SYNAPTIC EXCITATORY AND INHIBITORY INTERACTIONS AT DISTAL DENDRITIC SITES ON MITRAL CELLS IN THE ISOLATED TURTLE OLFACTORY BULB¹

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Received November 23, 1983; Revised March 6, 1984; Accepted March 7, 1984

Abstract

The olfactory nerves terminate exclusively on the distal dendritic tufts of mitral cells in the olfactory bulb, which makes this a favorable model for analysis of synaptic responses in distal dendrites. Intracellular recordings of responses to olfactory nerve volleys have been obtained in the isolated turtle olfactory bulb. Single mitral cells usually responded with excitatory postsynaptic potentials (EPSPs) to volleys in two different bundles, indicating convergence from separate receptor neuron populations. Paired volleys revealed long-lasting inhibition of a test EPSP by a conditioning volley. This could be shown to be independent of the inhibition of mitral cells by granule cell interneurons in the deeper layers. The results suggest that excitatory and inhibitory synaptic interactions in the glomerular layer are important in the processing of olfactory inputs. The results also provide an exception to the classical doctrine that synaptic inhibition is preferentially sited near the cell body and axon hillock in order to control impulse generation there. Our findings of inhibitory actions on distal dendrites of mitral cells may provide a model for similar actions on distal dendrites of other central neurons.

Neurons in the vertebrate central nervous system typically receive specific synaptic input on restricted portions of their dendrites or cell bodies. The relative positions of these different synaptic inputs are important factors for synaptic integration in the neuron (Rall, 1977; Shepherd, 1979).

In mitral cells of the vertebrate olfactory bulb, olfactory nerve (ON) input is rigidly restricted to a distal tuft of the primary dendrites in the glomeruli. In the isolated turtle olfactory bulb preparation, this ON input can be easily and selectively activated by a volley in an isolated ON bundle (Waldow et al., 1981). Because of the ability to stimulate all of the ONs which converge onto mitral cells in this preparation, together with the relatively effective electrotonic spread along the primary dendrites, the input from ONs to the distal dendrites can be recorded as a robust excitatory postsynaptic potential by a recording micropipette within the mitral cell soma (Mori et al., 1981b).

In addition to the distal excitatory input, mitral cells are known to receive synaptic inputs on different portions of their dendritic processes from two kinds of intrinsic neurons. Best understood are the synaptic inputs from granule cell dendrites, which are distributed on the mitral secondary dendrites, proximal portions of the primary dendrites, and the mitral cell

bodies (Price and Powell, 1970). These dendrodendritic synaptic inputs from the granule cells are known to be inhibitory (Phillips et al., 1963; Yamamoto et al., 1963; Rall and Shepherd, 1968; Nicoll, 1969; Mori and Takagi, 1978; Mori et al., 1981b; Jahr and Nicoll, 1982). Granule cells can be activated by a volley in the mitral cell axons in the lateral olfactory tract (LOT) or a volley in the ON (Mori and Shepherd, 1979; Mori et al., 1981b; Jahr and Nicoll, 1982). In contrast, the other main type of intrinsic neuron—the periglomerular (PG) short-axon cell—is strongly excited by ON volleys but is either unaffected or weakly inhibited by LOT volleys (Shepherd, 1963). The PG cell makes dendrodendritic and axodendritic synapses exclusively onto the distal portions of the mitral primary dendrites in the glomerular layer (Hinds, 1970; Reese and Brightman, 1970; Pinching and Powell, 1971; White, 1972). The evidence thus far is that, like the granule cells, the PG cells inhibit mitral cells through these synapses (Shepherd, 1971; Getchell and Shepherd, 1975).

Thus, mitral cells in the isolated turtle olfactory bulb provide an excellent opportunity for study of interactions between different synaptic inputs mediated by distinct interneuronal populations onto different portions of the neuronal dendritic tree.

In a previous report on the isolated turtle olfactory bulb, we studied several components of the intracellularly recorded synaptic potentials of mitral cells following stimulation of either the ONs or the LOT (Mori et al., 1981b, c). In the present study, we report analysis of interactions between distal synaptic responses to separate excitatory ON inputs, and between these and the proximal and distal inhibitory responses mediated by local neuronal circuits within the bulb.

¹ This work was supported by Grants NS-07609 and NS-19174 from the National Institute for Neurological and Communicative Disorders and Stroke.

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Materials and Methods

The experiments have been carried out on the olfactory bulb of the turtle, *Pseudemys scripta*. The preparation of the *in vitro* olfactory bulb and the methods for stimulating and recording have been fully described elsewhere (Mori et al., 1981a). Intracellular recordings were obtained from mitral cells lying mainly in the ventral portion of the olfactory bulb. In most cases, a suction electrode was used to stimulate the whole ventral ON. In seven experiments, however, the ventral ON was gently dissected apart into two small bundles, and bipolar silver electrodes were placed on each of the separated bundles. Shocks to the nerve were repeated very slowly to avoid long-lasting effects on ON excitability; the stimulus intervals for single or paired shocks were usually 2 or 4 sec. The strength of ON volley was adjusted to be just supramaximal for eliciting the large positive field potential in the granule cell layer (the responses in period III described by Waldow et al., 1981). The recording micropipettes were filled with 2 M potassium acetate and had DC resistances between 40 and 100 megohms.

Results

Convergence of ON inputs on a single mitral cell. A characteristic feature of the synaptic input of the ONs to the mitral (and tufted) cells is a large convergence at the glomerular tuft (Allison, 1953; Ramón y Cajal, 1955). To test whether a single mitral cell receives these converging inputs from olfactory axons running in different ON bundles, the ventral ON was dissected into two small bundles (ON₁ and ON₂). We then recorded intracellularly the responses of mitral cells to ON₁ and ON₂ stimulation. Mitral cells were identified by their antidromic spike responses (Fig. 1B) or a characteristic sequence of inhibitory potentials (see Mori et al., 1981a, b) following LOT stimulation. The records shown in Figure 1, B to D, were obtained from a typical cell. A single volley in ON₁ elicited an initial depolarization (E₁ component, arrow) with a spike potential (Fig. 1C). ON₂ stimulation also elicited an E₁ component but without any spike potential within the range of stimulus intensities used (Fig. 1D). Recordings from another cell are shown in Figure 1, E and F. In this mitral cell, an E₁ component with a superimposed spike was elicited by the ON₂ volley (Fig. 1F) as well as the ON₁ volley (Fig. 1E). The E₁ component is the EPSP elicited in the glomerular dendritic

branches by the ON synapses (Mori et al., 1981b); therefore, the above results indicate that these mitral cells receive ON inputs from both nerve bundles (ON₁ and ON₂). In nine mitral cells which showed convergence of excitatory synaptic inputs from ON₁ and ON₂, four cells responded with an action potential to both ON₁ and ON₂ volleys, three cells showed an action potential following either ON₁ or ON₂ volley, and the remaining two cells did not show any action potentials to either of the volleys within the range of stimulus intensities used.

Effects of conditioning ON volleys. The interactions of synaptic potentials in mitral cells were studied using paired ON volleys. An example is shown in Figure 2, A and B. In Figure 2A, seven traces were superimposed. After a conditioning volley, testing ON volleys were applied at different intershock intervals (indicated in Fig. 2 by arrows b to e). It can be seen that the testing ON volleys failed to elicit an action potential and that the shape of the synaptic response to a test volley changed with changes in the conditioning-test intervals.

In Figure 2B, the oscilloscope was triggered by both the conditioning and the test volley, and the responses to each volley were compared with a fast sweep speed. In each figure, the response to the conditioning volley is shown in the upper trace. A conditioning volley always elicited a spike potential arising from an EPSP (E₁ component). The spike was followed by a series of inhibitory and excitatory potentials (I₁, E₂, I₂, and I₃ components, as indicated by arrows in Fig. 2, A, Ba, and Bb; cf. Mori et al., 1981b, c). The traces of the test responses (indicated by an asterisk) start below the conditioning responses (because of the prolonged hyperpolarization (I₃ component) elicited by the conditioning volley). With conditioning-test intervals of 300 msec (Fig. 2Ba) and 400 msec (Fig. 2Bb), the spike of the test response was blocked, and the initial depolarization (E₁ component) showed a slower rising and falling phase. The I₁ and I₂ components of the test response were not seen clearly. When the conditioning-test interval was lengthened (Fig. 2B, d and e), the rising phase of the initial depolarization became steeper, and the depolarization was cut short by a hyperpolarizing potential. With further increase in the conditioning-test intervals (Fig. 2Bf, 2 sec), the E₁ compo-

Figure 1. Convergence of ON inputs onto single mitral cells. A, Schematic diagram of the experimental set up. ON₁, ON₂, separate ON bundles. B, Antidromic response of a mitral cell to a LOT volley. C and D, Orthodromic responses of the same cell to a volley in ON₁ (C) and ON₂ (D). E and F, Another mitral cell responding to an ON₁ volley (E) and ON₂ volley (F). E₁ indicates the EPSP component of the ON-evoked responses.

Figure 2. Effects of conditioning ON volley on the mitral cell response to the test ON volley. **A**, Superimposed tracings of the mitral cell responses to paired ON volleys of equal intensity at seven different intershock intervals. The times of test ON volleys are indicated by arrows. I_2 and I_3 in **A** indicate the I_2 and I_3 components of the mitral cell response elicited by the conditioning ON volley. **B**, Comparison of the mitral cell responses to the conditioning ON stimulation (upper traces) and the test ON volley (lower traces indicated by asterisk). The control and test responses were superimposed with a fast sweep speed. The test responses in **Bb**, **Bc**, **Bd**, and **Be** correspond to the test responses in **A** (indicated by arrows with corresponding letters **b**, **c**, **d**, and **e**). The components of the control ON response are indicated by E_1 , E_2 , I_1 , and I_2 in **Ba** and **Bb**.

nent of the test response increased in amplitude and finally gave rise to an action potential. Note in Figure 2**Bf** that the test response still starts from a slightly hyperpolarized membrane potential level and that the E_2 component is still depressed. In almost all of the mitral cells (25 of 26 cells) tested with the above method, the conditioning (just supramaximum) ON volley depressed all of the components (E_1 , E_2 , I_1 , I_2 , and I_3) of the test responses, although the degree and the time course of the depression of each component varied somewhat from cell to cell.

Time course of the depression of the test E_1 component. Since the E_1 component is known to be an excitatory synaptic potential generated by ON synapses in the terminal tuft of the mitral cell, it represents a distal synaptic input in the mitral cell. We have analyzed in detail the effect of a conditioning ON volley on the amplitude of this component. In most mitral cells, accurate measurement of the amplitude was difficult because of the superimposed action potential (Fig. 2). However, in four mitral cells with relatively high resting membrane potentials, it was possible to elicit the E_1 component without the action potential. In these cells, the peak amplitude was measured at various times after the conditioning ON volley. Figure 3**B** shows

a typical example. When a small background depolarizing DC current was injected (Fig. 3**Bc**), this cell showed the synaptic response with superimposed spike that was typical of mitral cells (Figs. 1 and 2).

Figure 3**Ba** shows the responses to conditioning and testing ON volleys of equal stimulus intensity. These responses are shown superimposed on faster sweeps in Figure 3**Bb**. The amplitudes of the E_1 components of the conditioning and test responses were measured at the times indicated by the dashed line in Figure 3**Bb**. The relative amplitude of the test response is plotted at different test intervals in Figure 3**A**. The depression of the E_1 component had a complicated time course at the intershock intervals between 0 and 200 msec. With an intershock interval of 200 msec, the amplitude of the E_1 component was reduced to approximately 40% of the control response. With increase in the intershock interval, the amplitude of the test E_1 component recovered gradually. The depression was present for a long time (up to about 1500 msec in this example) after the conditioning volley. In three other experiments a long-lasting depression (1 to 3 sec) of the E_1 component similar to that described above was found.

One of the possible causes of this depression could be an increase in membrane conductance of the soma and/or secondary dendrites of the recorded mitral cell, due to the IPSPs (I_1 , I_2 , and I_3 component) elicited by the conditioning volley. To check this, we have measured the time course of the membrane conductance change following the conditioning volley. The membrane conductance change was measured in the usual way, as a change in the amplitude of the voltage transient produced by injecting current pulses through the recording microelectrode using a bridge-balance circuit (Mori et al., 1981b, c). As shown by the open circles and dashed line in Figure 3**A**, an increase in membrane conductance was present for only a relatively brief period (about 150 msec) after the conditioning ON volley. After that, no increase in the membrane conductance was detected despite the great depression of the E_1 component of the test ON response.

Effect of conditioning LOT stimulation on the test ON-evoked E_1 component. Since supramaximal LOT stimulation elicits inhibitory potentials (I_1 , I_2 , and I_3 components) which are similar to those evoked by the ON stimulation (Mori et al., 1981b, c), we have examined the effect of a conditioning LOT volley on the responses to the test ON volley. In most mitral cells, a conditioning LOT volley blocked the test ON-evoked spike response. However, the amplitude of the E_1 component was not depressed by the conditioning LOT stimulation. An example of the effect of the E_1 component is shown in Figure 4. For comparison, the effect of the conditioning ON volley in this cell is shown in Figure 4, **Aa** and **Ab**. Note the depression of the E_1 component. In contrast, the amplitude of this component was not depressed by a conditioning LOT stimulation (see Fig. 4, **Ba** and **Bb**), despite the large IPSP elicited by the conditioning LOT volley. The difference in the effect between the conditioning ON volley and the conditioning LOT volley is clearly seen in the superimposed tracings in Figure 4**C**. The E_1 and E_2 components of the test response were not depressed by a conditioning LOT volley and were even slightly increased in amplitude (dotted line in Fig. 4**C**). In contrast, a conditioning ON volley greatly depressed the E_1 component and almost completely suppressed the E_2 component of the test response (Fig. 4**C**, dashed line).

Discussion

Convergence of distal excitatory inputs. The present results indicate the convergence onto a single mitral cell of excitatory synaptic input from ONs running in different ON bundles. Since the different ON bundles are likely to arise from olfactory receptor cells located in spatially different portions of the

Figure 3. A, Comparison of the time course of the suppression of the E_1 component of the test ON-evoked response (solid circle and solid line) with that of the changes in the membrane conductance (open circle and broken line) of the mitral cell following the conditioning ON volley. Ordinate, the relative amplitude of the E_1 component of the test ON response (solid circle) and that of the voltage drop produced by a hyperpolarizing current pulse (0.25 nA and 50 msec in duration) injection following the conditioning ON volley. They are calculated as percentages of the control (unconditioned) responses. Ba, An example of the responses to the paired ON volley. Bb, The same responses as in Ba were superimposed with a faster sweep speed (DC recording). Bc, The response of the same mitral cell to the ON volley during a small (0.1 nA) depolarizing current injection.

Figure 4. Comparison of the effect of the conditioning LOT volley with the conditioning ON volley on the test ON-evoked response. Aa and Ab, ON volley was applied as a conditioning stimulation. Ba and Bb, Conditioning LOT volley. The responses to the ON volleys (indicated by dashed underlines in Aa and Ba) were shown with a faster sweep speed in Ab and Bb, respectively. C, The control ON-evoked response (solid line), the test ON-evoked response following conditioning LOT volley (dotted line), and the test ON-evoked response following the conditioning ON volley (dashed line) were superimposed for the comparison of the amplitude of the E_1 component.

olfactory epithelium (Allison, 1953; Land, 1973; Land and Shepherd, 1974; Kauer, 1981), a single mitral cell may, thus, receive synaptic input from spatially distributed receptors in the olfactory epithelium. It is possible that convergence of the ON inputs from different ON bundles onto a given mitral cell occurs in one glomerulus. However, in the turtle olfactory bulb, mitral cells typically have more than one primary dendrite, each of which terminates in widely separated glomeruli (Mori et al., 1981a). Consequently, it is possible that olfactory axons

from different ON bundles terminate on different primary dendrites of a mitral cell.

Inhibition of distal excitatory responses. Waldow et al. (1981) reported that in the isolated turtle olfactory bulb, conditioning ON volleys cause a prolonged suppression of the summed synaptically evoked potentials and spike responses of mitral cells to a test ON volley (see also Orrego, 1961, and Iwase and Lisenby, 1965 for *in vivo* preparation). In agreement with this, the present study has shown a prolonged suppression of all of the components (E_1 , E_2 , I_1 , I_2 , and I_3) of the intracellularly recorded synaptic responses of mitral cells by a conditioning ON volley.

The E_1 component is an EPSP elicited monosynaptically at the terminal tuft of the mitral cell primary dendrites (Mori et al., 1981b; Nowicky et al., 1981). We have analyzed in detail the suppression of the E_1 component by conditioning ON and LOT volleys, in order to gain insight into the properties of these synapses and their relation to the local circuits of the olfactory bulb.

In the paired ON volley experiments, the E_1 component typically showed early partial recoveries followed by a prolonged suppression which lasted more than 1 sec (Figs. 2 and 3). Similar recovery cycles have been described for the period II activity of the summed ON-evoked potentials, which were interpreted as the synaptic excitatory and impulse response of mitral (and tufted) cells to an ON volley (Waldow et al., 1981).

In a previous study (Mori et al., 1981b), we have shown that the inhibitory I_2 component (and possibly also I_1) of the ON-evoked synaptic potentials is associated with a large increase in the membrane conductance of the mitral cell. Thus, one of the possible causes of the suppression of the E_1 component is a shunting effect of the conductance increase in the mitral cell membrane accompanying the I_1 and I_2 components. However, the time course of suppression of the E_1 component was quite different from that of the conductance increase (Fig. 3). The suppression of the E_1 component typically lasted more than 1 sec, while the duration of the membrane conductance increase (measured at the soma) varied in different cells between 100 msec and 1.5 sec (typically less than 400 msec; cf. Mori et al., 1981c). Consequently the conductance increase accompanying

the I_1 and I_2 components of the conditioning response cannot explain the long-lasting nature of the suppression of the E_1 component.

To examine further the above conclusion, we have used a conditioning LOT volley. LOT stimulation also elicits responses with I_1 and I_2 components quite similar to the ON-evoked component (Mori et al., 1981b). In agreement with the above conclusion, the conditioning LOT volley did not suppress the amplitude of the E_1 component of the test ON-evoked response (Fig. 4). The I_1 and I_2 components of the ON- and LOT-evoked responses have been suggested to represent initial and delayed activation of granule-to-mitral dendrodendritic inhibitory synapses (Mori et al., 1981b). These components occur mainly in secondary dendrites, proximal portions of primary dendrites, and somata of the mitral cells. Thus, the sites of membrane conductance increases accompanying the I_1 and I_2 components are spatially separated from the sites of the E_1 component generation in the glomeruli. This explains the lack of suppression of the E_1 component by conditioning LOT stimulation. The marked suppression of the E_1 component by conditioning ON stimulation, by contrast, suggests that the ON volley activates an additional inhibitory membrane conductance at or near the generation sites of the E_1 component, i.e., at or near the distal portions of the primary dendrites of mitral cell.

Intrinsic circuits mediating distal dendritic inhibition. As we have noted, an advantage of the olfactory bulb is that, in attempting to identify neuronal processes contributing to intrinsic circuits, one is aided considerably by the sharp histological lamination and localization of neurons and their synapses in separate layers. Within the glomerular layer, the main candidates for intrinsic elements are the PG cells. Morphological studies have shown that the PG cells receive type I (presumably excitatory) synapses from olfactory nerve terminals as well as from mitral and tufted cell dendrites (Andres, 1970; Hinds, 1970; Reese and Brightman, 1970; Pinching and Powell, 1971; Shepherd, 1972; White, 1972). As discussed in the introduction, physiological studies have shown that PG cells are, in fact, excited by these inputs and have provided evidence that the PG cell dendrites are, in turn, inhibitory onto the mitral and tufted cells at their terminal dendritic tufts in the glomerular layer (Shepherd, 1971; Getchell and Shepherd, 1975).

This close correlation of morphology and physiology does not rule out other mechanisms which might contribute to the results. One possibility is that a conditioning ON volley caused a prolonged suppression of transmitter release at the terminal arborizations of the ON fibers within the glomeruli. It is unlikely that this would come about by presynaptic inhibition, since no synaptic contacts have been observed on the terminal portions of the ON axons (Pinching and Powell, 1971). A generalized effect on the excitability of the presynaptic terminals, as by accumulation of extracellular K^+ , is another possibility. A referee pointed out the possibility that "impulse conduction failure in the terminal arborization of olfactory nerve axons may contribute to the observed suppression of the E_1 component." This would be by analogy with the failing of transmission that has been postulated to occur in branches of Ia fibers to motoneurons in responses to single volleys and the more extensive transmission, and hence larger EPSP, that occurs during post-tetanic potentiation (Lüscher et al., 1983). Such a mechanism is less likely in the present case, because of the lack of axonal branching (the ON axon is believed not to branch before reaching its target glomerulus and arborizes sparingly within the glomerulus (see Land and Shepherd, 1974)); the avoidance of conditioning tetanization; the use of very long interstimulus intervals (2 and 4 sec; see "Materials and Methods"); and the contrast between post-tetanic potentiation of EPSPs in the motoneuron and postconditioning

suppression of EPSPs in the mitral cell. Further experiments will be required to test adequately for the contributions of these and other possible mechanisms to the present results.

The distal local circuit inhibition at or near the terminal tuft of the mitral cell primary dendrites is likely to play an important role in synaptic integration within the glomerulus and control of transmission through the mitral cells (Shepherd, 1977, 1979). At the terminal tuft, there is a convergence of a large number of excitatory ON inputs (Allison, 1953; Ramón y Cajal, 1955). In addition, prolonged synaptic excitation of unknown origin occurs at or near the terminal tuft (Nowycky et al., 1982). These distal excitatory inputs are combined with the distal local inhibition shown in the present study; this local synaptic integration provides the basis for the initial processing of the olfactory input. Thus, the mitral cell provides a model for the integrative function of synaptic inhibition at distal dendritic sites, as is also found in crustacean receptor cell dendrites (Kuffler and Eyzaguirre, 1955). These stand in contrast to the more widely known examples of inhibitory inputs at or near the cell body, as in motoneurons (Eccles, 1964) or Purkinje cells (Eccles et al., 1967). The synaptic potentials in the glomerular tuft are the outcome of this complex distal integration and constitute the functional link for transmission to the mitral cell body. Contributing to this linkage are dendritic spike generation (Mori et al., 1982) and dendrodendritic synaptic output from the mitral cell primary dendrites.

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