Activation of GABA_A Receptors Causes Presynaptic and Postsynaptic Inhibition at Synapses Between Muscle Spindle Afferents and Motoneurons in the Spinal Cord of Bullfrogs

Yan-yi Peng and Eric Frank

The Graduate Program in Neuroscience, Northwestern University, Evanston, Illinois 60201, and Department of Neurobiology, Anatomy and Cell Science, University of Pittsburgh Medical School, Pittsburgh, Pennsylvania 15261

The functional role of GABA_A receptors in inhibition of synaptic transmission between muscle spindle afferents and spinal motoneurons was studied in the isolated spinal cord of bullfrogs. Extracellular recording from the ventral root showed that activation of GABA_A receptors by muscimol (primarily a GABA_A receptor agonist) at 50 μ M produced a 38% reduction in the amplitude of the excitatory postsynaptic potential (EPSP) evoked by stimulation of triceps muscle sensory afferents and a 66% reduction in the EPSP half-width, suggesting a large increase in the conductance of the motoneuronal membrane. Quantal analysis of unitary triceps EPSPs recorded intracellularly from motoneurons showed that muscimol reduced the quantal content of release (presynaptic inhibition). In addition, muscimol decreased the quantal size (postsynaptic inhibition) when the postsynaptic conductance change was large. Because the effects of muscimol were completely and reversibly blocked by 100 μ M bicuculline (a specific GABA_A receptor antagonist), both the pre- and the postsynaptic inhibition caused by muscimol were due to activation of GABA_A receptors. Activation of GABA_A receptors thus causes both pre- and postsynaptic inhibition of synaptic transmission between muscle afferents and spinal cord motoneurons in the frog.

In the previous paper, we demonstrated that activation of GABA_B receptors produces presynaptic inhibition of synaptic transmission between muscle sensory afferents and motoneurons in the spinal cord of bullfrogs. These results suggest that GABA_B receptors may be involved in the physiological inhibition of this synaptic pathway when conditioning stimuli are applied to other peripheral nerves. The GABA released by the conditioning stimuli could also activate GABA_A receptors, however, and this could lead to presynaptic inhibition as well. A major purpose of the present study was to determine directly whether GABA_A receptor activation produces presynaptic inhibition in this system.

There is also evidence for a possible contribution from post-

synaptic mechanisms. An increase of motoneuronal membrane conductance was found in cats (Cook and Cangiano, 1972; Sybert et al., 1980). The study by Clements et al. (1987) did not address the possibility that a postsynaptic mechanism might also contribute to the inhibition produced by conditioning volleys at synapses situated on distal dendrites of the motoneurons because they limited their quantal analysis to somatic or quasi-somatic EPSPs. Since in cat motoneurons the synaptic current is very brief relative to the motoneuronal membrane time constant, increase in membrane conductance will cause little reduction in EPSP amplitude (Edwards et al., 1976; Finkel and Redman, 1983). Thus, the question of whether postsynaptic inhibition contributes to inhibition in this pathway remains unanswered. In this study, we also investigated the postsynaptic effect of activation of GABA_A receptors at these synapses.

Materials and Methods

Dissections for intracellular recording of monosynaptic unitary EPSPs (MUEPSP) and for ventral root recording are described in Peng and Frank (1989). Intracellular recordings from the motoneurons and extracellular recordings from the ventral root, stimulation of single muscle afferent axons and various peripheral nerves, and the strength and frequencies of stimulation were all as described in Peng and Frank (1989). The analysis of VRPs and MUEPSPs is also described in Peng and Frank (1989).

For the ventral root studies and the intracellular studies of the MUEPSPs, the experimental protocols were similar to that described in Peng and Frank (1989) except that muscimol, a GABA_A receptor agonist, was used. As 50 μ M muscimol inhibited the ventral root potentials to approximately the same degree as 5 μ M baclofen (for details see Results), 20 or 50 μ M muscimol was used for the intracellular experiments.

To study the effect of bicuculline on blocking the inhibitory effects of baclofen or muscimol, we superfused the preparation with 0.1 mM bicuculline for 1 hr and then with either 0.1 mM bicuculline and 5 μ M baclofen or 0.1 mM bicuculline and 50 μ M muscimol. Recovery from the effect of baclofen was done in 0.1 mM bicuculline solution. As the effects of muscimol were practically irreversible under our experimental conditions (see also Johnston et al., 1978; Simmonds, 1982) whereas the bicuculline effects could be reversed within hours, the blocking effect of bicuculline on the inhibition of the VRP by muscimol was studied by comparing the VRP in 0.1 mM bicuculline and 50 μ M muscimol with that in muscimol alone.

(-)-Bicuculline methiodide and muscimol were purchased from Sigma. Stock solutions of (-)-bicuculline methiodide (10^{-3} M) were made by dissolving the chemical in normal saline directly. The muscimol solution was kept in the dark and used within 12 hr. The pH of all solutions was adjusted to 7.2 with 1 M NaOH. The perfusion rate of the bathing solution was 3.3 ml/min for all experiments except those using bicuculline, where it was 2.8 ml/min. It took 7 or 8 min to change the entire bathing solution.

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Correspondence should be addressed to Yan-yi Peng at her present address: Department of Physiology, University of Pittsburgh Medical School, 3550 Terrace Street, Pittsburgh, PA 15261.

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Results

Inhibition of population EPSPs by muscimol

Muscimol was used to study the effect of activation of GABA_A receptors on the ventral root potentials (VRPs) elicited by stimulation of muscle sensory afferents. As illustrated in Figure 1, muscimol inhibited the amplitude of the triceps-VRPs. Muscimol at 50 μ M reduced this amplitude by 38% ($n = 6$).

Muscimol (50 μ M) also shortened the halfwidth of these EPSPs by 52.5% ($n = 6$). This effect of muscimol on the time course of the falling phase of the monosynaptic VRPs can be seen more clearly when the voltage is plotted logarithmically against time (Fig. 1*B*). Under the conditions of these experiments, the time course of these population EPSP decays provides an approximate measure of motoneuron membrane conductance (refer to Peng and Frank, 1989). In contrast to the absence of a postsynaptic conductance increase with baclofen (see Figs. 3 and 4 in Peng and Frank, 1989), the large reduction of the halfwidth of these EPSPs suggests that muscimol caused a significant increase of the motoneuronal membrane conductance.

Finally, muscimol reduced the amplitude of the afferent potentials. The traces in Figure 1*A* show that increasing concentrations of muscimol caused larger reductions in the amplitude of both the afferent potential and the VRP. The effects of muscimol on the VRPs were extremely difficult to reverse.

Effects of muscimol on intracellularly recorded averaged MUEPSPs

In order to study the influence of GABA_A receptor activation on triceps-EPSPs more directly, we examined the effect of muscimol (20 and 50 μ M) on synaptic transmission between single muscle afferent axons and individual spinal cord motoneurons. The results from 7 sensory-motor units were analyzed in detail and are presented in Table 1. The averaged MUEPSPs for 2 of these units in the presence and absence of muscimol are shown in Figure 2 (for more examples refer to Fig. 19 in Peng, 1988).

A major effect of muscimol was a reduction in the peak amplitude of the chemical component of the MUEPSP. In 5 of the 7 units (units 1–5), muscimol (20 and 50 μ M) reduced the MUEPSPs by 14–79% (mean = 52.5%). In units 6 and 7, 20 μ M muscimol had no inhibitory effect on the amplitude of the MUEPSPs; these were also the units with very small peak amplitudes.

Muscimol also affected the time course of the MUEPSPs. For the 5 units in which muscimol inhibited the amplitude of the chemical component, the halfwidths were reduced by 20–66% (mean = 45%), and the time constants of the motoneuronal membrane were decreased by 27–85% (mean = 64%). In units 6 and 7, the halfwidth and time constant were also reduced by muscimol despite the absence of inhibition of MUEPSP amplitudes (refer to Table 1). However, the reductions of both halfwidth (mean = 11%) and time constant (mean = 30.5%) were less than for the other 5 units. Thus, muscimol consistently increased the membrane conductance of motoneurons. Less consistent effects were observed on the rise time and synaptic delay of MUEPSPs (refer to Table 1).

The main findings from these intracellular studies, then, confirmed those from the study of the VRPs. Activation of GABA_A receptors inhibited synaptic transmission between muscle spindle afferents and motoneurons, and also produced a profound increase of the motoneuronal membrane conductance. Could this increase account for the inhibition observed? This question

Figure 1. Effect of 50 and 100 μ M muscimol on triceps-VRPs. *A*, Triceps-VRPs before and after 50 and 100 μ M muscimol reached their maximum inhibitory effect. *Inset*, Afferent potentials at $1.5 \times$ gain and $10 \times$ sweep speed. *B*, Semilogarithmic plot of the traces in *A* at the same time scale. The final portion of traces in *A* are not shown in *B*.

was answered by analysis of the fluctuations of individual MUEPSPs.

Muscimol affected the quantal fluctuation of the chemical MUEPSPs

To assess whether the postsynaptic conductance increase could account for the observed inhibition, the deconvolution procedure was used to analyze the fluctuations of the MUEPSPs (for details of the deconvolution procedure, see Chaps. 2 and 3 in Peng, 1988; also see Materials and Methods in Peng and Frank, 1989). The results are listed in Table 1, and examples of 2 units are also shown in Figure 2.

Of the 7 units, 4 (units 1, 2, 3, 5) showed a sufficient amount of inhibition ($\geq 20\%$) to be useful for an analysis of the mechanism of inhibition. Three of these units had 2 sets of data in muscimol, making a total of 7 data sets, and for 6 of these sets, the quantal size could be estimated by measuring the amplitude differences between adjacent nonzero bins in the histograms (see Peng and Frank, 1989). Based on this analysis, muscimol inhibited the MUEPSPs via both pre- and postsynaptic mechanisms.

In 4 cases, MUEPSP amplitudes during perfusion with muscimol were reduced 20, 46, 50, and 64% with less than 15% reduction in quantal size, suggesting that the inhibition was virtually entirely presynaptic. Two of these cases (from unit 1) are illustrated in Figure 2*A*. Besides the constancy of quantal

Figure 2. Effect of muscimol on MUEPSPs. *A*, Unit 1 (as listed in Table 1). *B*, Unit 5. The calibration pulses on the falling phase of the averaged MUEPSP traces are 0.5 mV and 2.5 msec. The peaks of the semilogarithmic traces for each MUEPSP unit have been superimposed to facilitate the comparison of their slopes. The results of the deconvolution procedure for these units are shown on the right.

Table 1. Effects of muscimol on MUEPSPs

Unit	Solution (μM)	Sample size (n)	Amplitude ele/late (μV)	Amplitude _{ele} % of control	Amplitude _{chem} ^a % of control	Synaptic delay (msec)	Rise time ave/ln (msec)	Half-width (msec)	Halfwidth % of control	τ_m (msec)	Quantal size (μV)	Bin-width (μV)
1	Saline	405	46/602			1.9	4.8/4.8	13.8		17.4	135	33
	Muscimol(50)	381	38/482	82.6	79.9	2.1	4.1/4.1	9.4	68.1	12	123	33
	Muscimol(50)	293	27/300	58.7	49.1	1.7	3.7/3.6	7.5	54.3	7.1	120	33
2	Saline	889	33/350			1.7	4.1/4.2	20.2		32.2	94	30
	Muscimol(50)	910	16/157	48.5	44.5	2.3	3.1/3.1	6.8	33.7	5.7	?	30
3	Saline	614	71/360			2.4	5.4/5.3	27.7		36.5	84	20
	Muscimol(50)	663	45/200	63.4	53.6	2.4	4.4/4.3	12.6	45.5	17.4	86	25
	Muscimol(50)	685	35/128	49.3	32.2	3.1	5.3/5.4	12.4	44.8	12.5	69	25
4	Saline	685	108/862			1.5	3.9/?	16.8		28.7	105	33
	Muscimol(50)	728	96/742	88.9	85.7	2	3.7/?	12.1	72	21.1	100	33
	Saline	755	92/702	85.2	80.9	1.9	3.3/3.3	13.1	80	25.5	100	33
5	Saline	889	29/541			1.6	2.8/2.8	6.3		13.6	150	50
	Muscimol(20)	829	19/183	65.5	32.0	1.5	2.8/?	4.5	71.4	3.2	125	50
	Muscimol(20)	806	8/115	27.6	20.9	?	2.7/2.9	4.5	71.4	2.0	82	33
6	Saline	805	15/68			1.9	4.0/4.0	15.6		20.2		
	Muscimol(10)	668	15/68	100	100	3.1	4.6/3.8	14.9	95.5	14.8		
	Muscimol(20)	831	0/68	0	128	?	5.6/?	13.9	89.1	12.9		
7	Saline	684	/146				3.3/3.2	15.5		16.5	88	25
	Muscimol(20)	670	/148		101		3.7/3.5	13.8	89	12.4	100	25

Where there are 2 sets of data in muscimol, the second was taken at a later time or higher concentration. ele, electrical; chem, chemical; ave, average; ln, natural logarithm. ? indicates when it was not possible to make an accurate measurement.

^a When the MUEPSP unit had an early electrical component, the amplitude of the chemical EPSP was defined as the difference between the late and the electrical components.

size, an additional feature of this analysis that suggests presynaptic inhibition is the change in relative heights of the various nonzero bins; postsynaptic inhibition would simply shift each bin to the left, which was not observed. A further point is that the nonzero bins in the upper 2 histograms occur at approximately the same discrete amplitudes. As discussed in Peng and Frank (1989), this alignment of the nonzero bins before and after inhibition provides additional support for the idea that the reduction in MUEPSP amplitude was the result of the release of fewer quanta, i.e., it was presynaptic.

On the other hand, quantal sizes were significantly reduced by muscimol in 2 other cases. These cases (both from unit 5) are illustrated in Figure 2*B*. The second data set (bottom 2 histograms) shows this reduction in quantal size especially clearly. In the third histogram, the data were deconvolved with a bin width of 50 μV , which resulted in 4 nonzero bins that were adjacent to each other. Such a result would be expected if the quantal size had fallen to less than 100 μV . Therefore, the bin-width was reduced to 33 μV (fourth histogram), and the resulting deconvolution yielded 2 discrete peaks with a quantal size of 82 μV . In these cases, then, at least some of the inhibition produced by muscimol was the result of smaller quantal sizes, i.e., it was postsynaptic.

Theoretically, an increase in postsynaptic membrane conductance would inhibit the amplitude of the chemical MUEPSP only if it were sufficiently large to reduce the membrane time constant to the same order as the duration of the synaptic current. Indeed, the 3 data sets in which the quantal sizes were reduced at all were the only ones where the time constant of the motoneuronal membrane was reduced to less than 2.3 times the rise time of the MUEPSP (an approximate measure of the syn-

aptic current duration). Even in these cases, however, the amount of postsynaptic inhibition as judged by the reduction in quantal size (12, 17, and 45%) was insufficient to explain the entire reduction in MUEPSP amplitude (50, 66, and 79%).

Bicuculline completely blocked the inhibition produced by muscimol

Results of quantal analysis showed that muscimol at 20 and 50 μM caused both pre- and postsynaptic inhibition. Since muscimol is reported to have a slight affinity for GABA_B receptors (300 times less than baclofen or GABA: Hill and Bowery, 1981), it was possible that its presynaptic effect was the result of activation of GABA_B receptors. This possibility was tested by determining whether muscimol could still produce synaptic inhibition of the monosynaptic VRPs when most of the GABA_A receptors were blocked by bicuculline, a competitive antagonist of GABA_A receptors.

A convenient measure of GABA_A receptor activation in this system is the depolarization of primary afferent fibers by stimulation of other sensory fibers (PAD; Barker et al., 1975a, b; Nicoll and Alger, 1979). The dorsal root potential (DRP; recorded via a suction electrode on the cut central end of the dorsal root) represents the average PAD occurring in all the sensory fibers in the root. We therefore used the DRP to assess the effect of bicuculline on activation of GABA_A receptors (see Peng, 1988, for details). At 100 μM , bicuculline blocked most ($\geq 90\%$) or all of the DRPs, which were evoked by stimulation of the same or an adjacent dorsal root or the ventral root of the same segment, suggesting that this concentration would be sufficient to block the major fraction of presynaptic GABA_A receptors, and this concentration was chosen for the subsequent

Figure 3. Effect of 0.1 mM bicuculline on blocking the inhibitory effects of 50 μ M muscimol and 5 μ M baclofen on triceps-VRPs. All traces except those in *Bb* were collected during one experiment.

experiments to test the effects of muscimol. However, as illustrated in Figure 3*A*, this concentration also inhibited the amplitude of the VRPs by an average of 42% ($n = 13$, SE = 2.6%). We have no simple explanation for this effect. Other, more readily explicable effects of bicuculline on motoneurons were (1) an increase of spontaneous activity, (2) an increase in the halfwidth and occasional appearance of a second component with an amplitude larger than the monosynaptic component, and (3) an increase in the amplitude of the afferent potentials (visible in Fig 3*A*). All these effects are consistent with a reduction of synaptic inhibition caused by the background level of GABA_A receptor activation, presumably from the tonic release of GABA.

As illustrated in Figure 3*B*, after the inhibitory effect of bicuculline stabilized (50–70 min), addition of 50 μ M muscimol produced no additional inhibition of the VRP. In fact, the amplitude of the VRP increased by 9% (67.2% of the control value, $n = 12$, SE = 3%) compared with the amplitude in bicuculline alone (57.8% of control value). An additional assurance that GABA_A receptors were blocked by 0.1 mM bicuculline was that the falling phase of the VRP was not shortened by the addition of muscimol. Because muscimol's inhibitory effect on the amplitude of the VRP was blocked by bicuculline, its normal presynaptic inhibitory action (discussed above) results from its activation of presynaptic GABA_A receptors.

An alternative interpretation of these results is that bicuculline blocked GABA_B receptors as well as GABA_A receptors in

this system. Although there is no evidence for this suggestion, we tested it by measuring the amount of inhibition produced by baclofen in the presence of bicuculline. After superfusion with 100 μ M bicuculline, the addition of 5 μ M baclofen still inhibited the amplitude of the VRP by 30% ($n = 8$, SE = 1.3%) without decreasing the afferent potential (Fig. 3*Ca*). Furthermore, this inhibition was fully reversible within 50 min (Fig. 3*Cb*).

Effect of muscimol on impulse invasion into sensory afferent terminals

We have shown that activation of presynaptic GABA_A receptors by muscimol produces presynaptic inhibition of the EPSP in motoneurons. Because GABA_A receptor molecules are also Cl[−] channels (Schofield et al., 1987), how does the increase of Cl[−] conductance by GABA (Bormann et al., 1987) induce presynaptic inhibition? For the 6 units that had an early component (units 1–6), muscimol reduced the amplitude of this component by 11–100% (Table 1). Despite this reduction in the amplitude of the potentials in the afferent terminals, muscimol apparently did not cause intermittent invasion failures because the SD for the amplitude of the electrical components was within +2 to −7 μ V of that of the noise. In fact, in all these cases, muscimol reduced the SDs for the electrical component relative to that of the noise.

A critical test for intermittent invasion failures would be quantal analysis with the deconvolution technique. Unfortu-

nately, the amplitudes of the early components for 5 of these units were approximately the same size as the SD of the noise. Since the resolving power of the deconvolution procedure is limited by the SD of the noise, this technique could not be used for these units. In the remaining unit (unit 3), the deconvolution procedure showed that the electrical component did not fluctuate in either normal saline or muscimol even when its amplitude was reduced by 51%.

In the absence of postsynaptic inhibition, changes in the amplitude of the electrical component of the MUEPSPs can be used to assess changes in the amplitude of the depolarization in sensory afferent terminals. In 3 of the experiments with muscimol (unit 4 and the first set of traces with muscimol in units 1 and 3), there was no postsynaptic inhibition, as judged by the unchanged size of single quanta, yet the electrical component was reduced by an average of 20%. Furthermore, the amount of reduction in the electrical component is perfectly correlated with that in the chemical component ($R = 1.0$, $df = 2$), suggesting that in these cases, presynaptic inhibition was accompanied and possibly caused by a graded reduction in the depolarization of the muscle afferent terminals.

Discussion

GABA_A-induced presynaptic inhibition

Both the intracellular studies of the MUEPSPs and the ventral root recordings of population EPSPs demonstrated that muscimol (20 or 50 μM) inhibited synaptic transmission between muscle afferents and spinal cord motoneurons in bullfrogs. Quantal analysis of the fluctuation of MUEPSPs showed that this inhibition was entirely presynaptic as long as the time constant of the motoneuronal membrane was at least 2.3 times as long as the rise time of the MUEPSPs. Since 100 μM bicuculline completely and reversibly blocked the inhibitory effects of muscimol but not those of baclofen, the presynaptic inhibition caused by muscimol was due to the activation of presynaptic GABA_A, not GABA_B, receptors. These results are in agreement with those of Dunlap (1981), who found that in cultured chick dorsal root ganglion cells, 100 μM muscimol caused no observable activation of GABA_B receptors.

Activation of GABA_A receptors reduces the potential change that invades afferent terminals. When postsynaptic conductance changes are sufficiently small to cause no postsynaptic inhibition of the chemical component of the MUEPSPs, the electrical component is a reflection of the potential invading the presynaptic terminals. Muscimol was found to inhibit the electrical component even when it induced only presynaptic inhibition, as judged by the constant quantal size of the chemical component. Thus, unlike baclofen, muscimol reduces the potential change that invades the presynaptic terminals. The large increase in Cl⁻ conductance produced by activation of GABA_A receptors might cause intermittent conduction failures in the presynaptic terminals. However, our results from the unit where fluctuation in the electrical component could be analyzed by the deconvolution procedure argue that the potential can be reduced in a graded manner without causing invasion failures.

GABA_A-induced postsynaptic inhibition

We found that the amplitude of unitary EPSPs is reduced by postsynaptic inhibition only with large increases in postsynaptic conductance. When the synaptic current is brief compared with the time constant of the motoneuron, as has been reported for

cat spinal motoneurons (Finkel and Redman, 1983), most of the synaptic current is capacitive. Under these conditions, the amplitude of the EPSP will be largely independent of the postsynaptic membrane resistance. Only when the membrane resistance is reduced to such a degree that the time constant of the membrane is comparable to the time course of the synaptic current will the EPSP amplitude be reduced. Indeed, this is what we found. Instead of directly reducing the peak amplitude of the monosynaptic EPSPs, the physiological function of activation of postsynaptic GABA_A receptors might be the shortening of the falling phase of the EPSP. By reducing the duration of the depolarization, GABA_A activation could effectively reduce the period during which temporal summation occurs. Thus, it is possible that, rather than changing the amplitude of small individual EPSPs, this activation could modulate the overall firing pattern of the cell.

Comparison of the functional roles of activation of GABA_A and GABA_B receptors

Activation of both GABA_A and GABA_B receptors causes presynaptic inhibition at the synapses between muscle spindle afferents and spinal motoneurons. However, activation of GABA_A receptors produces postsynaptic inhibition of the motoneuron as well. Furthermore, activation of GABA_A receptors reduces the amplitude of the potential change that invades the afferent terminals, while GABA_B activation induces presynaptic inhibition without altering this potential change.

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