The quantal size at retinogeniculate synapses determined from spontaneous and evoked EPSCs in guinea-pig thalamic slices

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1. To determine the quantal size at retinogeniculate synapses, spontaneous and evoked excitatory postsynaptic currents (EPSCs) were recorded in twelve neurones of the dorsal lateral geniculate nucleus in guinea-pig thalamic slices using the whole-cell patch-clamp technique. We limited our study to the fast non-*N*-methyl-D-aspartate (NMDA) component of the EPSCs by adding the NMDA receptor antagonist DL-2-amino-5-phosphonovaleric acid to the perfusion medium.
2. Spontaneous EPSCs occurred at a frequency between 0·5 and 6·6 Hz (mean 2·5 Hz). The modal value of the peak conductance change of spontaneous excitatory events varied between cells from 102 to 179 pS.
3. EPSCs were evoked by electrical stimulation in the optic tract. The peak conductance change of EPSCs evoked by stimulation of a putative single input fibre ranged from 0·6 to 3·4 nS (mean 1·7 nS).
4. To resolve the quantal components of evoked EPSCs the external Ca^{2+} concentration was reduced and the external Mg^{2+} concentration increased for four cells. In this condition failures occurred and the amplitude histograms were multimodal with approximately equidistant peaks.
5. These multimodal histograms could be fitted by a sum of Gaussian functions with mean values corresponding to integer multiples of the modal value of the spontaneous EPSCs for the same cell. Thus, the quantal size of evoked EPSCs was the same as the modal value of spontaneous EPSCs. The mean of the apparent quantal conductance change was 138 pS. The estimated number of quanta released by stimulating a putative single input fibre in the control condition ranged from 4 to 27 (mean 13).
6. Paired-pulse facilitation was demonstrated with low external Ca^{2+} concentration. The quantal size remained unchanged from the first to the second response, consistent with a presynaptic mechanism of facilitation.

Forty years after the discovery of the quantal nature of neuromuscular transmission (del Castillo & Katz, 1954*a*), quantal transmission is still not unequivocally documented for excitatory synapses in the mammalian brain. The evidence for quantal transmission at the neuromuscular junction relied on two basic findings. First, evoked responses varied in steps of unit size. Second, this unit size was equal to the size of spontaneous 'miniature' events or quanta. For cells in the central nervous system the postsynaptic excitatory response evoked by stimulation of putative single presynaptic fibres has been reported to vary in steps of unit size (Redman, 1990; Kullmann & Nicoll, 1992; Stern, Edwards & Sakmann, 1992; Jonas, Major & Sakmann, 1993). These unit steps are evidence for quantal release of transmitter substance. However, at central synapses it has been difficult to demonstrate that a unit step in evoked responses has the same amplitude as miniature events (Korn & Faber, 1991).

The synapse between terminals of retinal ganglion cells and relay cells in the dorsal lateral geniculate nucleus (dLGN) is an interesting model system for studies of quantal transmission at central, excitatory synapses. First, many dLGN relay neurones receive their retinal input from a single retinal ganglion cell (Mastronarde, 1987). Second, the terminals of the retinal axon synapse on proximal dendritic regions at approximately the same electrotonic distance from the soma (Hamos, Van Horn, Raczkowski & Sherman, 1987). Third, the dLGN cells are electrotonically compact (Bloomfield, Hamos & Sherman, 1987; Crunelli, Leresche & Parnavelas, 1987).

This manuscript was accepted as a Short Paper for rapid publication.

To determine the quantal size at retinogeniculate synapses we recorded evoked and spontaneous synaptic currents in thalamic relay cells in the dLGN. Our results showed that the amplitude of the unit step in responses evoked by stimulation in the optic tract was the same as the amplitude of miniature events.

METHODS

Whole-cell patch-clamp recordings (Hamill, Marty, Neher, Sakmann & Sigworth, 1981) were made during voltage clamp of dLGN cells in thalamic slices (400 μm) from adult female guinea-pigs (200–350 g). The animals were deeply anaesthetized with halothane and decapitated. A block of the brain including the thalamus was rapidly removed and transferred to cold solution (4 °C) containing (mM): sucrose, 248; KCl, 2; KH_2PO_4, 1·25; $MgSO_4$, 2; $CaCl_2$, 2; $NaHCO_3$, 26; and glucose, 12 (pH 7·4, equilibrated with 95% O_2 and 5% CO_2). Slices were cut with a Vibraslice (Campden Instruments, Loughborough, UK). The slices were cut in a vertical plane at an angle of ~30 deg to the frontal plane. This preserved the optic tract input to dLGN cells in the slice. Recordings were made at 26–29 °C in a submerged chamber perfused continuously (2–3 ml min^{-1}) with a solution as described above except that 124 mM NaCl replaced the sucrose. The perfusion fluid was saturated with 95% O_2 and 5% CO_2. To block the action of γ-aminobutyric acid (GABA) on $GABA_A$ receptors (−)-bicuculline methochloride (20 μM) was added to the perfusion medium. The relatively high (−)-bicuculline methochloride concentration was chosen to avoid contamination of EPSCs by $GABA_A$ receptor-mediated Cl^- currents. DL-2-Amino-5-phosphonovaleric acid (APV, 50 μM) was added to block *N*-methyl-D-aspartate (NMDA) receptors.

Seals were established 'blindly', without prior cleaning of the tissue. Recordings were obtained with a patch-clamp amplifier (Axopatch-1C; Axon Instruments, Foster City, CA, USA). The patch pipettes, made from borosilicate glass tubing, were filled with 140 mM CsCl, 2 mM Mg-ATP, 300 μM GTP, 200 μM EGTA and 10 mM Hepes, pH 7·2 (adjusted with NaOH). The electrode resistance was 3–5 MΩ. The neurones were voltage clamped at holding potentials between −55 and −65 mV, unless otherwise indicated. No correction was made for liquid junction potentials, and no compensation was made for electrode resistance.

Electrical stimulation (rectangular current pulse, 50 μs duration, 5–200 μA amplitude) in the optic tract was made through a tungsten-in-glass microelectrode. After obtaining stable whole-cell recordings, the relationship between stimulus intensity and postsynaptic response was investigated for each cell. The stimulus intensity was adjusted to 20–30% above the threshold for evoking a unitary synaptic response. Either single stimuli, or pairs of stimuli separated by 40 ms, were applied every 1–3 s. Access resistance (8–20 MΩ) was monitored by 5 mV hyperpolarizing or depolarizing test pulses of 3–5 ms duration, starting 40 ms before each stimulus or stimulus pair. The signals were filtered at 2 kHz (Bessel filter of Axopatch-1C), digitized at 48 kHz for storage on digital audio tape, and later fed into a computer at 4–10 kHz. All data analyses were made off-line. Spontaneous events were identified by their characteristic shape, and by their short rise time (< 1 ms). Rise time was measured as the time between 20 and 80% of the peak amplitude. The amplitude of the EPSCs was measured from the digitized traces. The starting point and the peak of the EPSCs were determined visually from the traces without averaging. Background noise was determined by automatic computerized measurement of amplitude differences between arbitrarily selected pairs of points separated in time by 0·5 ms. Pairs of points that were located within a spontaneous EPSC were excluded. Amplitude histograms were made only for epochs during which the change of access resistance was less than 10%. The apparent peak conductances were calculated by dividing the measured peak currents by the estimated driving voltage, assuming a reversal potential of 0 mV.

RESULTS

Spontaneous and evoked EPSCs were analysed in twelve dLGN neurones. All neurones were assumed to be relay cells because low-threshold Ca^{2+} spikes could easily be elicited under adequate conditions (McCormick & Pape, 1988). In eight of the cells EPSCs could be evoked by electrical stimulation of a putative single input fibre. Complete quantal analysis based on a combination of spontaneous EPSCs and EPSCs evoked under conditions with low release probability was achieved in four of these cells.

Electrical stimulation in the optic tract evoked an excitatory synaptic current in the dLGN neurones that consisted of a fast and a slower component. The fast component was mediated by glutamate receptors of the non-NMDA type and the slower by NMDA receptors. We limited our study to the fast component by adding the NMDA receptor antagonist APV (50 μM) to the perfusion medium (Fig. 1*A*). The remaining evoked current was completely blocked by the non-NMDA glutamate receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, 10 μM; Fig. 1*B*). The current–voltage relation for the peak current was almost linear for negative holding potentials and reversed close to 0 mV (Fig. 1*C* and *D*), as expected for a fast EPSC mediated by non-NMDA glutamate receptors.

We restricted our analysis to single-fibre inputs judged from plots of EPSC amplitude *vs.* stimulus intensity (Fig. 2*A*). Single-fibre inputs were indicated in such plots by an abrupt increase of EPSC amplitude at the response threshold and no further increase with increasing stimulus intensity over a certain range (Jonas *et al.* 1993). The peak conductance change evoked by stimulation of a putative single-input fibre ranged from 0·6 to 3·4 nS (1·7 ± 1·1 nS; mean ± S.D.).

Spontaneous inward currents (Fig. 2*C*) with a rise time similar to that of the evoked EPSC (Fig. 2*B*) were observed in all cells studied. They occurred at a frequency between 0·5 and 6·6 Hz (2·5 ± 1·9 Hz). These currents reversed at positive holding potentials and were blocked by CNQX, as demonstrated on four of the cells. They were therefore regarded as spontaneous EPSCs. Amplitude histograms for the spontaneous EPSCs (Fig. 2*D*) showed that the amplitude of the majority of the EPSCs was approximately normally distributed around the modal value. However, a small number of the spontaneous EPSCs had larger

amplitudes that tended to be about double, and a few even triple the modal value. The amplitude histogram for each cell could be fitted by two or three Gaussian functions with means corresponding to integer multiples of the modal value (Fig. 2*D*). We therefore estimated the apparent quantal size by the modal value rather than by the mean amplitude of all spontaneous events. We determined the modal value as the mean of the first Gaussian. The peak quantal conductance change estimated from the modal value of the spontaneous EPSCs ranged from 102 to 179 pS between the different cells (138 ± 21 pS). The coefficient of variation of the first Gaussian ranged from 0·12 to 0·22 (0·15 ± 0·03).

To demonstrate that the smallest spontaneous EPSCs were 'miniature' events, we applied 1 μM tetrodotoxin in five cells until evoked synaptic responses were no longer present. The spontaneous EPSCs persisted during this treatment in all cells (Fig. 2*E*). For each cell, the amplitude histogram for the spontaneous EPSCs during tetrodotoxin application was similar to the histogram obtained without tetrodotoxin.

The background noise was estimated for each cell to study the contribution of such noise to the variance of the first Gaussian fitted to the spontaneous EPSCs. The frequency distribution of the noise was normally distributed around 0·0 pA (Fig. 2*D*, inset). The standard deviation of the background noise varied between the cells from 1·0 to 2·3 pA with a mean of 1·7 pA. We found no significant difference between the standard deviation of the first Gaussian of the spontaneous EPSCs and the standard deviation of the background noise ($P > 0{\cdot}05$, $n = 12$, Student's paired t test). Thus, it was not necessary to assume any quantal variance in addition to the background noise to account for the variance in the group of the smallest spontaneous EPSCs, suggesting that the quantal variance was small compared to the variance of the background noise.

To resolve the quantal components of evoked EPSCs, we reduced the release probability by reducing the Ca^{2+} concentration to 0·2 mM and increasing the Mg^{2+} concentration to 3·8 mM in the perfusion medium for

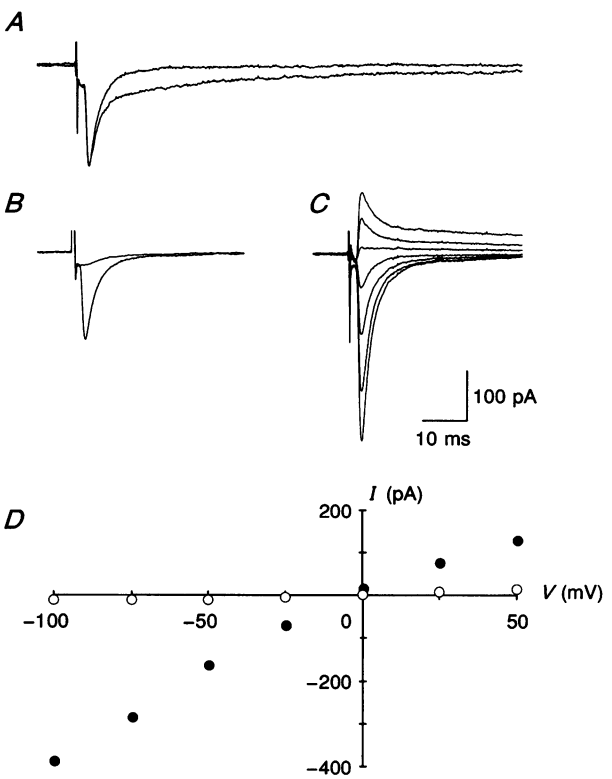

Figure 1. Evoked EPSCs in a thalamocortical neurone
A, EPSC (mean of 8 consecutive currents) at a holding potential of −50 mV evoked by optic tract stimulation in the presence of 20 μM (−)-bicuculline methochloride. Addition of 50 μM APV (upper trace) removed the slow component of the EPSC. *B*, fast EPSC (mean of 8) at a holding potential of −50 mV evoked by optic tract stimulation in the presence of 20 μM bicuculline methochloride and 50 μM APV. Addition of 10 μM CNQX (upper trace) blocked the EPSC. *C*, fast EPSCs evoked by optic tract stimulation in the presence of 20 μM bicuculline methochloride and 50 μM APV at different holding potentials (−100, −75, −50, −25, 0, 25 and 50 mV from bottom to top). Each trace is the mean of 8 consecutive currents. *D*, current–voltage relation for the peak of the fast EPSCs shown in *C*. ●, control condition; ○, in the presence of 10 μM CNQX.

four cells. In this condition failures and stepwise variation in the amplitude of the evoked EPSCs were observed (Fig. 2*F*). Amplitude histograms for the evoked EPSCs were multimodal (Fig. 2*G*) with approximately equidistant peaks in all four cells. The peak separation in all cases corresponded approximately to the modal value of the spontaneous EPSCs collected from the same epoch. A sum of Gaussian functions was fitted to the amplitude histograms on the assumption that the quantal size of the evoked EPSCs was equal to the modal value of the spontaneous EPSCs. The means of the Gaussian functions were integer multiples of the mean of the first Gaussian for the spontaneous EPSCs of the same cell. The standard deviation of the Gaussians was equal to the standard

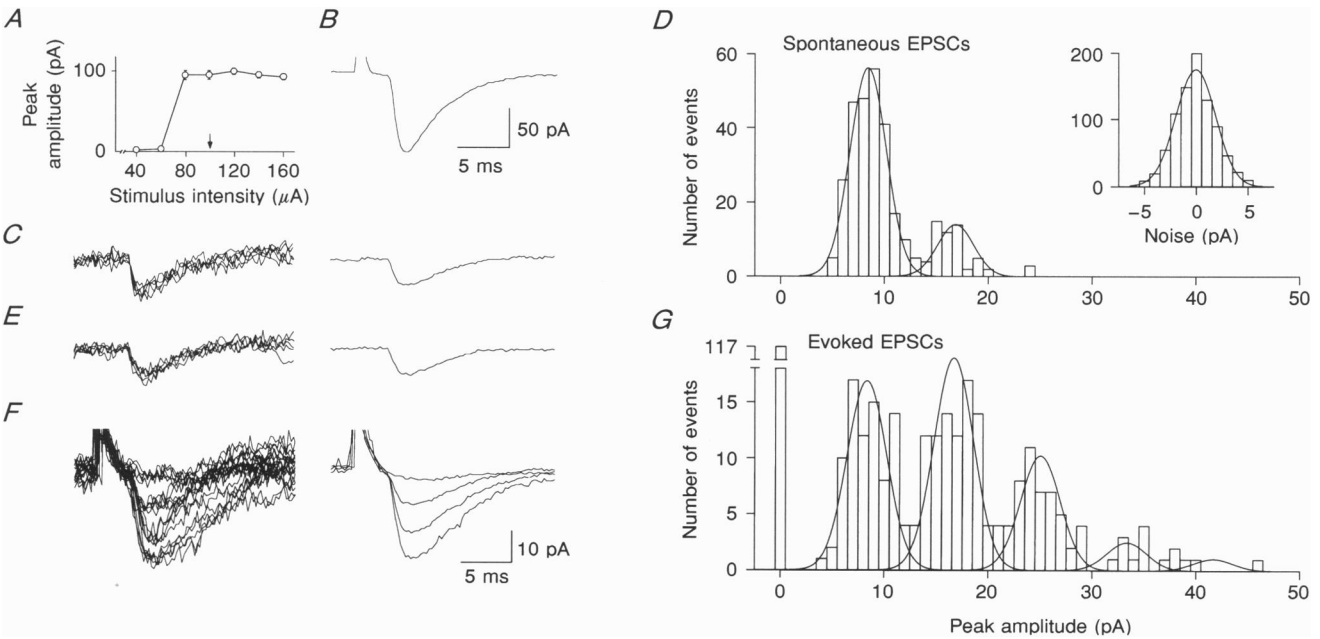

Figure 2. Quantal analysis of the EPSC in a voltage-clamped dLGN neurone at a holding potential of −63 mV in the presence of 20 μM bicuculline methochloride and 50 μM APV
A, mean peak amplitude of stimulus-evoked EPSCs as a function of stimulus intensity (50 μs current pulse). There were no failures for stimulus currents above 80 μA. Vertical bars represent the standard error of the mean ($n = 8$). The arrow indicates the stimulus intensity (100 μA) chosen for quantal analysis. *B*, average of 8 responses evoked at the stimulus intensity of 100 μA. Stimulus artifact is truncated. Rise time for the average trace, measured as the time from 20 to 80% of the peak amplitude, 0·6 ms. *C*, spontaneous synaptic currents. To the left, 5 superimposed single traces and to the right, average of 20 consecutive small events (< 12·3 pA in this case); rise time, 0·5 ms. *D*, amplitude histogram for spontaneous events ($n = 312$) detected during 3 min of recording in an external medium containing 0·2 mM Ca^{2+} and 3·8 mM Mg^{2+}; bin width, 1 pA. Two Gaussian functions were fitted to the amplitude histogram. The first Gaussian (mean 8·3 pA, standard deviation 1·8 pA) was fitted (minimum χ^2) to the group of small EPSCs (< 12·3 pA). The mean of the second Gaussian was twice the mean for the group of small EPSCs, the standard deviation was the same. The fit of the sum of the Gaussians to the amplitude histogram was tested with a χ^2 test ($P > 0{\cdot}21$). Inset, frequency distribution of background noise. The distribution shows the difference of current between pairs of points separated by 0·5 ms measured at 843 arbitrarily selected positions along the recording trace from which the spontaneous and evoked EPSCs were taken. The mean of the distribution was 0·0 pA and the standard deviation was 1·9 pA; bin width, 1 pA. *E*, spontaneous currents from the same cell in the presence of 1 μM tetrodotoxin. To the left, 5 superimposed single traces and to the right, average of 20 consecutive small events; rise time, 0·6 ms. *F*, synaptic responses recorded in an external medium containing 0·2 mM Ca^{2+} and 3·8 mM Mg^{2+}. To the left, 5 superimposed single traces at each of failure, single, double and triple unit size, arbitrarily selected, and to the right, corresponding averages of all responses to the first stimulus of a paired-pulse protocol ($n = 178$). *G*, amplitude histogram for evoked events ($n = 356$) as shown in *F*. Traces lacking detectable components with fast rise time (< 1 ms) were classified as failures. The histogram includes the response to both the first and the second stimulus of a paired-pulse protocol; bin width, 1 pA. The sum of five Gaussian functions was fitted ($P > 0{\cdot}27$; χ^2 test) to the amplitude histogram by the method of least squares. The means of the functions were integer multiples of the mean of the first Gaussian fitted to the spontaneous EPSCs (*D*), and the standard deviation was the same as for the background noise.

deviation of the background noise. Acceptable fits were obtained for all cells ($P > 0{\cdot}71$, 0·61, 0·27 and 0·16; χ^2 test).

To exclude the possibility that the peaks in the amplitude histograms represented binning or sampling artifacts, we varied the bin size and collected events from different time windows within the same epoch. In none of the cells did we detect any obvious change in peak locations with changes of bin size or time window.

We estimated the number of quanta released by stimulation of a putative single input fibre in the control condition (2 mM Ca^{2+}). The conductance change of the evoked EPSC was divided by the quantal size determined from spontaneous events for each cell. The resulting estimate ranged from 4 to 27 released quanta, with a mean of 13.

The effect of changing the release probability was also investigated by applying a paired-pulse stimulation protocol. In low external Ca^{2+} concentration all cells showed paired-pulse facilitation. This was demonstrated by fewer failures to the second stimulus than to the first, by a shift of the amplitudes toward higher numbers of unit steps, and consequently by a higher average response amplitude to the second stimulus than to the first stimulus (Fig. 3). We made separate amplitude histograms for the response to the two stimuli. Both amplitude histograms could be fitted by a sum of Gaussian functions with means equal to integer multiples of the mean of the first Gaussian fitted to the spontaneous EPSCs, and standard deviations equal to the standard deviation of the background noise (Fig. 3). Thus, no marked change of the quantal size was apparent from the first to the second response.

In line with the classical studies of the neuromuscular junction (del Castillo & Katz, 1954*a*), we also fitted a Poisson distribution to the amplitude histograms for the evoked EPSCs in the condition with low release probability (first response to paired-pulse stimulation in low external Ca^{2+} concentration). For three of the four cells, the amplitude histogram could be described by a Poisson distribution ($P > 0{\cdot}51$, 0·29, and 0·13; χ^2 test). The mean quantal content could be independently estimated from the proportion of failures and from the variance of the Poisson distribution (del Castillo & Katz, 1954*a*). For the cell illustrated in Figs 2 and 3, in the condition with low release probability, the observed quantal content was 0·89, the value estimated from the number of failures was 0·84, and from the variance, 0·91.

DISCUSSION

The amplitude of the unit step in excitatory responses evoked by stimulation in the optic tract in the condition with low external Ca^{2+} concentration was the same as the amplitude of miniature events. Thus, retinogeniculate synaptic transmission is quantal. The mean of the

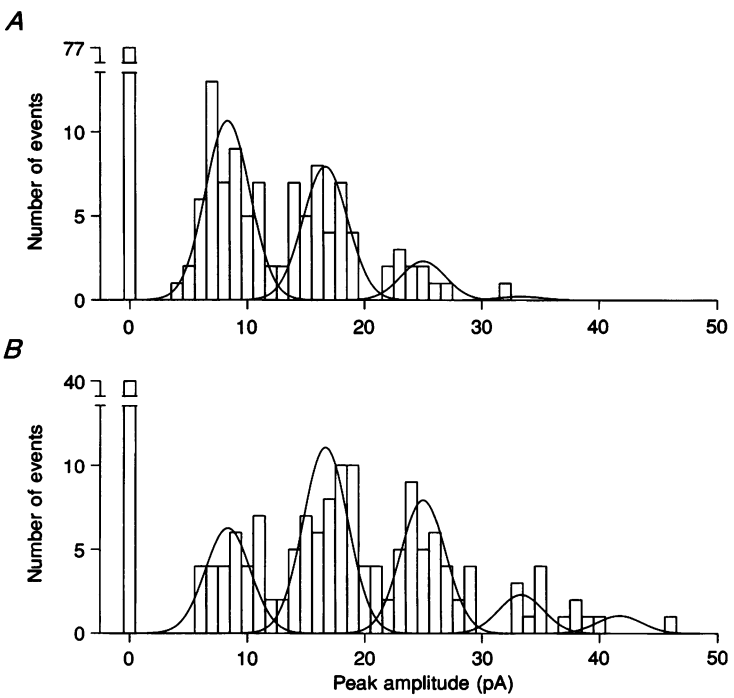

Figure 3. Paired-pulse facilitation for the cell illustrated in Fig. 2 recorded in an external medium containing 0·2 mM Ca^{2+} and 3·8 mM Mg^{2+}

The two stimuli were given at an interval of 40 ms. *A*, amplitude histogram for the response to the first stimulus. The mean amplitude was 7·4 ± 7·9 pA including 77 failures; bin width, 1 pA. The sum of Gaussians was fitted ($P > 0{\cdot}52$; χ^2 test) by the method of least squares as in Fig. 2*G*. *B*, amplitude histogram for the response to the second stimulus. The mean amplitude was 15·2 ± 11·1 pA including 40 failures. This implies a paired-pulse facilitation of 104%. Fit of Gaussians, $P > 0{\cdot}16$; χ^2 test.

apparent quantal size was ~138 pS. This estimate is nearly three orders of magnitude smaller than the estimated quantal size at the neuromuscular junction of frog muscle (~100 nS; Katz & Miledi, 1972).

The apparent quantal size is likely to be an underestimate of the true quantal peak conductance at the subsynaptic membrane. Since the synapses are not located at the soma, the synaptic currents as measured in the soma will inevitably be distorted due to space clamp errors. Our relatively high access resistance adds a further voltage-clamp error. Because of the rapidity of the synaptic events, the attenuation of the synaptic currents due to these two factors might have been significant. However, the synapses under study have advantages compared to many other dendritic synapses in that they are located close to the soma (Hamos *et al.* 1987) on electrotonically compact cells (Bloomfield *et al.* 1987; Crunelli *et al.* 1987) at approximately the same electrotonic distance from the soma (Hamos *et al.* 1987). These advantages were probably crucial for the successful use of miniatures to predict the quantal size in evoked events.

It was unnecessary to assume any quantal variance in addition to the background variance to obtain acceptable fits of the quantal model for evoked events. This suggested that the quantal variance was small. A firm estimate of the quantal variance was precluded by the slight differences in the procedure of measurement for synaptic events and noise, and by the limited number of synaptic events obtained within periods of stable recording conditions.

Our estimate of the quantal peak conductance is similar to estimates obtained from evoked unitary responses mediated by non-NMDA receptors at excitatory synapses on stellate cells in the neocortex (~100 pS; Stern *et al.* 1992), and at mossy fibre–CA3 synapses in the hippocampus (105–177 pS; Jonas *et al.* 1993). Accordingly, the processes at these different synapses seem to be basically equivalent. The data from the Schaffer collateral–CA1 synapse in the hippocampus are less clear (cf. e.g. Kullmann & Nicoll, 1992; Raastad, Storm & Andersen, 1992).

The conductance of single non-NMDA receptor channels in CA3 neurones of the hippocampus has been estimated at 8·5 pS (Jonas *et al.* 1993). If the channels are similar in dLGN neurones, the apparent quantal conductance change we obtained would correspond to the simultaneous opening of about sixteen channels. This is probably an underestimate of the number of open channels per EPSC, because the apparent quantal conductance change was most probably an underestimate of the quantal peak conductance at the subsynaptic membrane.

The amplitude histogram for spontaneous EPSCs, whether in the presence of tetrodotoxin or not, could be fitted by a sum of Gaussian functions with peak separation approximately equal to the quantal size. This suggests that the amplitude of the miniature EPSCs from the retino-geniculate synapses is quantally distributed. Quantal distribution of miniature events has also been reported for the neuromuscular junction (Liley, 1957), for cells in autonomic ganglia (Bornstein, 1978) and for inhibitory synapses in hippocampal slices (Edwards, Konnerth & Sakmann, 1990; Ropert, Miles & Korn, 1990).

The estimated number of quanta (4–27) released by stimulation of one retinal afferent may not be very different from the number of synaptic contacts that a given retinal ganglion cell may have on a single dLGN cell. For class 1 cells in the cat the number of synaptic contacts ranges from 4 to 47 (Robson, 1993). If the value is similar in the guinea-pig, this suggests that the number of quanta released at any given synaptic contact by an action potential in the retinal afferent is small, and could be as low as one. On the other hand, the multimodal miniature distributions suggest that more than one quantum may be released at a single synaptic contact.

The paired-pulse experiments demonstrated paired-pulse facilitation in the condition with low external Ca^{2+} concentration. Whereas the mean size of the EPSC increased from the first to the second response, the amplitude histograms for the response to the two stimuli could be accounted for by the same quantal size. This indicates a presynaptic locus of change for the paired-pulse facilitation, as was the case at the neuromuscular junction (del Castillo & Katz, 1954*b*).

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Acknowledgements

We are grateful to Dr Morten Raastad for valuable discussions and helpful suggestions during the experiments. We thank Mr Bruce Piercey for programming assistance, Professor Jan Jansen, Professor Terje Lømo and Dr Ragnhild Paulsen for reading the manuscript, and Professor Per Andersen for laboratory facilities and support.

Received 20 June 1994; accepted 2 September 1994.