

Relation Between Rise Times and Amplitudes of GABAergic Postsynaptic Currents

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SUMMARY AND CONCLUSIONS

1. We recorded rise times and amplitudes of spontaneous GABAergic inhibitory postsynaptic currents (IPSCs) in melanotopes of *Xenopus laevis*. Average rise times did not vary with amplitude, but the rise times of larger IPSCs were less variable. A simple linear one-step Markov model for channel opening following the binding of a transmitter molecule can quantitatively account for the average rise time and its coefficient of variation as a function of amplitude. Our results indicate that the observed variations in the rise times are not due to variations in transmitter concentrations, but result from stochastic variations in the opening of the receptor channels.

INTRODUCTION

The amplitudes of synaptic currents in the CNS are generally several orders of magnitude smaller than in the neuromuscular end plate. Recent evidence suggests that in central synapses, as in the end plate, the concentration of neurotransmitter that is reached directly after exocytosis is very high (reviewed in Jonas and Spruston 1994). This would mean that in the CNS the postsynaptic receptors are saturated by neurotransmitter. Nevertheless, in many neurons the amplitudes of the spontaneous, "miniature" synaptic currents contain a large amount of variation (e.g., Llano and Gerschenfeld 1993; Raastad et al. 1992; Takahashi 1992). The cause of this variability is still a matter of debate. Both presynaptic factors, like variations in vesicle sizes and vesicle filling, and postsynaptic factors, such as the stochastic behavior of postsynaptic receptor channels or variations in the total number of receptors at different synapses, have been suggested as possible causes (reviewed in Stevens 1993; Van der Kloot 1992). The amplitudes of spontaneous GABAergic synaptic currents in melanotopes of *Xenopus laevis* are also very variable (Borst et al. 1994b). Peak amplitudes corresponded to the simultaneous openings of between 2 and 200 postsynaptic receptor channels. The major cause of this variability appears to be a large variability of the quantal size between synapses (Borst et al. 1994b). A variance analysis of the decay phase of the inhibitory postsynaptic currents (IPSCs) indicated that synaptic γ -aminobutyric acid-A (GABA_A) receptors have a high probability of opening after binding GABA (Borst et al. 1994a). Therefore the gating of the channels is probably not contributing much to the observed variability. In an earlier paper we observed that smaller IPSCs have more variable rise times than larger IPSCs, but their average time courses did not differ (Borst et al. 1994b). Here we develop a simple model for the rising

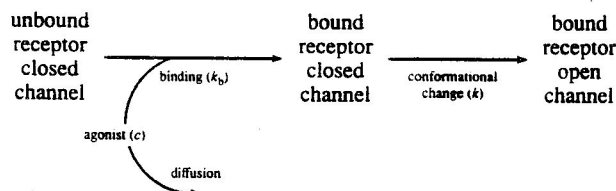
phase of the postsynaptic currents that assumes postsynaptic receptor saturation, the opening of all bound receptor channels, and large differences in the number of receptors at different synapses. With this model we are able to quantitatively account for the measured variabilities.

METHODS

In situ patch-clamp recordings from melanotopes of *X. laevis* were made as described in Borst et al. (1994b).

RESULTS

During the rising phase of a synaptic current, the ligand-gated ion channel binds agonist and undergoes a subsequent conformational transition that opens the channel. Therefore the rising phase can be modeled with the following, simplified scheme



This process can be quantitatively studied by rapidly applying different concentrations of agonist to an outside-out patch. In the case of the GABA_A receptor, it was found that the rising phase could be well described by a single-exponential function of time for a wide range of GABA concentrations (Maconochie et al. 1994). A single exponential means that there is a single rate-limiting step. So, although the GABA_A receptor may bind more than one GABA molecule, there is one rate-limiting step before opening. Maconochie et al. reported a sigmoidal relationship between the rate of opening and the logarithm of the concentration of the applied GABA. For low concentrations (<10 μ M) the opening rate can be taken to be the binding rate $k_b c$ where k_b is the binding constant and c is the concentration of the applied GABA. For high concentrations (>1,000 μ M) binding can be considered immediate and the conformational change becomes the rate-limiting step. Maconochie et al. found the rate constant of this conformational change to be $\sim 6,000$ per second.

The in vivo concentration of agonist in synapses is unknown. However, a simple calculation shows that a high concentration is likely to be reached shortly after exocytosis. Assuming that a vesicle contains $\sim 10^4$ neurotransmitter

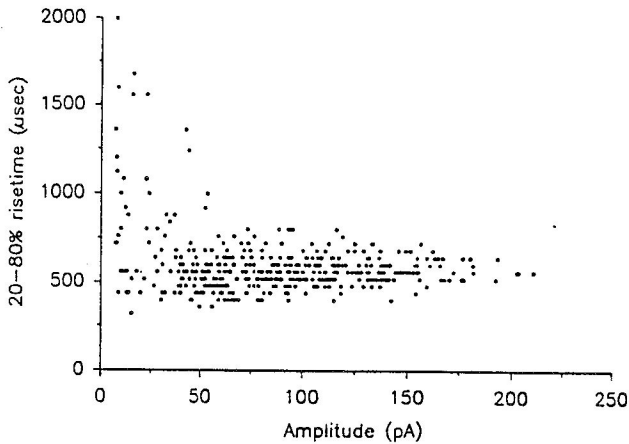


FIG. 1. Rise time vs. amplitude scatter chart for a large number of spontaneous GABAergic inhibitory postsynaptic currents (IPSCs). The holding potential was -80 mV. Series resistance was 33 M Ω ; membrane capacitance was estimated to be 3.4 pF. Currents were filtered at 2 kHz (Bessel filter, -3 dB).

molecules (in Van der Kloot 1991 and Shupliakov et al. 1992, this order of magnitude was reported for cholinergic and glutamatergic vesicles respectively) and that the synaptic cleft is cylindrical with a height of ~ 0.05 μm and a radius of ~ 0.5 μm (Busch and Sakmann 1990), a concentration of a few millimolar is reached after the agonist has spread homogeneously. This concentration is well in the range where binding is no longer the rate-limiting step. If the agonist is released at a point in the center of the cleft, then the standard formula for diffusion in two dimensions, $\bar{r}^2 = 4Dt$, tells us how far an average agonist molecule has diffused after time t . Using a value of $D = 3.0 \cdot 10^{-10}$ m^2/s for the diffusion constant in the synaptic cleft (Busch and Sakmann 1990), we find that after 0.05 ms an average molecule has diffused to half the cylindrical radius and that after 0.2 ms about half of all the molecules have already reached the edge of the cleft. This is clearly faster than the rise time of ~ 0.5 ms. Here we therefore assume that in the in situ and in vivo situation, rapid binding takes place in the first 0.1 ms when the agonist concentration is high and that the subsequent conformational change is the rate-limiting step.

Figure 1 is an amplitude versus rise time scatter diagram for a large number of spontaneous IPSCs in a melanotrope in the intermediate lobe of the pituitary gland of *X. laevis*, as reported in Borst et al. (1994b). Melanotropes are small spherical cells, allowing a good spatial voltage clamp and a high signal-to-noise ratio during in situ patch-clamp recordings. The good signal-to-noise ratio makes it possible to obtain the single-channel amplitude of the synaptic GABA_A receptor channels directly from the IPSCs (Borst et al. 1994b). There was only one conductance level, of ~ 22 pS. An analysis of the decay phase of these currents showed that GABA has a high efficacy, i.e., almost all transmitter bound receptors are in the open state (Borst et al. 1994a). The peaks of the IPSCs generally did not exceed 250 pA. This means that at the peak at most ~ 200 receptors have bound GABA and that the vast majority of the $\sim 10^4$ neurotransmitter molecules diffuses out of the cleft without ever having bound. If the exocytosis of a vesicle of agonist leads to the opening of all channels on the postsynaptic side of

a synaptic connection, then the wide range of amplitudes (covering 2 orders of magnitude) in Fig. 1 can be explained by assuming that a large number of synapses converge onto a single cell, each synapse with its own characteristic amplitude (Borst et al. 1994b). Each synaptic connection has its own characteristic amplitude, but because of noise (the source of which we will address later in this paper), measured amplitudes from that synapse form a narrow distribution around the characteristic amplitude. Eventually these distributions overlap to form the apparent continuum.

Next we will set up with a simple model for agonist-receptor dynamics in the synaptic cleft after the release of a vesicle of GABA.

Suppose that N receptors are present on the postsynaptic face of a particular synapse. After exocytosis they bind in a negligibly small time and the subsequent conformational change, with a transition rate k , determines how fast they open. Because the voltage is held constant and there is only one conductance level, the current is directly proportional to the number of open channels. In the treatment below we give the current in units of open channel current; this keeps the formulae concise and allows us to use the notions "number of open channels" and "current" interchangeably. The increase per unit of time (dx/dt) of the number of open channels x equals the transition rate k multiplied by the number $N - x$ of remaining closed bound channels, and this leads to a differential equation for the number of open channels

$$\dot{x} = k(N - x) \quad (1)$$

where the dot denotes differentiation with respect to time. In reality, the channels will of course close again. However, the decay of a postsynaptic current is much slower than the rising phase (Hille 1992), so on the time scale of the rising phase closing can be neglected. Equation 1 is a linear first-order differential equation, and with $x(0) = 0$ we find for the current a simple exponential relaxation

$$x(t) = N(1 - e^{-kt}) \quad (2)$$

The time t_{α_1, α_2} that it takes the current to go from $\alpha_1 N$ to $\alpha_2 N$, where $\alpha_1 = 0.1$ or 0.2 and $\alpha_2 = 0.8$ or 0.9 is generally taken as a measure for the rise time. Substituting $\alpha_1 N$ and $\alpha_2 N$ for $x(t)$ and solving Eq. 2 leads to

$$t_{\alpha_1, \alpha_2} = \frac{1}{k} \ln\left(\frac{1 - \alpha_1}{1 - \alpha_2}\right) \quad (3)$$

The amplitude N is not present in this formula and it is obvious that experiment (Fig. 1) affirms this independence of the average rise time on the amplitude. The average 20–80% rise time in Fig. 1 is ~ 0.5 ms, leading to a rate $k \approx 3,000$ per second. Such a rate is close to the above-mentioned $6,000$ per second that was obtained with high concentrations of GABA on outside-out patches, indicating that the concentration of GABA reached during the rising phase is indeed very high (Maconochie et al. 1994).

Even though the postsynaptic receptors are probably saturated with neurotransmitter during exocytosis, both the amplitudes and the rise times of the IPSCs in melanotropes of *X. laevis* are very variable (Fig. 1). Much of the variability is due to the presence of multiple synapses, but even if a cell received only a single synapse, the amplitudes and rise times would still vary. We call the data points from a single synapse

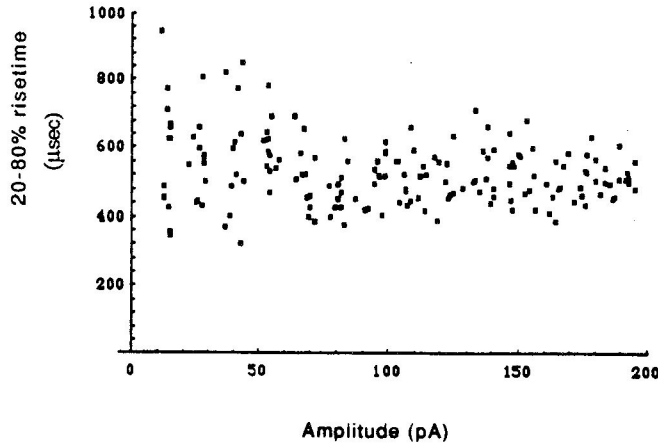


Fig. 2. Idealized, computer-generated rise time-amplitude scatter chart. The amplitude is the number of open channels multiplied by the single-channel amplitude of 1.7 pA. Fourteen synaptic connections with $N = 8, 16, 24, \dots, 116$ receptors on the postsynaptic face were simulated. From each connection there are 12 IPSCs, i.e., 12 points in the chart. The open channel noise factor is $\xi = 0.25$. The standard deviation for the horizontal distribution around each cluster point was $\xi_1 N$ times the open channel current (see text). The standard distribution for the vertical distribution around each clusterpoint was determined by Eq. 9. The rise times were subsequently corrected for the effects of RC filtering (time constant 112 μ s) and the Bessel filter (corner frequency 2 kHz).

a "cluster." Figure 1 can be thought to be built up from many different clusters. Next we will derive formulae for the height (i.e., the variability in the rise times) and the width (i.e., the variability in the amplitudes) of such a cluster.

The GABA_A receptor in *Xenopus* melanotropes has a large amount of open channel noise (Borst 1993), as has also been reported for the GABA_A receptor in superior cervical ganglion neurons (Newland et al. 1991). Because of open channel noise, a peak current with N open channels will not always give rise to exactly N times the single-channel current. Instead we get a Gaussian distribution with a standard deviation of $\xi_1 \sqrt{N}$ around the amplitude N , where x is the standard deviation as a fraction of the average current for one open channel. For the simulation that generated Fig. 2 we used $x = 0.25$, which is close to the experimentally observed 0.21 that was reported by Newland et al. (1991).

Second, we obtain an estimate for the height of a cluster, i.e., we will calculate the standard deviation in t_{α_1, α_2} . We view Eq. 1 as describing the average of a discrete Markov process, where from $t = 0$ onward, each of the N channels has a constant transition probability k to get to the absorbing open state. In the resulting exponential relaxation to N open channels, the probability density distribution for one channel to open at time t is an exponential one

$$p(t) = ke^{-kt} \quad (4)$$

average and variance are easily found to be k^{-1} and k^{-2} respectively. If one channel has a probability of $\exp(-kt_0)$ of remaining closed until at least $t = t_0$, then the probability for m channels to all remain closed until at least $t = t_0$ equals $\exp(-mkt_0)$. When N channels are involved, the probability density distribution for the duration t_n that exactly n channels ($0 \leq n < N$) are open is again exponential

$$p(t_n) = k(N-n)e^{-k(N-n)t_n} \quad (5)$$

where average and variance are now of course $[k(N-n)]^{-1}$

and $[k(N-n)]^{-2}$. The variance in the time it takes to go from 0 to αN ($0 \leq \alpha \leq 1$) open channels is obtained by summing all the variances according to Eq. 5 from 0 to αN open channels

$$\sigma_\alpha^2 = \frac{1}{k^2} \sum_{n=0}^{\alpha N} \frac{1}{(N-n)^2} = \frac{1}{k^2} \int_0^{\alpha N} \frac{1}{(N-u)^2} du = \frac{1}{Nk^2} \frac{\alpha'}{1-\alpha} \quad (6)$$

The step from the sum to the integral is actually an approximation, but in our final result the inaccuracy due to this will be very tiny. For the variance $(\Delta t_{\alpha_1, \alpha_2})^2$ in the rise time t_{α_1, α_2} we thus obtain

$$\sigma_{\alpha_2}^2 - \sigma_{\alpha_1}^2 = \frac{\alpha_2 - \alpha_1}{k^2 N (1 - \alpha_2)(1 - \alpha_1)} \quad (7)$$

From Eq. 3 we have $k = (t_{\alpha_1, \alpha_2})^{-1} \ln [(1 - \alpha_1)/(1 - \alpha_2)]$ and for the coefficient of variation, which is the standard deviation $\Delta t_{\alpha_1, \alpha_2}$ divided by the average t_{α_1, α_2} we thus derive

$$\frac{\Delta t_{\alpha_1, \alpha_2}}{t_{\alpha_1, \alpha_2}} = \sqrt{\frac{\alpha_2 - \alpha_1}{(1 - \alpha_2)(1 - \alpha_1)}} \frac{1}{\ln\left(\frac{1 - \alpha_1}{1 - \alpha_2}\right)} \sqrt{\frac{1}{N}} \quad (8)$$

So the height of the clusters is expected to decrease as the inverse of the square root of the amplitude. For the 20–80% rise time we have

$$\frac{\Delta t_{0.2, 0.8}}{t_{0.2, 0.8}} = \frac{\sqrt{15}}{4 \ln 2} \sqrt{\frac{1}{N}} \quad (9)$$

Figure 2 is a computer-generated rise time-amplitude scatter chart. The clusters overlap, even though only 14 synaptic connections are present. At every synaptic connection the eventual rise time is the net result of the independent action of N channels, so by the central limit theorem (Feller 1957; Van Kampen 1992) we can assume the rise times to be normally distributed. Technically, this theorem only applies as $N \rightarrow \infty$, but in our case the convergence to a Gaussian distribution for increasing N is very rapid. So for the generation of Fig. 2 we took Gaussian distributions of rise time and amplitude at each synaptic connection. The obtained rise times were subsequently corrected to incorporate the effect of the series resistance, membrane capacitance, and Bessel filter.

It can also be understood qualitatively that the standard deviation among rise times decreases with amplitude. Going from left to right in Figs. 1 and 2, the rise time remains constant but the number N of discrete steps that is involved in the "rise" becomes larger and increasingly approaches a nonstochastic continuum limit in which the coefficient of variation vanishes as $1/\sqrt{N}$ and the system becomes deterministic according to Eq. 1.

Figure 3 depicts the quantity $\Delta t_{0.2, 0.8}/t_{0.2, 0.8}$ (cf. Eq. 9) as a function of amplitude and shows a very good quantitative agreement between the formula of Eq. 9 and the experimental data of Fig. 1. Equation 9 contains no adjustable model parameters, and the fact that experiment bears out the $1/\sqrt{N}$ dependency as well as the coefficient of $(\sqrt{15})/(4 \ln 2)$ is an indication that the assumptions behind our model were valid.

DISCUSSION

The relation between rise times and amplitudes of postsynaptic currents is difficult to study in the CNS. Most synaptic

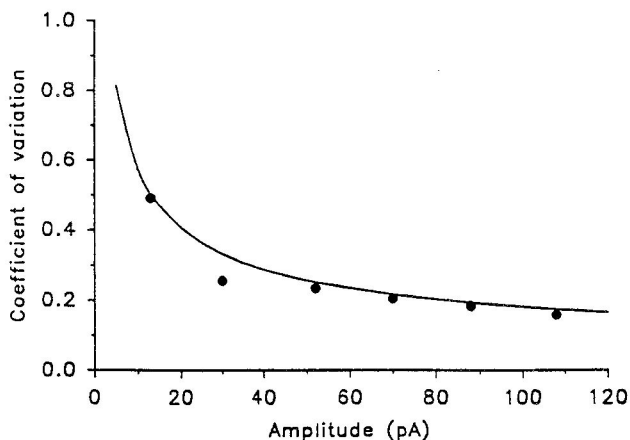


FIG. 3. Ratio of the standard deviation in the rise time and the rise time itself as a function of the amplitude. Solid line: theoretical prediction according to Eq. 9. Dots: data from Fig. 1 taken in 20-pA bins after each rise time was corrected for the effect of the Bessel filter and the combination of series resistance and membrane capacitance, using a lookup table constructed by filtering simulated IPSCs, as described by Silver et al. (1992).

currents enter in dendrites, and it is very difficult to obtain an adequate spatial clamp of currents that enter at some distance from the soma (Rall 1967; Spruston et al. 1993). Furthermore, the time course of, for instance, glutamatergic synaptic currents is so fast that even if the synapses are located in the vicinity of the soma, they may be considerably distorted as a result of the limited speed of the voltage clamp (Jonas et al. 1993; Silver et al. 1992). We therefore studied synaptic transmission in a spherical cell to avoid spatial clamp problems. In addition, the GABAergic synaptic currents that we recorded are generally slower than the currents through α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptors. We looked at spontaneous miniature synaptic currents, because they presumably result from the release of a single vesicle (Katz 1969), thus avoiding variations in the rise time as a result of vesicles not being simultaneously released.

Many elaborate models involving many parameters have been constructed for the mechanism behind a postsynaptic current, and these models have been studied analytically and numerically (Busch and Sakmann 1990; Friboulet and Thomas 1993; Madsen et al. 1984; Parnas et al. 1989; Wathley et al. 1979). It is a pleasant surprise that the rise time versus amplitude scatter chart that we recorded can be quantitatively accounted for with a linear one-step model and that there are verifiable implications of the model (like Eq. 9) that contain no model parameters whatsoever. The relation between rise times and amplitudes that we observed in melanotropes resembles the data obtained in stellate cells of the cerebellum (Llano and Gerschenfeld 1993). So our model may also apply to other GABAergic synapses. Because it is difficult to measure the time course of glutamatergic synaptic currents accurately, it is not possible at present to say whether our model can also be used to describe the situation at glutamatergic synapses.

We have assumed that the conformational change after the binding is the rate-limiting step; it is in principle also possible to match the data of Fig. 1 to a model where the binding of agonist is rate limiting. However, this would im-

ply additional constraints. A quantity $k_b c$ would then have to play the role of the k in our treatment, where k_b is the binding constant of the agonist and receptor and c is the agonist concentration in the synaptic cleft. This c would have to be approximately constant for the entire duration of the rising phase, i.e., ~ 0.5 ms. But we have seen in the previous section that this is not a very valid approximation. Furthermore, this c must be the same for every synapse. With the vesicle contents being roughly the same for all releases, this would have to imply that all the involved synaptic clefts must have the same volume. This seems very unlikely, because a large variability of synaptic bouton sizes on single cells has been observed (reviewed in Lisman and Harris 1993; Pierce and Lewin 1994).

The good correspondence of the variability of the synaptic currents with the predictions of this simple model again stresses the inevitability of stochastic variations in the time course of small synaptic currents (Faber et al. 1992). Apparently such variations are already quite large even when there are no agonist-bound closed states or variations in neurotransmitter concentrations. Because the melanotropes do not have processes, dendritic filtering is not an issue in the analysis of the rise times. When an attempt is made to use the rise times to estimate where in the dendritic tree the postsynaptic current entered (Ulrich and Lüscher 1993), it is important that the effects of stochastic variations are distinguished from the effects of dendritic filtering.

Our results favor a model of fast synaptic transmission in the CNS in which the time course of synaptic currents is determined by the properties of the ligand-gated ion channels and not by presynaptic factors like vesicle diameter or vesicle filling.

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