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Postsynaptic effects of GABAergic synaptic diversity: regulation of neuronal excitability by changes in IPSC variance

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Abstract

GABAergic synaptic inputs to principal cells are heterogeneous in terms of their anatomical, molecular and physiological properties. Whether diversity in GABAergic synaptic inputs affects the efficacy of GABAergic inhibition is not understood. Here we show that alterations in the heterogeneity of IPSC populations arriving at single cells can significantly modify the effects of GABAergic inputs on neuronal excitability. The effects of IPSC diversity were examined in a computational model that incorporated experimentally measured values for spontaneous IPSCs and CA1 pyramidal cell electrophysiological properties. The simulations showed that increased variance in the conductance or decay of IPSCs could potently modulate the firing rate of the postsynaptic cells. The actual direction of the IPSC variance-induced modulation in postsynaptic cell discharges depended on the mean IPSC conductance and mean decay time constant around which the variance was introduced, as well as on the degree of depolarization and firing of the postsynaptic cell. Further analysis of the underlying mechanisms determined that these effects of IPSC variance on neuronal excitability were entirely predicted from the non-linear actions of IPSCs on action potential generation. The variance effects on neuronal excitability could be strong enough to overcome even large changes in mean IPSC conductance, demonstrating that increased mean synaptic conductance (or increased mean IPSC or IPSP) alone does not necessarily imply a more effective inhibition, a finding which has important implications for epilepsy research. These data show that the degree of heterogeneity of the GABAergic synaptic inputs to principal cells can powerfully modulate the efficacy of GABAergic inhibition. The results indicate the functional importance of the diversity of interneurons in cortical and hippocampal circuits, and suggest that plastic changes in GABAergic synaptic diversity may modulate neuronal excitability under both normal and pathological conditions.

Keywords: $GABA_A$; IPSC; Interneuron; Epilepsy; Diversity

1. Introduction

Many different types of hippocampal GABA-releasing interneurons (reviewed in Freund and Buzsáki, 1996) appear to have evolved to regulate principal cell activity through a large matrix of possible mechanisms (Hausser and Clark, 1997; Destexhe et al., 2001; McBain and Fisahn, 2001). Perisomatic GABAergic synaptic inputs arising from basket cells and axo-axonic cells, by virtue of their close proximity to the action potential generation site and their large conductance, can powerfully modulate the threshold for activation of principal cells, and they are also effective in synchronizing sub- and suprathreshold membrane potential oscillations in spatially distributed postsynaptic neurons (Qian and Sejnowski, 1990; Soltesz and Deschênes, 1993; Ylinen et al., 1995; Cobb et al., 1995; Traub et al., 1998). In contrast, dendritic GABAergic inputs originating from distinct interneuron types are ideally positioned to locally modulate excitatory synaptic inputs, prevent backpropagation of fast action potentials in the dendrites and inhibit dendritic Ca^{2+} electrogenesis (Buzsáki et al., 1996; Miles et al., 1996; Tsubokawa and Ross, 1996). Interneuronal diversity is further magnified by the fact that, within each interneuronal class, there are several subtypes, each with characteristic properties (Freund and Buzsáki, 1996). A further source of heterogeneity is that, although a high degree of specialization and precision can be observed among the many interneuronal classes, interneuronal characteristics exhibit some variance even within

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subgroups (Gulyás et al., 1993; Parra et al., 1998; Pawelzik et al., 2002). In addition to factors related to the diversity in interneuronal parameters, variance in synaptic mechanisms, e.g., in $GABA_A$ receptor composition, desensitization, modulation, occupancy, and in transmitter concentration and uptake, can also contribute to the heterogeneity of GABA synapses to principal cells (Kapur et al., 1997; Jones and Westbrook, 1997; Engel et al., 1998; Hajos et al., 2000; Maccaferri et al., 2000; Nusser et al., 1997, 2001). As a consequence of the diversity of GABAergic synaptic inputs to postsynaptic neurons, spontaneous or miniature IPSCs (sIPSCs and mIPSCs, respectively) recorded from a single cell include events with at least an order of magnitude difference in amplitude and kinetics (Soltesz et al., 1995; Nusser et al., 1997).

An added source of interneuronal diversity comes from short- and long-term synaptic plasticity at both the inputs and the outputs of interneurons within neocortical and hippocampal circuits (Csicsváry et al., 1998; Reyes et al., 1998; Gupta et al., 2000) that may regulate a variety of functions, including learning and memory, and may also play important roles in various forms of neurological disorders. Although GABAergic synapses were initially thought to be lacking the ability to undergo activity-dependent long-term modification, various pre- and postsynaptic forms of long-lasting plasticity of GABAergic synapses have been described recently (Nusser et al., 1998; Chen et al., 1999). These short- and long-lasting modifications of GABAergic synaptic transmission, together with the frequently unusual mechanisms of long-term plasticity of the excitatory inputs to GABAergic interneurons (McMahon and Kauer, 1997; Alle et al., 2001; Perez et al., 2001; Ross and Soltesz, 2001), demonstrate that the GABAergic system is reactive and dynamically modifiable, adding a novel dimension to the various sources of diversity within interneuronal networks.

Based on the above results, it seems reasonable to assume that the degree of GABAergic synaptic diversity that a single postsynaptic cell receives, e.g., as manifested by the variance of sIPSC amplitude or decay, is determined by the number and activity states of the various presynaptic interneuronal classes, as well as by the momentary state of the local pre- and postsynaptic plasticity mechanisms at each synaptic input site. Consequently, changes in GABAergic synaptic variance may take place as a result of alterations in any of these various factors. Prominent alterations in GABAergic diversity may also occur in some forms of neurological diseases, e.g., following the selective loss of dendritically projecting interneurons in epilepsy (Cossart et al., 2001). However, whether alterations in the heterogeneity in GABAergic synaptic inputs to single cells influence neuronal excitability is not well understood.

Recently, it has been shown that changes in the variance in several functionally important interneuronal properties can significantly alter the input–output functions, rhythmicity and synchrony of principal cells and interneurons (Aradi and Soltesz, 2002). In that previous analysis on the effects of interneuronal variance on neuronal excitability (Aradi and Soltesz, 2002), the focus was exclusively on processes upstream from the GABAergic synapse. As a logical next step towards understanding the functional consequences of interneuronal diversity, here we tested the hypothesis that variance in IPSC conductance and decay kinetics can alter the firing rates of principal cells. These computational modeling data indicate that the degree of heterogeneity of GABAergic inputs can significantly modulate the excitability of postsynaptic neurons. These results have important implications for our understanding of the role and evolution of interneuronal diversity, and they also suggest that alterations in variance may be a novel form of GABAergic plasticity that could significantly contribute to states of altered neuronal excitability, e.g. in seizure disorders.

2. Methods

The multicompartmental model of CA1 pyramidal cells, constructed with the NEURON software (Hines and Carnevale, 1997), was described previously in detail (Chen et al., 2001; see also the website indicated in that paper). Briefly, the model cell included sodium, delayed rectifier potassium and h-currents. The passive parameters, as well as the properties and distribution of the voltage-gated conductances were determined from experiments and from published values (described in Chen et al., 2001). In order to examine the effects of different populations of IPSCs (e.g., groups of IPSCs with or without variance) on action potential firing rates, the CA1 model neuron was depolarized using a somatically injected positive current (I_{depol}) so that the cell fired tonically at around 10–20 Hz, approximating the frequency of firing of CA1 principal cells (11.7 Hz) measured experimentally during 500 ms-long depolarizing 300 pA current pulses from –60 mV. Each simulation run was 10 sec long. The results in this paper are based on a total of about 1500 simulations.

The perisomatic IPSCs were modeled using exponential functions: $I_{syn} = g_{syn} \cdot (V - E_{syn})$, where $g_{syn} = g_{syn}^{max} \cdot norm \cdot (\exp^{-t/\tau decay} - \exp^{-t/\tau rise})$, where "norm" is a normalizing factor (see below). The simulated perisomatic IPSCs were modeled using the amplitude (conductance) and kinetics of mIPSCs measured experimentally. The experimentally determined mean and standard deviation of the mIPSCs ($mean_{exp}$ and SD_{exp}) for amplitude and rise and decay kinetics were as follows (measured from pooled mIPSC data from n = 3 randomly chosen CA1 pyramidal cell recordings

from the control data set in Chen et al., 1999): IPSC conductances: $mean_{exp}$ = 0.896nS with SD_{exp} = 0.459nS; IPSC rise time constant: $mean_{exp}$ = 1.2 ms; the rise time constant of the simulated IPSCs was kept constant, i.e., SD = 0; decay time constants: $mean_{exp}$ = 6.8 ms and SD_{exp} = 3.4 ms. Note that SD_{exp} reflects the variance of the IPSC conductance and decay in individual cells, not the SD of the means between neurons. In the model, the amplitude (or the decay time constant) was either kept the same across the population of IPSCs arriving at the model cell (SD = 0), or the values were increasingly scattered around the population mean (e.g., Fig. 1). For simplicity, Gaussian distributions were used to generate populations of IPSCs with identical means but different variances in the model (real mIPSC distributions are skewed towards larger values, but are usually well fitted by the sum of a few Gaussians). Because changing the decay time constant also altered the amplitude of the simulated bi-exponential IPSCs, the IPSC amplitude was kept constant by a normalizing factor ("norm" in the second equation above) when the variance in the decay time constant was studied: $norm = -1/((\tau_{rise}/\tau_{decay})^{\tau decay/(\tau decay-\tau rise)} - (\tau_{rise}/\tau_{decay})^{\tau rise/(\tau decay-\tau rise)})$.

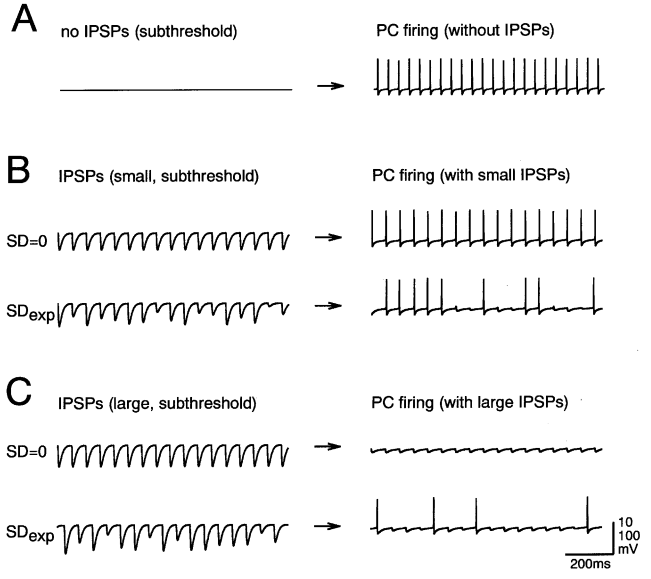

Fig. 1. Altered heterogeneity in the peak conductance values of IPSC populations significantly changes the efficacy of inhibition. In this and all subsequent figures, changes in IPSC heterogeneity were carried out by alterations in the width (variance), but not the mean, of the IPSC peak conductance distributions. *Left panels*: IPSPs (for clarity, the IPSPs are shown with the cell being kept just below firing threshold); *Right panels*: Modulation of the firing of the postsynaptic principal cell (PC) as a result of the IPSPs. (A) The PC firing rate is illustrated when no inhibitory synaptic inputs arrived at the PC. In (B), IPSPs were generated with the same mean IPSC peak conductance, but with either SD = 0 (upper trace) or with the experimentally measured standard deviation (SD_{exp}) (lower trace). Note the decreased PC firing with increased heterogeneity in the IPSPs. In this figure, the mean peak IPSC conductance was equal to 12 times the mean mIPSC conductance = 10.75 nS (for similar effects around a smaller mean conductance, see Fig. 4), and the SD_{exp} was 5.51 nS (see Methods). The IPSC peak conductance values were generated by random draws from Gaussian distributions with the same mean but with either SD = 0 or with SD_{exp}. (C) Similar to B, but the mean IPSC conductance was increased (to 16.13 nS, with a concomitant increase in SD_{exp} to 8.26 nS to keep the coefficient of variation unchanged). Note that, with the larger mean IPSC conductance in C, the PC firing rate was increased with enhanced heterogeneity of the IPSCs.

In this study, we were interested in the effects of variance in the conductance or decay of populations of IPSCs. Therefore, it is important to emphasize that changes in the variance of the conductance or decay in a population of IPSCs (without changes in the mean conductance or mean decay) do not alter the mean charge transfer. The lack of change in the charge transfer with alterations in the variance of IPSC populations can be shown in various ways. For example, for a single IPSC, the charge transfer (CT), i.e., the area under the curve, is $CT = A\cdot(\tau_{decay}-\tau_{rise})$, where A is amplitude. If A shows a Gaussian distribution around a mean value (A_{mean}), the mean CT will be $CT_{mean} = A_{mean}\cdot(\tau_{decay}-\tau_{rise})$. Therefore, the variance in the amplitude does not change the CT_{mean}. In other words, the CT_{mean} depends only on the mean amplitude, and if the mean amplitude does not change, the mean charge transfer will not change either. Similarly, if the decay shows a Gaussian distribution, $CT_{mean} = A\cdot(\tau_{decay,mean}-\tau_{rise})$, indicating that the variance in decay time constants alone (without changes in the mean τ_{decay}) does not change the mean CT.

The experimentally measured mean mIPSC conductance ($mean_{exp}$) was considered to be the synaptic conductance of a single GABAergic synapse in the model. For stronger synaptic inputs, the $mean_{exp}$ conductance was multiplied by an integer, and, in order to keep the covariance the same, the SD_{exp} was also increased accordingly. For example, for 7 synchronously activated synapses (simulating an average single basket cell input to the soma), the mean was 7 times the $mean_{exp}$, i.e., 6.27 nS, and the SD of the Gaussian of the conductance values was increased to 7 times the SD_{exp}, i.e., 3.21 nS. In general, the amplitude of the synaptic strength $A = W\cdot Gauss(mean_{exp};SD_{exp})$, where W was an integer between 1 (the strength of a single synapse) and 35. Since a single postsynaptic principal cell receives about

7 synapses on its perisomatic region from each basket cell, 35 synapses correspond to about five simultaneously activated basket cell inputs to a single cell, which is close to the estimated number of basket cells that converge on a single principal cell (Freund and Buzsáki, 1996). The frequency of "tonic" IPSCs arriving at the model neuron through a somatic synapse was taken from experimental values for sIPSCs in CA1 pyramidal cells (16.5 Hz, n = 3; in most computations, the frequency of the IPSCs was kept constant, i.e., SD = 0; in some cases, the experimentally measured SD_{exp} = 7.7 Hz was used; again, SD_{exp} reflects the variance in the timing of the events in individual cells, not the variance of the means between cells).

3. Results

3.1. Effects of variance in IPSC conductances

Do changes in the variance of the peak IPSC conductances, without alterations in the mean IPSC conductance, affect the inhibitory action of IPSCs on postsynaptic cell firing? In order to answer this first question, inhibitory conductances were included in the soma of a model principal cell (PC) that was depolarized by steady positive current injection to induce tonic firing (Fig. 1A). When the mean injected synaptic conductance was relatively small and there was no variance in the conductance of the IPSCs, the IPSPs could not shut down the PC firing (Fig. 1B, upper traces). However, when the experimentally measured standard deviation was introduced in the IPSC conductance, the PC firing was decreased (Fig. 1B, lower traces). Note that the decrease in PC firing took place in spite of the fact that the mean IPSC conductance was the same in both cases in Fig. 1B (SD = 0 and SD_{exp}). Therefore, these data showed that changes in the variance of the synaptic conductance of a population of inhibitory inputs, even without alterations in the mean conductance, modulate the excitability of the postsynaptic cells.

When the mean IPSC conductance was increased in the model, increased variance had the opposite effect on neuronal excitability (Fig. 1C). As shown in Fig. 1C (upper traces) a larger IPSC conductance could shut down the PC firing at this particular level of postsynaptic depolarizing current injection. With these larger IPSCs, increasing variance in the synaptic conductance (again, without changing the mean IPSC conductance value) resulted in an increase in the average discharge rate of the postsynaptic cell (Fig. 1C, lower traces). Taken together, the results shown in Fig. 1 indicate that the introduction of heterogeneity in GABAergic synaptic inputs can have either an excitability-decreasing or -increasing effect, depending on the mean amplitude of the inhibitory synaptic conductances. To our knowledge, this is the first demonstration of an effect of IPSC heterogeneity on neuronal excitability.

3.2. Explanation of the direction of the changes caused by altered variance in IPSC conductance

Next, we sought to understand the reasons underlying the decrease or increase in firing rates caused by changes in IPSC variance. Since the direction of the change in PC spike rates depended on the mean IPSC conductance, we examined the effects of increasing IPSC conductances on PC firing in a situation where SD =0 (e.g., the upper two traces on the left side of Fig. 1B, C). As the mean IPSC conductance was increased from zero, initially there was little effect on PC firing (Fig. 2A), since the resulting IPSPs were too small. At around a certain critical conductance value, the mean IPSC conductance was large enough to cause a near-complete inhibition of PC spiking. In the case illustrated in Fig. 2, the critical value was 15 simultaneously activated GABAergic inputs (15 times the mean mIPSC conductance). Note that, as shown below, the exact position of the region of non-linearity in the input–output plots (i.e., where inhibition became strong enough to

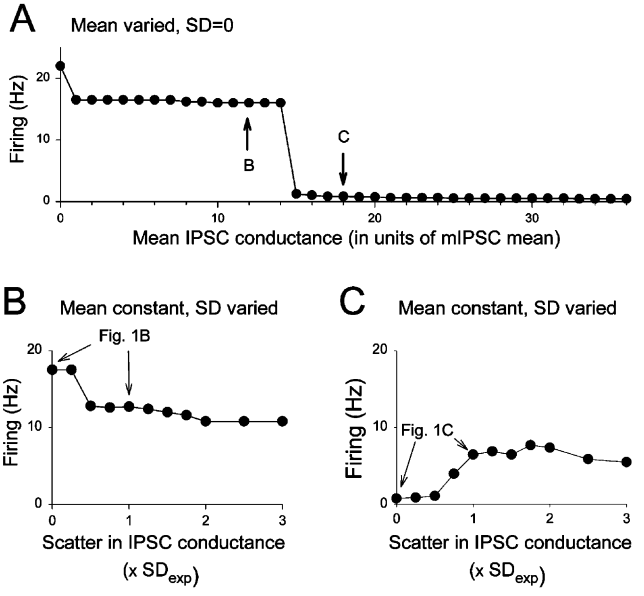

Fig. 2. Analysis of the effects of variance in IPSC conductances on firing rates (inhibitory efficacy). (A) Firing rates of the model PC is plotted against the IPSC conductance (in units of the experimental mean mIPSC conductance = 0.896 nS). Note that, at around 15 times the mean mIPSC conductance (for similar effects at around smaller conductances, see Fig. 4), inhibition became strong enough to shut the cell down, resulting in a region of non-linearity in the input–output curve. (B) Increasing the variance (from 0 up to 3 times SD_{exp}) around the mean IPSC conductance left of the region of non-linearity in the input–output plot (indicated by the letter "B" in panel A) resulted in a decrease in the PC firing. (C) Increasing the variance around the mean IPSC conductance right of the non-linearity (indicated by "C" in panel A) increased PC firing. The depolarizing current injected into the cell to induce tonic firing was I_{depol} = 0.137 nA.

shut the postsynaptic cell down) was dependent on the degree of excitation (simulated by I_{depol}), as well as on parameters of the inhibitory inputs, e.g., on the amplitude, decay and temporal distribution of the sIPSCs, and the value of the reversal potential for chloride (E_{Cl}).

The non-linear nature of the PC spiking versus mean IPSC conductance curve (Fig. 2A) explained the findings in Fig. 1. When the mean IPSC conductance was to the left of the region of non-linearity in the input–output curves (i.e., the IPSCs were relatively small, as in Fig. 1B), the introduction of variance generated IPSC conductances that were both smaller and larger than the population mean. The smaller IPSC conductances did not cause much of a change in the PC firing, but the IPSC conductances that were larger than the critical point were able to inhibit PC firing. For example, if the mean IPSC conductance was equivalent to 12 synapses (12 times the mean mIPSC conductance; indicated as point "B" in Fig. 2A), the PC firing was around 17 Hz (Fig. 1B and Fig. 2A). The scattering of the IPSC conductances around this mean value (randomly drawn from a Gaussian distribution) generated, on average, equal numbers of IPSC conductances that were smaller or larger than this mean value. A smaller IPSC conductance (e.g., 9 synapses, i.e., 3 synaptic strengths smaller than the mean) still resulted in a PC firing of about 17 Hz (Fig. 2A). However, an IPSC conductance of 15 (i.e., 3 unitary conductances larger than the mean in this example) could cause a complete inhibition of PC firing (Fig. 2A). Therefore, two IPSCs with synaptic conductances of 12 allowed the PC to fire at 17 Hz, but two IPSCs with conductances of 9 and 15 (average = 12) decreased the average PC firing below 17 Hz. This finding was quantified in Fig. 2B for different degrees of scatter in the IPSC conductances around their mean values (again, SD_{exp}, the experimentally measured standard deviation in mIPSC conductances in single CA1 pyramidal cells, was taken as a unit).

When the mean IPSC conductance fell on the right of the critical region of non-linearity in the input–output curve shown in Fig. 2A (i.e., when the mean IPSC conductance was relatively large, as in Fig. 1C), increasing the variance in the peak IPSC conductance values had the opposite effect. In this case, when the variance was large enough, there were ISPCs that fell on the left side of the critical value in Fig. 2A, allowing a temporary increase in PC firing. Therefore, with larger IPSCs (i.e., when the mean IPSC fell on the right side of the sudden non-linearity in the input–output curve, as in point "C" in Fig. 2A), increasing heterogeneity resulted in an increase in PC excitability (Fig. 2C).

Note that in both cases (Fig. 2B,C), introduction of variances with SD_{exp} values was sufficient to modulate the average firing rate of the postsynaptic cell, indicating that the naturally occurring degree of variability in GABAergic inputs may be large enough to influence neuronal excitability. Furthermore, these results indicate that the effect of a particular amount of variance around a given mean value can be predicted from the input–output curves (see below for further details).

3.3. IPSC conductance versus IPSP amplitude, and overcoming the effects of increased mean IPSCs by enhanced variance

A possible caveat is that the doubling of an inhibitory conductance does not generate twice as large IPSPs, because peak IPSPs are limited by and converge towards E_{Cl}. Therefore, although the mean of the Gaussian distributions of the IPSC conductances did not change with increasing variance (i.e., only the width of the Gaussians was altered), the mean of the resulting IPSPs may have decreased slightly due to the limitation on the larger synaptic potentials imposed by E_{Cl}. Indeed, the mean of the peak amplitudes of the IPSPs in Fig. 1B with SD_{exp} was smaller (on average by 0.31 mV) than with SD = 0, even though the mean peak IPSC conductance values were precisely the same in the two populations of inhibitory events. Since in this case (in Fig. 1B and in Fig. 2B) SD_{exp} actually decreased the firing rate of the postsynaptic cell, the slight decrease in peak IPSPs could not explain the increased inhibition of firing. On the other hand, a similar decrease (–0.42 mV) in the peak IPSPs with increased heterogeneity (from SD = 0 to SD_{exp}) in the conductance values of the IPSCs was also present in Fig. 1C, where the introduction of variance enhanced PC firing rates. In this case (in Fig. 1C and in Fig. 2C), therefore, a decrease in the peak IPSPs could have caused the enhanced excitability.

To exclude the possibility that the variance-induced decrease in the mean peak IPSP, and not the increased variance itself, caused the enhancement of the firing rate (e.g., in Fig. 1C, or in Fig. 2C), we conducted additional simulations. The general strategy was to compensate (or even overcompensate) for the decrease in the mean peak IPSP values with increased IPSC variance by enhancing the mean IPSC conductance, and show that even under these conditions, increasing variance in the conductance of IPSCs still resulted in an enhancement of the discharge rate of the postsynaptic cell.

The results are shown in Fig. 3. As before, the variance in the IPSC conductance was increased from SD = 0 to SD_{exp} (Fig. 3A, B), however, at the same time, the mean IPSC conductance was also increased by 50% in Fig. 3B compared to Fig. 3A. The 50% increase in conductance overcompensated the variance-induced drop in IPSPs, since the mean of the IPSPs in Fig. 3B was 1.11 mV larger than in Fig. 3A. In spite of the 50% larger conductance and the larger mean IPSCs and IPSPs, the firing rate of the postsynaptic cell in Fig. 3B was higher than in Fig. 3A. These results (and additional, similar simulations not shown here) unequivocally showed that,

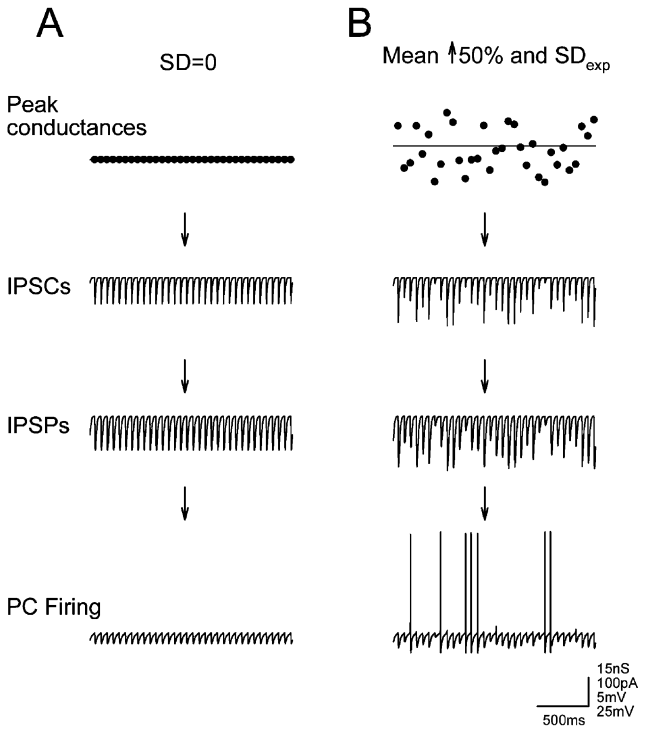

Fig. 3. The importance of heterogeneity over mean values. This figure illustrates that enhanced variance can oppose and negate any effects of changes in means. In this case, a decrease in inhibitory efficacy took place with enhanced variance, in spite of a strong increase in mean peak IPSC conductance. (A) There was zero variance in the peak conductance of the IPSCs (upper panel). (B) The mean peak IPSC conductance was increased by 50% from A, but variance was also introduced (SD_{exp}) (upper panel). In A, the mean of the peak synaptic conductance was 16.13 nS, and SD = 0. The corresponding IPSCs, IPSPs (subthreshold I_{depol} = 0.12 nA), and PC firing (suprathreshold I_{depol} = 0.137 nA) are also shown below the upper panel. Note that the firing of the postsynaptic cell on the right is *increased* in spite of the 50% increase in the inhibitory synaptic conductance (and in spite of the increases in the mean IPSCs and IPSPs).

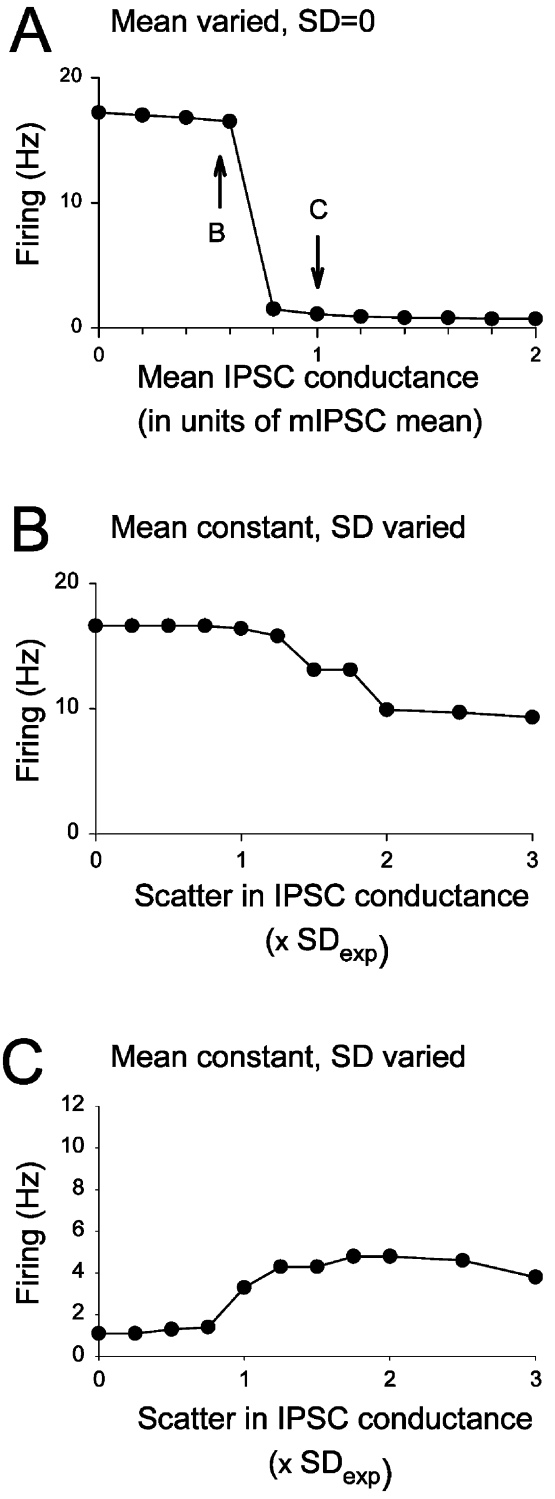

Fig. 4. Variance-effects at the conductance of a single synapse. The strength of the inhibitory synapse was decreased to 1 times the mean mIPSC peak (0.896 nS), but the variance effects remained essentially the same as with stronger IPSC conductance values shown in the previous figures. The I_{depol} was decreased to 0.136 nA from the values reported in the previous figures in order to enable the modulation of the firing rates by the lower synaptic input strength. (A) Input–output curve (as in Fig. 2A) is shown, with the PC firing plotted against IPSC conductances ranging from 0 to 2 times the mean mIPSC conductance. (B) When the distribution of the IPSC conductances was made increasingly wider (up to 3 times SD_{exp}) around a mean IPSC conductance value that was on the left of the region of non-linearity in the input–output curve ("B" in panel A) decreased PC firing. (C) When the increased variance occurred around a mean value that was on the right of the region of non-linearity ("C" in panel A), the PC spike rate was increased.

in the simulations illustrated in Fig. 1C and Fig. 2C, it was not the decrease in the IPSP mean amplitude (as a result of the increased variance in the IPSC conductance) that caused the increase in firing rate.

In addition, these data demonstrate that increased mean synaptic conductance (or increased mean IPSC or IPSP) alone does not necessarily imply a more effective inhibition, a finding that may have important implication for epilepsy research. These results also show that the

effects of increased variance can actually overcome the modulations in firing rate due to changes in mean values.

3.4. Effects of variance in the conductance of a single synapse

In the previous simulations, the critically important region of non-linearity in the input–output plots occurred at synaptic conductance values corresponding to several synchronously activated inhibitory synapses (10 times the mean mIPSC peak conductance and above). Do the principles of the variance effects on neuronal excitability outlined above apply at smaller synaptic input strengths as well? To answer this question, simulations were carried out using the conductance of a single synapse, i.e., around the mean mIPSC conductance values. In these simulations, the I_{depol} steady excitatory input was slightly decreased so that a single inhibitory synapse (with the events still occurring at 16.5 Hz with SD = 0 in the inter-event interval, as before) could substantially decrease the postsynaptic cell's firing rate. As shown in Fig. 4A, the non-linearity in the input–output curve (with this particular combination of parameters) occurred at a conductance slightly lower than the mean mIPSC conductance. Increased variance caused the expected effects predicted from the previous simulations. When the mean conductance value of the population of IPSCs with variances fell to the left of the region of non-linearity on the input–output plot (e.g., point "B" in Fig. 4A), the increased variance led to a decrease in PC firing (Fig. 4B). The opposite outcome was observed, as predicted, when the mean conductance of the population of IPSCs with variances fell to the right of the region of non-linearity (point "C" in Fig. 4A, and Fig. 4C).

3.5. Effects of variance in inter-event intervals

In the previous simulations, the IPSCs always arrived at one particular frequency (the mean frequency of the experimentally observed sIPSCs, see Methods), with zero variance in the inter-event intervals. Additional simulations were carried out to determine whether the general conclusions described above regarding the effects of variance also applied in a more realistic scenario, i.e., when the sIPSC inter-event intervals had a certain amount of variability. Fig. 5 illustrates the results obtained in the case of the parameters used in the simulations in Fig. 4, except that the IPSCs now had the experimentally observed variance in their inter-event intervals. In other words, the simulations illustrated in Figs. 4 and 5 both used the conductance of a single synapse (the mean mIPSC conductance), but the IPSCs arrived in a regular fashion at 16.5 Hz in Fig. 4, whereas in Fig. 5 the IPSCs arrived at the same 16.5 Hz mean frequency but with a SD_{exp} = 7.7 Hz. Fig. 5A shows the traces with either no variance in the peak conductance of the IPSCs

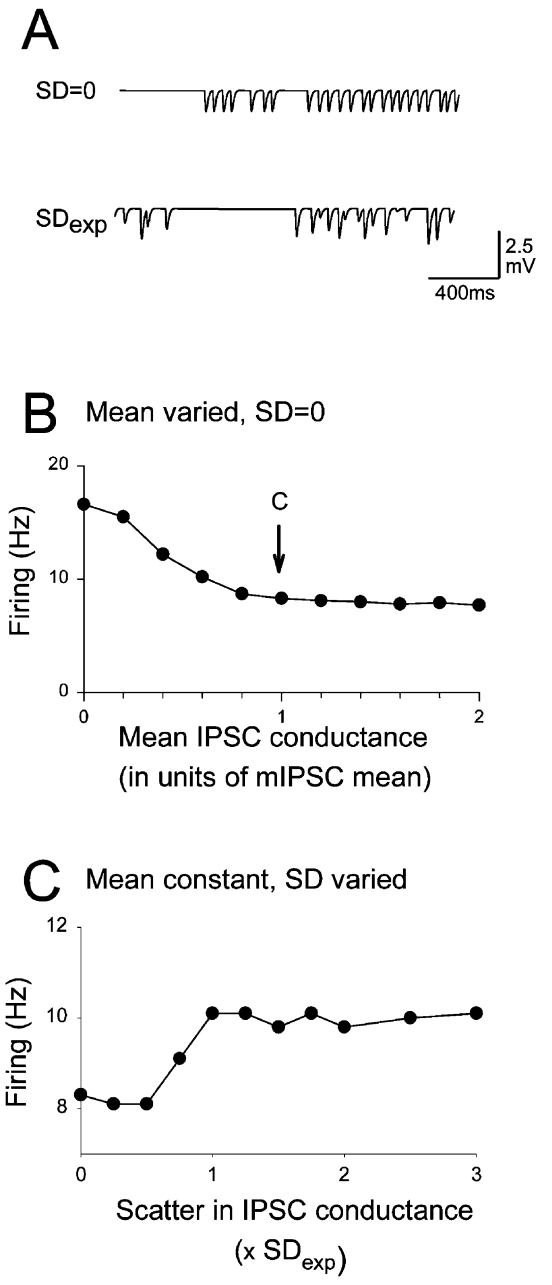

Fig. 5. Introducing variance in the timing of the IPSCs changes the shape of the input–output curves, but not the nature of the effects of altered variance in IPSC conductances on spike rates. In this figure, the effects of variance in the conductance of IPSCs were studied under conditions when variance (SD_{exp} = 7.7 Hz) was also introduced in the timing of the events around the mean (16.5 Hz) IPSC frequency. Note that SD = 0 and SD_{exp} in A–C refers to variance in the peak conductance of the IPSCs (the variance in the frequencies was always present throughout this figure). Furthermore, note that the unitary IPSC peak conductance (and all other parameters, except the frequency variance), was the same as in the previous figure. (A) Irregularly generated IPSPs with zero (upper trace) or with SD_{exp} variance (lower trace) in their peak IPSC conductances are shown (with the cell being kept just subthreshold). (B) Input–output curve (compare with Fig. 4A). (C) The effect of increasing the width of the distribution of the IPSC conductances around the mean ("C" in panel B); compare with Fig. 4C.

(SD = 0) or the experimentally observed variance (SD_{exp}). The input–output curve (with SD = 0 in the peak conductance) is shown in Fig. 5B. Interestingly, the introduction of variance in the inter-event intervals resulted in a broadening of the region of non-linearity (compare Fig. 4A and Fig. 5B), to the extent that in the case of Fig. 5B one could no longer talk about a critical "point". The reason for the broadening of the previously sharp shoulder in the input–output curves had to do with the fact that the events with a non-zero variance in their inter-event intervals were more likely to arrive in clusters, i.e., at a transiently higher or lower rate than the average frequency. When the IPSCs arrived in a brief cluster, they could inhibit spike generation relatively better than the IPSCs that occurred at a regular pace during the same time window (simply because there were more IPSCs during the same period of time). Therefore, the brief IPSCs clusters caused a drop in the firing frequency as one moved from zero IPSC conductance towards larger values (compare the firing frequency in the region of 0 to the mean mIPSC conductance in Fig. 4A and 5B). However, during the times when the IPSCs occurred at frequencies lower than average, the PC was more excitable (compare the firing frequency between 1 to 2 times the mean mIPSC conductance in Fig. 4A and 5B). In summary, introduction of the variance in the timing of IPSCs altered the input–output curves in such a way that the region of non-linearity became broader. Since the non-linearity was still present, symmetrical scattering of the individual peak IPSC conductance values around an unchanged mean (point labeled "C" in Fig. 5B) resulted in the predicted alteration in the PC firing rate (Fig. 5C).

3.6. Effects of variance in the decay of IPSCs

Similar to the heterogeneity in the experimentally recorded sIPSC and mIPSC amplitude values, the decay of IPSCs recorded from single cells also shows a wide distribution. Thus, we compared the effects of populations of IPSCs with and without variances in the decay time constants on the firing rates of the postsynaptic cell. In the subsequent simulations, for simplicity and clarity, the IPSCs arrived rhythmically (SD = 0 in the inter-event intervals), and the IPSC conductance was larger than the mean mIPSC conductance (usually 7 times larger, to simulate the input from a single presynaptic basket cell). Similar to what was described for the variance in the peak conductance, the variance in the decays was also introduced without changing the mean decay time constant of the IPSCs. As shown in Fig. 6, the effects of heterogeneity in the IPSC decay were very similar to those discussed above in relation to variances in the IPSC amplitudes. Again, in situations where IPSCs with faster mean decays could not shut down the PC firing when all decays were identical (SD = 0), increasing the variance to the experimentally measured values (SD_{exp})

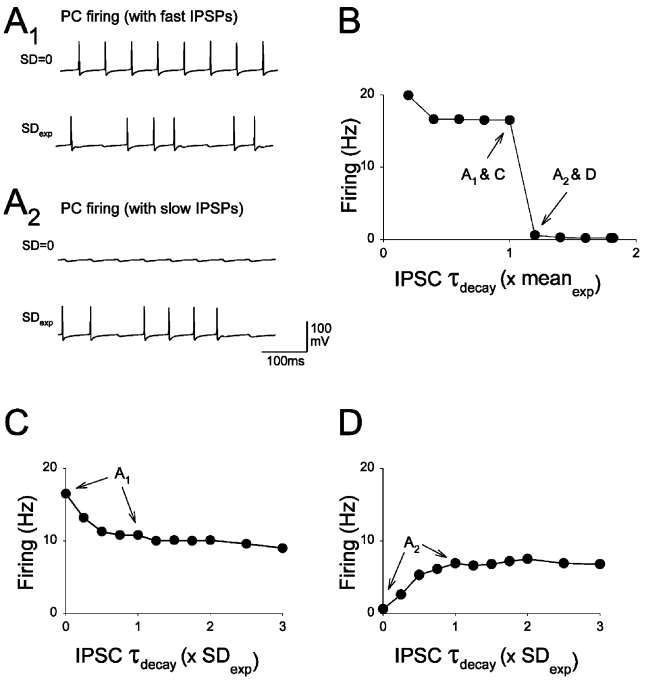

Fig. 6. Changes in the variance of the decay time constant of the IPSC conductance, without alterations in the mean, affect the postsynaptic firing. (A_1) The firing of the PC is shown in response to IPSPs with or without variance in the decay time constants of the underlying conductance. The IPSC decay time constant values were randomly drawn from Gaussian distributions around the $mean_{exp}$ = 6.8 ms (note that mean IPSC peak conductance was unchanged at 6.27 nS) with SD = 0 (upper trace), or with SD_{exp} = 3.4 ms (lower trace). (A_2) Similar to A_1, except the mean decay time constant (of the IPSC conductance) was increased to 8.2 ms, and SD_{exp} to 4.1 ms. (B) Input–output curve, with the PC firing as a function of the IPSC decay time constant. (C, D) Increasing variance around the faster (A_1) IPSC decay (just left of the region of non-linearity in panel B) resulted in a decrease in PC firing (C), while increasing variance around the slower decay (A_2) led to an increase in the PC spike rate (D) (I_{depol} = 0.137 nA throughout this figure).

resulted in a decrease in the spike rate of the PC (Fig. 6 A_1). In contrast, when IPSCs with larger mean decays could completely inhibit the PC firing (in response to a given amount of steady excitation), increasing the variance in the decay resulted in an increase in excitability (Fig. 6 A_2). These findings are further quantified in Fig. 6 B, C and D. Fig. 6 B shows the region of non-linearity in the input–output plot, i.e., the critical value of the decay time constant (with SD = 0) that could cause a sudden drop in PC firing. When the variance was introduced around mean decay values that fell to the left of the critical value (Fig. 6 A_1 and C), increasing the scatter in the decay time constants resulted in a drop in the average firing rate of the postsynaptic neuron. When the mean decay was larger than what was required to completely inhibit the cell (at this given combination of parameters of IPSC conductance, I_{depol}, inter-event and E_{Cl} values; see below), increased variance in the IPSC decay time constants enhanced the PC spike rate (Fig. 6 A_2

and D). Therefore, the effect of the increased variance in both the amplitude and the decay of the IPSCs could be entirely predicted from the relative positions of the mean amplitude (or decay) and the region of non-linearity on the input–output graphs.

3.7. Factors influencing the position of region of non-linearity in the input–output curves

Given the importance of the position of the region of non-linearity in the IPSC (input) versus PC firing (output) plots (e.g. Fig. 2 A and 6 B) in determining the effects of increased heterogeneity in GABAergic synaptic inputs, we examined some of the factors that modulated it. As shown in Fig. 7 A, shifting E_{Cl} towards the depolarizing direction from its normal value of –65 mV to –55 mV caused a rightward shift in the cut-off point in the input–output curve. This rightward shift could be simply explained by the fact that when E_{Cl} moved closer to the average membrane potential of the neuron (note that the model cell was always depolarized from rest by I_{depol} to induce tonic firing, see Methods), the resulting IPSCs (and IPSPs) became smaller as a result of the decrease in driving force. The IPSCs with the smaller driving force, naturally, needed a relatively larger decay time constant (or conductance) in order to shut down the firing of the postsynaptic neuron, hence the rightward shift towards larger decay time constants in Fig. 7 A with a more depolarized E_{Cl}. Again, increasing variance in the IPSC decay time constants resulted in the predicted modulation in the excitability of the postsynaptic neuron (in the illustrated example in Fig. 7 B, since the mean decay was to the left of the critical cut-off point in Fig. 7 A, increasing variance resulted in a decrease in the PC firing rate). Note that the more depolarized E_{Cl} required a larger variance before it showed an effect in Fig. 7 B, since with the rightward shift in the critical point with E_{Cl} = –55 mV, the variance had to increase relatively more before some IPSC decays in the population of inhibitory events could become larger than the critical point.

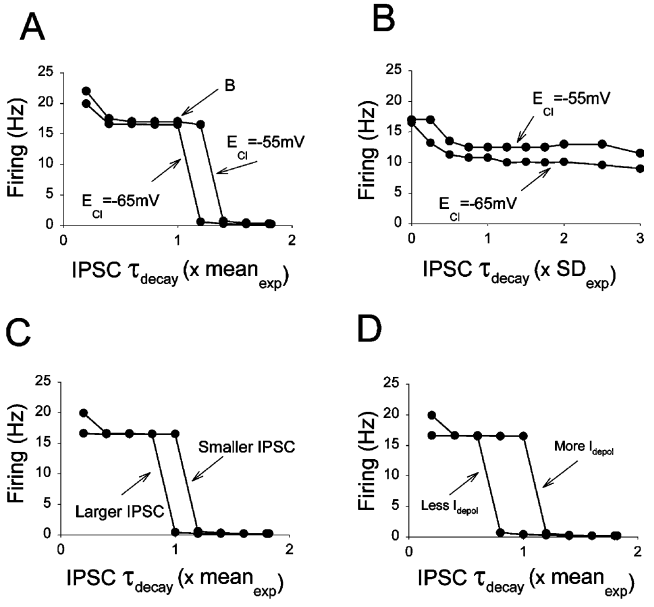

Fig. 7. Parameters that determine the position of the region of non-linearity in the input (IPSC)–output (PC firing) curves. (A, B) The position of the region of non-linearity in the input–output curve was moved to the right in A with a depolarizing shift in the reversal potential for chloride (E_{Cl}). For explanations of the effects shown in this figure, see text. Panel B shows the corresponding plots for the PC firing versus increased variance in the IPSC decays. The mean IPSC conductance was 6.27 nS with zero variance, the mean decay time constant was 6.8 ms, the decay time constant SD_{exp} = 3.42 ms, and I_{depol} = 0.137 nA. (C) The input–output curve was also modified by changes in the mean IPSC amplitude. The "Smaller (mean) IPSC" was 6.27 nS, whereas the "Larger IPSC" was 31.36 nS. The mean IPSC decay time constant was 6.8 ms, and I_{depol} = 0.137 nA. (D) The input–output curve was also modified by the strength of the excitation, modeled by the depolarizing current injection. "More I_{depol}" was 0.137 nA, whereas "Less I_{depol}" was 0.136 nA. The IPSC mean conductance in D was 6.27 nS, and the IPSC mean decay time constant was 6.8 ms.

Additional simulations also showed that, as could be predicted from qualitative considerations, smaller mean IPSC conductance required larger mean IPSC decay time constant to completely inhibit the postsynaptic cell (Fig. 7 C). Similarly, increasing the tonic excitatory input (simulated with increased I_{depol}) resulted in a situation where a larger mean IPSC decay time constant was needed to shut down the PC firing, leading to a rightward shift of the region of non-linearity in the input–output curve with increasing amount of excitatory inputs (Fig. 7 D).

4. Discussion

4.1. GABAergic diversity and its effects on neuronal functions

The heterogeneity in the GABAergic synaptic inputs to hippocampal and neocortical neurons have been observed in anatomical, molecular (e.g., subunit composition of the $GABA_A$ receptors at distinct synaptic sites belonging to different sets of presynaptic interneurons) and physiological (e.g., the characteristically wide distribution of mIPSC amplitudes) studies (Gulyás et al., 1993; Soltesz et al., 1995; Jones and Westbrook, 1997; Nusser et al., 1997; Reyes et al., 1998; Maccaferri et al., 2000; Megias et al., 2001). However, the impact of diversity on the efficacy of GABAergic functions is not understood. Our general strategy was to alter the variance in the conductance and decay of IPSCs and observe the effects on the excitability of the postsynaptic cell. We used computational modeling techniques in this study in order to be able to separate the effect of changes in variance from changes in means, which is difficult to achieve using currently available experimental tech-

niques. Furthermore, in this study we chose to focus on the efficacy of inhibition on spike discharge rates as a major, physiologically and pathophysiologically relevant end-point. The insights gained from this investigation are likely to be useful in subsequent studies on variance effects of GABAergic inputs on functions other than pure "inhibition" (e.g., synchronization of postsynaptic cells) (Lytton and Sejnowski, 1991; Soltesz and Deschênes, 1993; Cobb et al., 1995; Traub et al., 1998; White et al., 2000), particularly since heterogeneity is known to modulate interneuronal synchrony (Golomb and Rinzel, 1993; Wang and Buzsáki, 1996; Tiesinga and Jose, 2000; Aradi and Soltesz, 2002). In a previous investigation on the role of interneuronal diversity on excitability, significant effects of changes in variance in a large number of cellular parameters (action potential adaptation, resting membrane potential, excitatory input frequency and phase, leak current, anatomical projections, etc.) were shown on neuronal excitability and synchrony during both steady-state and dynamically changing conditions (e.g., theta and 40 Hz oscillations and bursts of excitatory inputs) (Aradi and Soltesz, 2002). However, in these previous studies, the effects of the heterogeneity in the GABAergic synaptic inputs on excitability had not been addressed.

4.2. Implications of changes in IPSC variance

The main findings of this paper are that (1) changes in the variance in the conductance and decay of IPSCs, without alterations in mean IPSC characteristics, can significantly regulate neuronal excitability as measured by changes in firing rates sustained by tonic excitation; (2) increased GABAergic synaptic diversity can either increase or decrease spike rates depending on the parameter values (especially IPSC size, decay, intensity of depolarizing inputs and E_{Cl}); (3) the effects of the enhanced heterogeneity in IPSCs could be entirely predicted from the position of the non-linearity in the IPSC versus spike rate input–output curves with respect to the mean IPSC conductance or decay and the degree of the variance increase; and (4) that an increase in the mean synaptic conductance (or mean IPSCs or IPSPs) does not necessarily indicate stronger inhibition, since alterations in the variance can overcome the effects of the increased mean (e.g., Fig. 3).

These results have several interesting implications. In most studies of altered neuronal excitability changes (e.g., on normal activity-dependent GABAergic synaptic plasticity or on the development of seizures), the emphasis is usually on finding changes in the means of various parameters of inhibition. However, as the present data show, in agreement with previous results (Aradi and Soltesz, 2002), alterations in the variances of parameters of GABAergic neurons can also have a significant impact on the input–output functions of postsynaptic cells, with the potential to affect a wide range of physiologically important behaviors including information processing characteristics of the network, as well as modifications in seizure threshold. Therefore, in studies aimed at determining potential changes in GABAergic systems under normal or pathological conditions, attention should be paid to possible alterations in parameter variances, especially since the majority of the commonly used statistical test would not indicate significant changes if the means do not change in an experimental paradigm (for statistical tests designed to detect changes in variances even without changes in means, such as the variance ratio F test and the non-parametric Conover Squared Rank test, see Aradi and Soltesz, 2002). Although alterations in variance in certain interneuronal cellular properties have been experimentally observed (Aradi and Soltesz, 2002), we are not yet aware of data that show unchanged means with altered IPSC variances after experimental manipulations (perhaps, at least partly, because no attention has been paid to the possibility that such alterations may take place). Nevertheless, the heterogeneity of inhibitory inputs are likely to change in a number of scenarios. For example, inhibition of a specific group of interneurons by another group of interneurons (Gulyás et al., 1996), or the selective loss of an interneuronal class following seizures (Cossart et al., 2001), may all result in a short- or long-term decrease in the diversity of GABAergic synaptic inputs to a postsynaptic cell. On the other hand, increased heterogeneity of inhibition could take place in a postsynaptic cell if a previously relatively silent group of presynaptic interneurons increase their activity levels. Heterogeneity of the inhibitory inputs is likely to undergo alterations during early development, with the sequential innervation of principal cells by different presynaptic interneuronal classes (Khazipov et al., 2001), or with the developmentally regulated changes in $GABA_A$ receptors (Hollrigel and Soltesz, 1997). Alterations in the variance of GABAergic inputs may also occur as a result of forms of activity-dependent presynaptic modulation that selectively affect only subgroups of GABAergic terminals (e.g., from endocannabinoids; Wilson and Nicoll, 2002). Although in many of these situations the possible changes in IPSC variances are likely to occur together with alterations in IPSC means, appropriate statistical analyses, perhaps with the help of computational modeling, may be able separate the relative importance of the plastic changes in means versus variances in parameters of GABAergic synaptic inputs to postsynaptic cells.

4.3. Considerations for experiments to study the effects of GABAergic diversity

The present data also provide some practical guidance for future experimental studies on the possible effects of

variance in GABAergic inputs on neuronal excitability. Namely, our results indicate the importance of the region of non-linearity in the input–output curves in predicting the effects of a given amount of variance. Thus, in general, if one is interested in how heterogeneity in parameter X (e.g., synaptic conductance, decay, or any other parameter such as resting membrane potential, etc.) may affect a dependent variable Y (e.g., postsynaptic firing, or synchrony), the first step is to measure the effect of X in a relatively large parameter range (with X being changed in small steps, with zero SD at each step) on variable Y, in order to construct the input–output curve. Once this input–output relationship is known, the region of X values where the non-linearity occurs (if it occurs) can be located. If the actual, in situ X values are relatively close to this region of non-linearity, even small increases in variance in X should produce significant changes in measure Y in subsequent experiments, even without changes in the mean X value of a population of synaptic events, as indicated in the simulations presented in this study. The farther away the mean X value is from the region of non-linearity, the larger variance will be needed to exert a significant change in the dependent variable. It is interesting that in our simulations the experimentally measured degree of heterogeneity (SD = 1 times the SD_{exp}) in IPSC conductance and decay could often produce modulations in PC firing rates. However, a better knowledge of the actual shape and position of the region of non-linearity from experiments from real neurons will be needed to safely conclude that the level of naturally existing biological variance in GABAergic synaptic inputs is sufficient to influence neuronal excitability. The actual effects of IPSC variance on PC firing in real neurons might also be influenced by the degree of action potential adaptation (note that our model postsynaptic cells showed sustained firing rates), as well as by changes in sIPSC frequency (higher sIPSC frequencies with many coincident IPSCs could modulate the effects of IPSC variance; Gauck and Jaeger, 2000; Salinas and Sejnowski, 2000). The shape of the non-linearity in the input–output curves in real neuronal systems (e.g., the oscillation frequency versus IPSC decay plot in Whittington et al., 1995) is also likely to be influenced by variances in several IPSC parameters (e.g., note the changed non-linear regime in the input–output curves before and after the introduction of scatter in the timing of the sIPSCs in Fig. 4A versus Fig. 5B) (Tiesinga et al., 2002).

4.4. Potential implications for the evolution of GABAergic diversity

The underlying, albeit frequently unstated assumption regarding the existence of the numerous types of interneurons in the hippocampus and neocortex is that each interneuronal class evolved to serve a certain set of specific functions, such as distal dendritic feed-forward inhibition, generation of theta oscillations, etc. Although a great deal of specialization can be observed in interneuronal subtypes, it is also possible that the boundaries separating interneuronal classes and subclasses may not be absolute, especially when more than a single parameter is taken into account during classification (Parra et al., 1998). Therefore, diversity exists both in terms of the high number of the currently recognized interneuronal "species", as well as in terms of the cell-to-cell variance in parameter values measured from anatomically or physiologically identified interneurons (for further references, see Aradi and Soltesz, 2002). Ultimately, at the level of the postsynaptic cells, the diversity of the presynaptic interneuronal populations is reflected as the heterogeneity in the synaptic GABAergic inputs, which can be detected electrophysiologically as variances in the conductance, rise time, or decay of spontaneous IPSCs (Soltesz et al., 1995; Nusser et al., 1997). Since, as the present study demonstrates, variance in IPSCs may have significant effects on neuronal excitability, it will be important to investigate whether the diversity of GABAergic synapses is regulated in an activity-dependent manner in neurons, perhaps similar to the homeostatic processes found to take place under certain conditions following alterations in activity levels in neuronal networks (Turrigiano and Nelson, 2000). Such a mechanism would indicate that the evolution of interneuronal subtypes may be influenced not just by specific functional requirements, but also by constraints related to the influence of changes in GABAergic diversity on the excitability levels of postsynaptic neuronal populations.

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