2-Deoxyglucose–Induced Long-Term Potentiation of Monosynaptic IPSPs in CA1 Hippocampal Neurons

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Krnjević, Krešimir and Yong-Tao Zhao. 2-Deoxyglucose–induced long-term potentiation of monosynaptic IPSPs in CA1 hippocampal neurons. J. Neurophysiol. 83: 879–887, 2000. In previous experiments on excitatory synaptic transmission in CA1, temporary (10–20 min) replacement of glucose with 10 mM 2-deoxyglucose (2-DG) consistently caused a marked and very sustained potentiation (2-DG LTP). To find out whether 2-DG has a similar effect on inhibitory synapses, we recorded pharmacologically isolated monosynaptic LTP). To find out whether 2-DG has a similar effect on inhibitory synapses, we recorded pharmacologically isolated monosynaptic LTP. 2-DG was applied both in the presence and the absence of antagonists of inhibitory postsynaptic potentials (IPSPs; under current clamp) and synapses, we recorded pharmacologically isolated monosynaptic LTP. 2-DG was applied both in the presence and the absence of antagonists of N-methyl-D-aspartate (NMDA). In spite of sharply varied results (some neurons showing large potentiation, lasting for >1 h, and many little or none), overall there was a similar and significant potentiation of IPSP conductance, both for the early (at ~30 ms) and later (at ~140 ms) components of IPSPs or IPSCs: by 35.1 ± 10.25% (mean ± SE; for n = 24, P = 0.0023) and 36.5 ± 16.3% (for n = 19, P = 0.038), respectively. The similar potentiation of the early and late IPSP points to a presynaptic mechanism of LTP. Overall, the LTP was statistically significant only when 2-DG was applied in the absence of glutamate antagonists. Tetanic stimulations (in presence or absence of glutamate antagonists) only depressed IPSPs (by half). In conclusion, although smaller and more variable, 2-DG–induced LTP of inhibitory synapses appears to be broadly similar to the 2-DG–induced LTP of excitatory postsynaptic potentials previously observed in CA1.

INTRODUCTION

There have been numerous studies of long-term potentiation (LTP) at excitatory synapses (Bliss and Collingridge 1993; Larkman and Jack 1995; Wang et al. 1997), but only few on isolated inhibitory synapses (Komatsu 1994, 1996; Komatsu and Iwakiri 1993; Oda et al. 1995; Xie et al. 1995), including the hippocampus from mature guinea pigs (Xie et al. 1995) and very young rats (McLean et al. 1996). A major reason for this dearth of information is that inhibitory postsynaptic potentials (IPSPs), unlike excitatory ones (EPSPs), cannot be easily recorded as extracellular fields. Compelling evidence requires intracellular recording. Moreover, because inhibitory neurons can seldom be stimulated selectively (without concomitant activation of other cells and axons), IPSPs can be obtained independently of excitatory synaptic activity only if EPSPs are suppressed by blockage of glutamatergic synapses (Davies et al. 1990; Neuman et al. 1988). Previous studies have reported that such monosynaptic IPSPs in visual and hippocampal cortex of young rodents can be potentiated by tetanic stimulation; but the resulting LTP differs from LTP of EPSPs in being independent of N-methyl-D-aspartate (NMDA) receptor activation (Komatsu 1994; McLean et al. 1996; Xie et al. 1995) and variably affected by chelation of intracellular Ca^{2+} (cf. McLean et al. 1996; Xie et al. 1995).

Temporary replacement of glucose by 2-deoxyglucose (2-DG) very predictably elicits LTP of EPSPs in CA1 neurons (Tekkök and Krnjjević 1995, 1996). Although 2-DG suppresses glycolysis by selectively blocking hexokinase (Tower 1958), even prolonged removal of glucose has no comparable effect on EPSPs (Krnjević and Tekkök 1996). Like many other forms of LTP, 2-DG–induced LTP (2-DG LTP) is NMDA receptor dependent, but it is not suppressed by intracellular application of a chelator (Zhao and Krnjjević 2000).

Its very unusual characteristics (notably its unique independence of postsynaptic depolarization and [Ca^{2+}] increase) make 2-DG LTP an exceptionally interesting form of synaptic plasticity. Albeit without an obvious physiological correlate, the fact that a temporary metabolic disturbance causes such highly reproducible and sustained enhancement of synaptic transmission, apparently by a purely presynaptic mechanism, has a wider significance both for the understanding of LTP type plastic changes in general and possible pathological manifestations resulting from metabolic disorders.

In the present experiments, we examined the effects of 2-DG on monosynaptic inhibitory potentials (IPSPs) or currents (IPSCs; isolated pharmacologically by glutamate antagonists) recorded intracellularly from CA1 pyramidal layer neurons with sharp microelectrodes. A preliminary report of these results has appeared as an abstract (Krnjević and Zhao 1998).

METHODS

Young Sprague-Dawley male rats (110–180 g) were obtained from Charles River (St. Constant, Quebec, Canada). After decapitation under deep halothane or ether anesthesia, the brain was quickly removed and the hippocampus dissected out in ice-cold oxygenated saline. Transverse slices (400 μm thick) were cut with a Vibroslice (Campden Instruments, Loughborough, UK). They were kept for at least 1 h at room temperature in artificial cerebrospinal fluid (ACSF) containing (in mM) 124 NaCl, 3.0 KCl, 2.0 CaCl_2, 2.0 MgCl_2, 1.25 NaH_2PO_4, 26 NaHCO_3, and 10 glucose; being continually aerated with carbogen (95% O_2, 5% CO_2) the ACSF had a pH ~7.3. Slices were then transferred to a recording chamber where they were submerged under 0.1–0.2 mm of flowing carbogenated ACSF and kept at 34 ± 0.5°C.

The sharp microelectrodes were pulled from thin-walled borosilicate glass tubes (1.2 mm OD, WP Instruments, New Haven, CT). After filling with 3 M KCl or 4 M K acetate, they had resistances of 60–80 MΩ. In some electrodes, 10–50 mM QX-222 or QX-314 (Astra Pharma, Ontario, Canada) was also added.
FIG. 1. Example of 2-deoxyglucose (2-DG)-induced long-term potentiation (LTP) of monosynaptic inhibitory postsynaptic potential (IPSP). Sequence of traces (each is average of 8) was recorded with 4 M K acetate electrode. Times post various tests and resting potentials are indicated. A: initially, sharp excitatory postsynaptic potential (EPSP) is followed by biphasic IPSP. B: in presence of glutamate antagonists [45 μM 6,7-dinitroquinoxaline-2,3-dione (DNQX) and 50 μM D, L-aminophosphonovalerate (APV)] only biphasic IPSP remains. C: IPSP shows little change after wash in ACSF for 20 min, at start of 2-DG application. D: near end of 15 min exposure to 2-DG [in artificial cerebrospinal fluid (ACSF)], there is characteristic hyperpolarization (to −77 mV) and early IPSP especially is much reduced. E: although cell is still hyperpolarized 12 min after return to standard ACSF, both components of IPSP are much enhanced. F–H: after reapplication of DNQX and APV, both phases of IPSP remain potentiated. I: trace recorded 15 min after double tetanic stimulation (twice 100 Hz for 1 s) shows depression rather than further potentiation. J: IPSP was even more depressed after low-frequency stimulation (LFS); 1 Hz for 15 min. K: picrotoxin (200 μM) abolished early IPSP, leaving only trace of late IPSP. L: continuous paper trace illustrates time course of changes produced by 2-DG (in same neuron); note slow hyperpolarization and depression of IPSPs (transient deflections on bottom trace) during 2-DG application and their subsequent recovery and potentiation, as well as 3 tests of input resistance with 200-ms current pulses (shown on accelerated traces) that reveal 30% drop in resistance near the end of 2-DG application.

FIG. 2. IPSP/\(V_m\) plots for IPSPs illustrated in Fig. 1 show increase in slope as a result of 2-DG treatment. A and B: data are for early and late IPSP (measured at 20 and 190 ms from stimulus artifact, respectively). C: histograms of corresponding resting and IPSP conductances \((G)\) calculated as described in METHODS (±SE). Note both early and late \(G_{IPSP}\) are increased after 2-DG, and much reduced by 2 sets of tetanic stimulations (TET); there is little further change after 1-Hz stimulation for 15 min, but early \(G_{IPSP}\) is selectively suppressed by picrotoxin (200 μM).
Half-maximal synaptic responses were evoked by stimuli applied at intervals of 20 s through insulated nickel-chromium wires placed in the stratum radiatum. To obtain monosynaptic IPSPs/IPSCs, excitatory synaptic transmission was suppressed by adding glutamate antagonists to the superfusate (Davies et al. 1990; Neuman et al. 1988). The agents used were either the wide-spectrum blocker kynurenate (Sigma; 2–3 mM) or a combination of 6,7-dinitroquinoxaline-2,3-dione (DNQX; 25–50 μM) and d,l-aminophosphonovalerate (APV; 40–50 μM). In several experiments, we also attempted to elicit tetanic LTP of the monosynaptic IPSPs/IPSCs by high-frequency stimulation of stratum radiatum (2 100-Hz volleys, each lasting 1 s, separated by a 20-s interval).

For current-clamp recordings of IPSPs, the signals were amplified by an Axoclamp 2 (Axon Instruments, Burlingame, CA) in bridge mode. For voltage-clamp recordings of IPSCs, the signals were amplified in the discontinuous clamp mode, operating at a frequency of 3 kHz, a gain of 25 nA/mV, and an upper bandwidth limit of 300 Hz; the usual precautions were taken to optimize the efficacy of the clamp. In all experiments, IPSPs/IPSCs were recorded over a range of potentials so that IPSP/IPSC conductances (GIPSP and GIPSC) and reversal potentials (Vr) could be compared before and after a 2-DG application. Thus GIPSP was obtained directly from the slope of IPSC/Vm plots of voltage-clamp data. But for current-clamp data, GIPSP was calculated from the following relation: IPSP/Vm = GIPSP/(GIPSC + Grest) (Takeuchi 1977), where Grest (resting conductance) was obtained from plots of Vm as function of injected currents. All slopes were calculated by fitting linear regressions to the data. Changes in slopes after 2-DG applications were expressed as percentage of the initial control slope; the standard error of the ratio of post–2-DG to control GIPSP (GIPSP/Grest) was taken as [V2 + V1(V2/G2)^1/2]/G2 (Mellor 1931), where V is the variance of the corresponding slope.

### Experimental protocols

**IN CURRENT-CLAMP MODE.** After a period of stable recording of control isolated IPSPs, 2-deoxy-d-glucose (2-DG; Sigma) was applied by equimolar replacement of 10 mM glucose in ACSF. Superfusion

### TABLE 1. Changes in early and late components of monosynaptic IPSPs and IPSCs observed ~30 min after end of 2-DG applications (in absence or presence of glutamate antagonists)

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<thead>
<tr>
<th>2-DG Applied in Absence of GLU Antagonists</th>
<th>2-DG Applied in Presence of GLU Antagonists</th>
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<tr>
<td>Early IPSPs/IPSCs (at ~30 ms)</td>
<td>Late IPSPs/IPSCs (at ~140 ms)</td>
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<tr>
<td>Mean increases in GIPSP</td>
<td>39.8 ± 31.5 (5)</td>
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<tr>
<td>Mean increases in GIPSC</td>
<td>32.4 ± 14.3 (10)*</td>
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Values are mean increases ± SE as percent above initial baseline; number of cells is in parentheses. Data under current clamp and voltage clamp from cells exposed to 2-DG in the absence and presence of glutamate antagonists are presented separately. For IPSCs, the values of G were calculated from the corresponding plots of IPSP vs. Vm (as described in methods). IPSPs, inhibitory postsynaptic potentials; IPSCs, inhibitory postsynaptic currents; 2-DG, 2-deoxyglucose; GLU, glutamate. *P < 0.05 (for significant increase).
with standard glucose-containing ACSF was later resumed, and recording continued for 30–60 min. In some experiments, glutamate antagonists were present throughout. In others, the slice was “washed” with ACSF for 20–30 min to remove the antagonists before applying 2-DG, to minimize interference with any NMDA-sensitive effects of 2-DG. Although a longer period of wash might have been desirable, previous evidence shows that the LTP-blocking action of APV can be reversed by washing for periods of only 20–30 min (Wigström et al. 1986). The glutamate antagonists were reapplied subsequently. Before ending, picrotoxin (Sigma; 100–200 μM) was applied to confirm that the early IPSP was indeed GABA_A receptor mediated; typically, the late IPSP was very small or absent after such prolonged recordings.

UNDER VOLTAGE CLAMP. The pharmacologically isolated IPSCs were recorded over a range of holding potentials (V_h) before the start of the 2-DG application, and for 30–60 min after the return of glucose-containing ACSF. In several experiments, the slices were “washed” to remove kynurenate or APV and the voltage-clamp interrupted during the 2-DG application to minimize block of any NMDA receptor and/or voltage-sensitive effects of 2-DG. The glutamate antagonists and the voltage clamp were then reapplied.

Means ± SE are given throughout. The significance of differences was assessed by Student’s t-test.

RESULTS

Intracellular penetrations into the stratum pyramidale of CA1 yielded a total of 24 stable recordings, adequate for the purpose of these experiments: 11 were under current clamp and 13 under voltage clamp. As described under METHODS, monosynaptic IPSPs or IPSCs were isolated by bath application of glutamate antagonists, and 2-DG was applied for periods of 11–22 min, either after washing out antagonists or in their presence.

Observations under current clamp

The recordings were made with K acetate- or KCl-containing sharp microelectrodes.

2-DG APPLIED IN THE ABSENCE OF GLUTAMATE ANTAGONISTS. Figure 1 illustrates IPSPs recorded from a CA1 neuron. The initial trace (A), obtained at the initial resting membrane potential (V_m) of −69 mV while superfusing with standard ACSF, shows a characteristic EPSP/IPSP sequence evoked by stratum radiatum stimulation. After addition of DNQX (45...
2-deoxyglucose-induced LTP of IPSPs

μM) and APV (50 μM), only a biphasic IPSP remained (B), which was recorded at several levels of $V_m$ (see IPSP/$V_m$ plots in Fig. 2, A and B). Superfusion with blocker-free ACSF was resumed for 20 min to wash out APV before 10 mM 2-DG (replacing glucose) was applied for 15 min (Fig. 1, C and D); note the hyperpolarization typically elicited by 2-DG (Zhao et al. 1997). In the present case, it did not fully reverse after the return of standard (glucose-containing) ACSF (E). The glutamate antagonists were then reapplied to eliminate any EPSP, and further traces were recorded for over 1 h from the end of the 2-DG application. The traces F–H clearly show a marked potentiation of the monosynaptic IPSP, in spite of some persistent hyperpolarization. A true and sustained potentiation is further suggested by the steeper IPSP/$V_m$ slopes for data obtained at 25 and 65 min post–2-DG, both for the early and the late IPSP (measured at 20 and 190 ms from the stimulus artifact, Fig. 2, B and A, respectively); from these slopes, we calculated (see METHODS) the values of $G_{IPSP}$ illustrated in Fig. 2C.

Tetanic stimulation did not cause any further potentiation, but rather depressed the IPSP to near its initial amplitude (Figs. 1I and 2C), and low-frequency stimulation (LFS) had little effect (Figs. 1J and 2C). Picrotoxin (200 μM) fully suppressed the remaining early IPSP (Figs. 1K and 2C). The continuous paper trace in Fig. 1L shows the time course of the initial changes in IPSPs (small downward deflections), as well as the hyperpolarization and resistance fall elicited by 2-DG.

For most of these five cells, the changes in $G_{IPSP}$ were less pronounced. Thus in Fig. 3, although inset traces from two cells appeared larger 21 (A) and 28 (B) min after treatment with 2-DG, in the corresponding IPSP/$V_m$ plots (data for early IPSP, measured at $\approx$30 ms) there was a substantial shift to the left and only a small increase in slope. Much of the apparent potentiation of the IPSP can therefore be ascribed to a negative shift in reversal potential. When $G_{IPSP}$ was calculated from these slopes (taking into account changes in resting $G$, as described in METHODS) the post-2-DG changes were 21% increases and decreases, respectively, for the cells in Fig. 3, A and B. For this group of five cells treated with 2-DG in the absence of glutamate antagonists, only three showed a clear LTP of $G_{IPSP}$; the mean data (summarized in Table 1) indicate post–2-DG $G_{IPSP}$ increases by 40% for the early IPSP and 72% for the late IPSP (measured at $\approx$30 and 200 ms, respectively), but these were not statistically significant.

2-DG APPLIED IN THE ABSENCE OF GLUTAMATE ANTAGONISTS. In six cells, post–2-DG changes in $G_{IPSP}$ ranged from 0 to 107% for the early IPSP and from $-40$ to 83% for the late IPSP. From Table 1, where these data are also summarized, the mean increases were by 43% for the early IPSP (just significant) and only 3.8% for the late IPSP.

Observations under voltage clamp

All these recordings were done with KCl-containing sharp microelectrodes [in some cases with QX-314 added to depress the late, GABA$_A$ receptor–mediated event (Nathan et al. 1990)]. To have more comprehensive information about 2-DG–induced changes, IPSCs were routinely recorded over a wide range of holding potentials, before and at several intervals after the usual applications of 2-DG (substituted for glucose for 10–20 min).

FIG. 5. Histograms summarize post–2-DG increases in $G_{IPSC}$ indicated by corresponding IPSC/$V_m$ plots in Fig. 4. Error bars indicate SE, calculated as described in METHODS.

2-DG APPLIED IN THE ABSENCE OF GLUTAMATE ANTAGONISTS. Twelve neurons were studied. Representative data are illustrated by the traces (A–C) and IPSC/$V_m$ plots (D–F) of Fig. 4. These monosynaptic IPSCs were all recorded from one neuron while applying DNQX and APV: in A is a control series; B and C, obtained 25 and 65 min after superfusing 2-DG (in antagonist-free ACSF) for 21 min, show marked and lasting enhancement of the IPSCs. From these and other data, the amplitude of the IPSCs (measured at 3 points: 6, 30, and 100 ms after the stimulation artifact) was plotted as function of $V_m$; the corresponding plots for data obtained at 25, 45, and 65 min post-DG [as well as the initial, pre–2-DG control data (open circles and thicker lines)] are shown for the very early IPSC (D, measured at 6 ms), the early IPSC (E, at 30 ms), and the later IPSC (F, at 100 ms). The changes in $G_{IPSC}$ calculated from the slopes of these plots are given by the histograms of Fig. 5: LTP-like major increases of the earlier components were sustained for >1 h; but the small late component, although it also increased initially, later ran down owing to the presence of QX-314 in the electrode.

Comparable data from another neuron in this group are illustrated as IPSC/$V_m$ plots in Fig. 6, A–C; the changes in $G_{IPSC}$ are summarized by the histograms in Fig. 6D. In agreement with the current-clamp experiment of Figs. 1 and 2, tetanic stimulation applied 1 h post–2-DG abolished the 2-DG–induced potentiation. Although the changes in $G_{IPSC}$ shown by these 12 neurons varied greatly (between $-63$ and 320%), the early $G_{IPSC}$ (at 30 ms) increased significantly by 32% (P <
Although comparable, the 40% increase in late \( G_{IPSC} \) was not significant.

**2-DG APPLIED IN THE PRESENCE OF GLUTAMATE ANTAGONISTS.** Two of the three cells in this group showed 30–80% increases in \( G_{IPSC} \). The IPSCs of the third cell were sharply and increasingly depressed post–2-DG; IPSC/\( V_m \) plots of these data are illustrated in Fig. 7, A–C, as a possible example of 2-DG–induced long-term depression (LTD). The mean change for these three cells was not significant (Table 1).

**Overall effects of 2-DG on both IPSPs and IPSCs**

Notwithstanding the great variability of individual results, ranging from apparent LTD to large LTP, overall there was a clear indication of a significant and similar post–2-DG potentiation of both early and late components of \( G_{IPSP} \) (Table 2).

**EARLY IPSP/C.** Changes in early \( G_{IPSP} \) observed >30 min post–2-DG in 24 neurons (under either current or voltage clamp) gave a very significant mean increase by 35.1 ± 10.25% (mean ± SE; for \( t = 3.42, P = 0.0023 \)). Although 2-DG was applied for times varying between 10 and 20 min (15.7 ± 0.61 min), there was no correlation between the changes in \( G_{IPSP} \) and the duration of 2-DG application (\( r = 0.034; P = 0.875 \)).

For 15 of these cells, 2-DG was applied in the absence of glutamate antagonists: the corresponding mean increase was by 34.9 ± 13.52% (\( P = 0.022 \)). For the other nine cells, exposed to 2-DG in the presence of the antagonists, the mean change was very similar (35.4 ± 16.5), but its significance was dubious (\( P = 0.064 \)). These data are summarized in Table 3.

**LATE IPSP/C.** Changes in late \( G_{IPSP} \) were observed 35 ± 2.3 min post–2-DG in 19 neurons (not 24 because in 5 neurons late IPSPs were too small to be analyzed). Although even more variable than the data for the early IPSP/C, these estimates gave a virtually identical overall mean increase by 36.5 ± 16.3% (\( P = 0.038 \)). These changes also showed no correlation to the duration of 2-DG applications (\( r = 0.237; P = 0.33 \)). On the other hand, there was a highly significant correlation between changes in late and early IPSP/Cs: for \( n = 19 \), \( r \) was 0.974 (\( P = 10^{-6} \)).

The mean potentiation by 2-DG was more pronounced when it was applied in the absence of glutamate antagonists (increase by 55.9 ± 21.9%; for \( n = 11 \), \( P = 0.029 \)); whereas applications in their presence produced an obviously nonsignificant mean change of 9.8 ± 22.4% (for \( n = 8 \)).

**Posttetanic LTP**

While recording monosynaptic IPSPs or IPSCs from six cells, we attempted to elicit LTP by tetanic stimulation. In four cases, the tetani were applied in the presence of glutamate antagonists, in the other two, in their absence. Whether tested...
“pure” IPSPs, uncontaminated by EPSPs, which limits the numbers of useful recordings, especially when comparing with experiments on field EPSPs.

Although an unevenly reproducible phenomenon, 2-DG-LTP of these inhibitory synapses is more consistent than appears at first sight. When all the changes in $G_{IPSC}$ obtained under current and voltage clamp were viewed together, significant increases were evident for both the early and the late IPSP/C. The relatively modest potentiation [on the average ($\approx 35\%$) only $\sim \frac{1}{2}$ that typically seen with field EPSPs (Tékók and Krnjević 1995)] may indicate a less pronounced action of 2-DG on inhibitory terminals, but it may be a reflection of the technical problems and long duration of the experiments.

**NMDA receptor dependence of 2-DG-LTP**

In some cells, IPSPs or IPSCs were potentiated even when 2-DG was applied in the presence of glutamate antagonists. But when all the data were grouped accordingly (Table 3), although the mean potentiation was similar ($\approx 35\%$) in both groups, it was significant (for both early and late IPSP/C) only for the cells exposed to 2-DG in the absence of antagonists. The less consistent changes seen when antagonists were present suggest that NMDA receptors play some role in 2-DG-LTP induction of IPSPs; this conclusion, however, can only be tentative in view of the somewhat smaller number of observations in the second group (9 vs. 15 for the early IPSP/C). These results are thus only in partial agreement with the experiments on EPSPs, where 2-DG-LTP was consistently prevented by APV (Tékók and Krnjević 1995). Some residual block of NMDA receptors, unavoidable because of the relatively short periods of wash out, may in part be responsible for the smaller mean LTPs observed in the present experiments.

**Mechanism of 2-DG-LTP of IPSPs**

Is 2-DG-LTP initiated in the postsynaptic neuron? We know that 2-DG raises the cytoplasmic [Ca$^{2+}$] of CA1 pyramidal neurons (Tékók et al. 1999). Therefore Wang et al.’s (1995) finding that injections of the $\alpha$-subunit of the calcium/calmodulin-dependent protein kinase II (CAMKII) into CA1 pyramidal cells elicits a lasting potentiation of monosynaptic fast IPSPs could explain our observations. Because of several discrepancies, we concluded that the rise in [Ca$^{2+}$] was probably not the main trigger for 2-DG-LTP of EPSPs; but this does not

**TABLE 2.** Global data show that 2-DG elicits similar long-term potentiation of early and late IPSP or IPSC

<table>
<thead>
<tr>
<th>Overall mean increase in $G_{IPSP/IPSC}$, %</th>
<th>Early IPSPs or IPSCs (at 32.1 ± 1.68 ms)</th>
<th>Late IPSPs or IPSCs (at 147 ± 11.6 ms)</th>
</tr>
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<tbody>
<tr>
<td>$G_{IPSP/IPSC}$, %</td>
<td>35.1 ± 10.25 (24)*</td>
<td>36.5 ± 16.3 (19)$^\dagger$</td>
</tr>
<tr>
<td>Time when measured</td>
<td>34.5 ± 1.95</td>
<td>34.6 ± 2.26</td>
</tr>
<tr>
<td>Duration of 2-DG</td>
<td>15.7 ± 0.61</td>
<td>15.7 ± 0.65</td>
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<td>application, min</td>
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Values are means ± SE calculated from both current- and voltage-clamp data, obtained with 2-DG applications in absence and presence of glutamate antagonists. Number of cells is in parentheses. The values of $G$ were obtained as described in the legend of Table 1. For abbreviations, see Table 1. *P < 0.01, †P < 0.05.
A postsynaptic mechanism of expression cannot be easily reconciled with the strikingly similar 2-DG-LTP of the early and late components of the IPSP/C. Although generated by quite different receptors and ionic channels (Krnjević 1997), they showed strongly correlated changes. Because 2-DG is unlikely to have a similar effect on the very different GABA_A and GABA_B receptors, a presynaptic mechanism must be viewed as a serious possibility; in keeping with a similar conclusion about 2-DG-LTP of EPSPs (Tekkök et al. 1999; Zhao and Krnjević 2000), the most likely target is syntaxin, which is involved in synaptic vesicle docking (Bennett et al. 1992), as well having NMDA receptor properties (Smirnova et al. 1993).

**Tetanic LTP of monosynaptic IPSPs**

The main point of interest is that our attempts to elicit posttetanic LTP failed: the consistent effect being sustained depression. Because the majority of the tests were done in the presence of an NMDA antagonist, these results partly disagree with those of previous studies of monosynaptic IPSPs. In visual cortex (Komatsu 1994; Komatsu and Iwakiri 1993) and in CA1 (Xie et al. 1995) or CA3 (McLean et al. 1996), tetanic LTP was seen more often than LTD in the presence of NMDA antagonists. The apparent difference may be owing to the small number of tests in our experiments; or a combination of dissimilar recording site, species, temperature and age in the earlier experiments.

In conclusion, in these experiments on monosynaptic IPSPs and IPSCs (isolated by pharmacological block of glutamate ionotropic receptors), evidence was obtained that 10- to 20-min applications of 2-DG can induce a LTP-like sustained enhancement of inhibitory transmission. The comparable enhancement of early and late IPSPs favors a pre-rather than a postsynaptic mechanism of LTP. In this respect, and also the nonsignificant potentiation when 2-DG was applied in the absence of glutamate antagonists, this effect resembles that produced on EPSPs. Thus albeit less pronounced and more variable, these findings suggest that 2-DG has similar effects on excitatory and inhibitory synapses in the hippocampal CA1 region.

We are grateful to Astra Pharma Inc., Ontario for a supply of QX-314. Y. T. Zhao was on leave from the Neurology Department, Liu Hua Qiao Hospital, Guang Zhou, China.

This research was financially supported by the Medical Research Council of Canada.

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Received 2 July 1999; accepted in final form 8 October 1999.

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**TABLE 3. 2-Deoxyglucose–induced long-term potentiation of IPSPs and IPSCs is sensitive to glutamate antagonists**

<table>
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</tr>
<tr>
<td>Mean increases in G_IPSP/IPSC- %</td>
<td>34.9 ± 13.5 (15)*</td>
<td>55.9 ± 21.9 (11)*</td>
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<tr>
<td>Time post–2-DG, min</td>
<td>32.0 ± 2.4</td>
<td>33.1 ± 3.1</td>
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<tr>
<td>Duration of GLU application, min</td>
<td>15.2 ± 0.88</td>
<td>15.1 ± 0.95</td>
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