near-maximal inhibition of synaptic transmission, a similar inhibition of synaptic transmission produced by bath superfusion with adenosine is not sufficient to induce significant subsequent potentiation of the fEPSP response. In addition, the activation of adenosine receptors is not necessary for the expression of the temperature-induced potentiation, because the receptor antagonist theophylline had no effect on the potentiation. Finally, although activation of NMDA receptors is an essential initial step in several types of synaptic plasticity, it does not appear to play any role in temperature-induced potentiation, because the magnitude of the temperature-induced potentiation was unaffected by the presence of a competitive NMDA receptor antagonist.

Most experimental paradigms that induce LTP in hippocampal slices use specific patterns of synaptic stimulation, such as tetanic,[3] theta burst[20,21] or primed burst[29] stimulation. Other experimental approaches have demonstrated that under some conditions, an LTP-like process can occur in the absence of synaptic stimulation, as with potentiation induced by either pharmacological agents[16,32] or anoxia.[8,9] Temperature-induced potentiation might share common mechanisms with other forms of potentiation, such as an increase in intracellular calcium. In this case an increase in cell calcium must be independent of NMDA receptor activation, and may occur via release from intracellular stores.[30] Because of the depressant effect of endogenous adenosine, it is difficult to determine whether the potentiation occurs upon increasing the temperature, or upon its return to the baseline temperature. However, even in the presence of an adenosine receptor antagonist, the response is inhibited at the higher temperature, suggesting that either potentiation has not occurred, or it is masked by the inhibition until the temperature is returned to baseline.

The potentiation observed here shows striking similarity to that induced by application of cAMP.[32,33] Application of a membrane-permeable cAMP analog induces a decrease in synaptic transmission, similar to that seen during the temperature increase, and probably mediated by adenosine receptors.[4,10,33] Upon removal of the cAMP analog, a potentiation is observed which is immediate and long lasting.[32,33] In both the temperature-induced potentiation and the cAMP-induced potentiation, the magnitude of the potentiation does not decrease over time. This is unlike most forms of stimulation-induced LTP, where there is an initial decremental phase of potentiation that occurs immediately after the stimulation. One possible mechanism is that the temperature change independently increases cAMP levels, and is thus mechanistically similar to cAMP-induced LTP. In support of this, increased temperature has been shown to increase cAMP levels in other cell types.[19]

The sustained increases in the fEPSP response observed in these experiments were not paralleled by changes in the presynaptic fiber spike, confirming a synaptic locus for this phenomenon. Furthermore, the increases in fEPSP responses occurred throughout the response range, suggesting that these changes were not restricted to either threshold or maximal responses. Although previous studies have shown persistent postsynaptic hyperexcitability after either adenosine application or hypoxia,[11] this was not accompanied by changes in either the presynaptic fiber spike or fEPSP, and thus may reflect a different underlying mechanism.

Although previous studies in golden hamster[14] and rat[23] have demonstrated that temperature increases of the same magnitude used in the present study induce decreases in synaptic transmission that have been linked to direct release of adenosine through the nucleoside transporter, subsequent potentiation of the fEPSP was not specifically noted. However, in these previous studies, the rate of the temperature increase and decrease was considerably slower (approximately 1°C/min[23] compared to 3.5°C/min), and the magnitude of the fEPSP decrease was somewhat smaller, albeit not significantly, than that observed here (61% inhibition[23] vs 71% in the current experiments). While potentiation was observed occasionally in the previous study, it occurred in a small minority of slices. Thus, it appears likely that the rate of the temperature change may be an important variable in producing the potentiation. However, a temperature-induced potentiation of the population spike has been previously reported to occur with a much slower temperature

change (0.3°C/min),[5] and was observed only in slices from young, but not aged rats. The present experiments only evaluated young adult hippocampal slices, and the ability of the present paradigm to produce potentiation in aged animals has not been explored. Furthermore, the physiological relevance of this temperature-induced potentiation remains to be determined.

Previous studies have shown that adenosine can modulate plasticity in both *in vivo* and *in vitro* models of learning. Acute application of adenosine inhibits several forms of long-lasting plasticity, including LTP[1,2] (but see Ref. 25) and long-term depression (LTD).[18] In the current study, the adenosine released during the temperature increase clearly did not prevent expression of the potentiation, nor did direct application of adenosine alone induce potentiation. In the small number of slices where adenosine receptors were blocked, the subsequent potentiation was slightly enhanced, albeit not significantly. However, the trend in this direction is consistent with previous reports indicating that adenosine receptor blockade can enhance the induction of LTP.[12,28] Nevertheless, an interaction between adenosine and this form of plasticity appears weak at best.

CONCLUSIONS

A transient temperature increase produces two apparently unrelated effects. These include an adenosine-mediated synaptic depression, which is observed during the period when the temperature is increased, and a non-adenosine-mediated potentiation of glutamatergic transmission that is apparent as soon as the temperature is returned to baseline. This potentiation is persistent, and does not depend on activation of NMDA receptors for its initiation. A temperature increase may mobilize directly some cellular constituents that participate in the induction, the expression or the maintenance of persistent alterations in synaptic strength, and thus provide a valuable experimental paradigm for their elucidation.

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