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Reversible inactivation of the medial septum: selective effects on the spontaneous unit activity of different hippocampal cell types

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The contribution of septal afferents to spontaneous hippocampal single unit activity was examined by reversibly inactivating the medial septal nucleus using microinjections of the local anesthetic lidocaine. Septal inactivation reduced spontaneous firing of cells in stratum granulosum and in the hilar/CA3 region for periods of up to about 15 min. The firing rates of CA1 complex-spike (pyramidal) cells, however, were not changed, although CA1 theta cells (inhibitory interneurons) exhibited a significant reduction in spontaneous rate. One interpretation of this pattern of results is that the output of CA1 pyramidal cells is maintained roughly constant in spite of reduced input from CA3 because of a proportional reduction in feedforward inhibition. This interpretation is consistent with Marr's[22] formulation of the manner in which the hippocampus implements distributed associative memory. Alternatively, afferents to CA1 originating from regions other than CA3 may play a larger role in regulating CA1 output than previously assumed.

INTRODUCTION

The hippocampus receives input from two major projections, one from the entorhinal cortex and the other from the medial septum. Entorhinal terminals generate by far the largest percentage of hippocampal afferent synapses[19,23]. Medial septal afferents are concentrated in the fascia dentata and CA3, and are comparatively sparse in CA1[46]. While these terminals constitute a much smaller projection than the entorhinal system, their concentration on granule cell somata or inhibitory interneurons in the dentate region[15,16,37] places them in a position to influence dramatically information flow through the hippocampus. Indeed, it has been shown that prestimulation of the medial septum increases the excitability of granule cells[2]. This change in excitability probably results from a medial septal-induced reduction in feedforward activation of inhibitory interneurons[5,6,12,29]. The present study further examines septal influences on hippocampal physiology by assessing the effects of reversible inactivation[20,34,38–40] of the medial septum on spontaneous hippocampal single unit activity.

Septal influences on hippocampal unit discharge rates have been examined in freely behaving and immobilized animals[8,13,27,28,36,48]. However, while some studies suggest that afferent lesions alter sensory stimulation effects on hippocampal unit firing rates, other studies fail to report such effects. Additional concerns regarding these lesion experiments make them difficult to evaluate. For example, since relatively prolonged postsurgical recovery was required, synaptic reorganization or retrograde degeneration probably influenced test responses. Moreover, since control and test unit responses were usually obtained from different cells, the findings may have been subject to sampling biases. To circumvent some of these problems, in the present study we *reversibly* inactivated the medial septal area using microinjections of lidocaine. The inactivation effects are immediate, and last about 15 min. We

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were thus able to monitor the *same* hippocampal cells before, during, and after treatment.

In a subset of animals, we also conducted preliminary experiments involving lidocaine injection into the ipsilateral entorhinal cortex, the supramammillary nucleus, or the contralateral hilus. These systems were of interest since there is anatomical evidence suggesting that they contribute most of the non-septal afferents[41,45,50] to the dentate gyrus. Furthermore, it has been shown that stimulation of these afferents produces significant physiological alterations in the hippocampus. For example, it is well established that electrical stimulation of perforant path fibers produces large excitatory postsynaptic potentials in hippocampal cells[4]. Electrical stimulation of supramammillary cells increases granule cell excitability by inhibiting perforant path-induced basket cell discharge[29]. Finally, prestimulation of the contralateral hilus has been shown to attenuate the perforant path-induced population spike[7,11] and to activate unit discharge near stratum granulosum[7,10].

A preliminary report of the results of this study has been presented in abstract form[30].

MATERIALS AND METHODS

Twelve nine-month-old Fischer-344 male rats were obtained from Charles River Laboratories (Kingston, N.Y.). All rats were allowed to adapt to the laboratory for two–four weeks before participating in this study. Experiments were conducted between 09.00 and 19.00 h. Lights were on in the colony room between 06.00 and 18.00 h.

Food and water were removed 24 h before surgery. Rats were initially anesthetized with 33 mg/kg Nembutal (50 mg/ml; i.p.), then maintained under anesthesia by continuous infusion of 25 mg/kg Nembutal (0.075 ml/h). Holes were drilled at the following stereotaxic coordinates (according to Paxinos and Watson[32]): the medial septum (A-P 0.7 mm anterior to bregma, L 0.0 mm, D-V –5.5 mm), the supramammillary nucleus (A-P –4.5 mm, L 1.0 mm, D-V –8.0 mm), and the ipsilateral entorhinal cortex (A-P –8.2 mm, L –4.7 mm, D-V –6.0 mm). In 5 rats, a hole was also drilled above the contralateral dorsal hippocampus (A-P –4.0 mm, L –2.4 mm, D-V –3.3 mm). A 2 mm-square hole was drilled above dorsal hippocampus to facilitate multiple penetrations of the recording electrode in the same rat (A-P –3.8 to –4.2 mm, L –2.2 to –2.4 mm). Identification of the final depth for the recording electrodes was determined physiologically and by stereotaxic depth. To aid in the identification of stratum granulosum units as granule or basket cells[29], stimulating electrodes (114 μm Teflon-coated stainless steel wire) were placed in the angular bundle of 3 rats at the following coordinates: A-P –8.1 mm, L –4.4 mm, D-V –3.0 mm. During recording sessions, the skull holes were covered with saline-soaked cotton. Reference and ground leads were soldered to jewelers screws which were secured to the skull.

At the end of each experiment, the rat was first perfused with 0.9% NaCl, then 10% formalin. The brains were removed placed in formalin-filled containers for 24 h, then allowed to sink in 30% sucrose formalin for 48 h. Frozen sections (40 μm-thick) were stained with Cresyl violet for examination of electrode tracts and injection sites.

Single units were recorded using the stereotrode technique essentially as described by McNaughton, O'Keefe, and Barnes[26]. This procedure involves independently recording cellular activity through two lacquer-coated tungsten wires (20 μm diameter; California Fine Wire) bonded together with Epoxylite. Each wire was insulated up to the tip. After cutting with sharp scissors, the exposed electrode tips were plated with gold. Final impedances were 200–300 kΩ (tested at 1 kHz). The incoming signal from each channel was amplified 5000–10,000 times, then bandpass filtered between 600–800 Hz to 6 kHz. The analog signals were passed through a window discriminator such that if the signal from either channel exceded a predetermined threshold, a 1 ms sampling period began. During the sampling period, the maximum and minimum voltages of each analog signal, as well as the latency of these values from the onset of the sampling period, were calculated in hardware by a spike preprocessor (FMZ Electronics). A PDP-11/23 computer collected the 8 spike parameters and logged the time of each event. These parameters were subsequently used to isolate single units from the multiunit record according to a multidimensional cluster analysis program (McNaughton, unpublished) which allowed one to iden-

tify (by visual inspection) the set of boundaries, or thresholds, associated with each unit. The advantage of the cluster analysis approach is that, since it provides multidimensional windows, one is able to obtain more accurate separation of single units. A discussion of the improved quality of unit isolation that can be achieved through use of the stereo data collection procedure has been provided by McNaughton et al.[26]. Detailed documentation of an improved version of the cluster separation technique used in the present report can be obtained from Brainwave Systems (Broomfield, CO).

Micropipettes (tip o.d., 40 μm) filled with a solution of 2% lidocaine (Sigma; dissolved in 0.9% NaCl, pH adjusted to 7.0 with 10 N NaOH) were lowered into target nuclei before insertion of the recording electrode. Each lidocaine micropipette was connected to a polyethylene tube (PE 20), which in turn was connected to a 1 ml syringe. The tube was graduated, thereby permitting one precisely to monitor the movement of the meniscus as air pressure was manually applied. Injections were calibrated such that when the meniscus moved 1 unit, 0.1 μl of solution was ejected. This injection procedure represents a modified version of that reported by Malpeli and Schiller[20].

Schiller et al.[40] have demonstrated the relatively non-toxic inactivation effects of repeated injections of lidocaine into central nervous system nuclei. Thus, each rat received several injections of lidocaine over the course of the day. Following acquisition of baseline unit activity for 15 min, lidocaine was injected into either the medial septum (0.3 μl), the supramammillary nucleus (0.4 μl), the ipsilateral entorhinal cortex (0.5 μl), or the contralateral hilus (0.4 μl) over a period of about 10 s via the pipette that was positioned just dorsal to the target site. To control for spread of the lidocaine to the recording site, some injections were made approximately 1 mm above the medial septum.

RESULTS

A total of 153 units recorded in the hippocampus were separated into 4 groups. Units encountered in CA1 were classified as theta or complex-spike cells according to criteria of Fox and Ranck[14] and Ranck[33]. CA1 cells that fired single action potentials of short duration were classified as theta cells (n = 25), while cells that fired bursts of multiple spikes were classified as complex-spike cells (n = 43). Individual action potentials of complex-spike cells were of longer duration (300-400 μs) than those of theta cells (200-300 μs). Short duration, single spiking units recorded near the supra- and infrapyramidal blades of the dentate gyrus were referred to as stratum granulosum units (SG; n = 56). Complex-spike cells found in the dentate region were located about 200–800 μm below the suprapy-

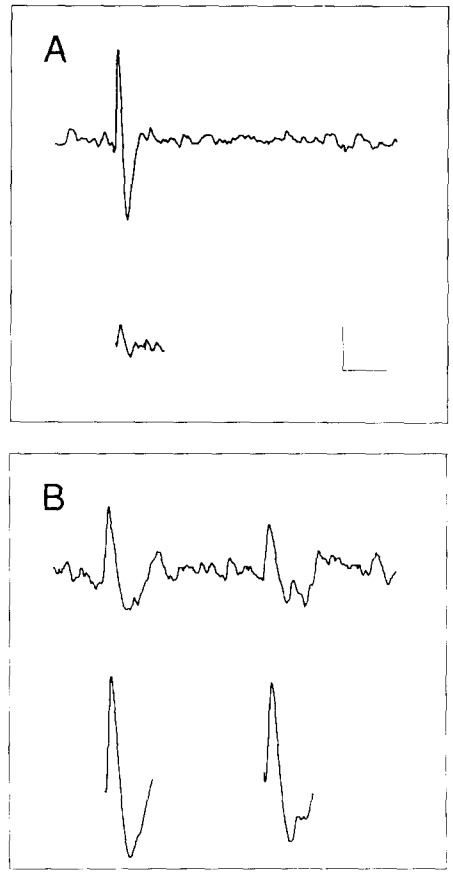

Fig. 1. Analog traces of a CA1 theta cell (A) and a CA1 complex-spike cell (B) recorded with the stereotrode. The upper trace in each panel represents the signal on the X channel and the lower trace represents the signal on the Y channel. A DC offset was introduced into the Y channel output to the oscilloscope (except during the 1 ms sampling period) to permit one to check for sampling of the correct window. The complete trace was available to the computer. Complex-spike cells typically fired bursts of multiple spikes while CA1 theta units discharged single spikes. Individual spike durations were 350 μs for the complex-spike cell and 250 μs for the theta cell. Calibration: A, 120 μV, 1 ms; B, 57 μV, 1 ms.

ramidal blade. These units were referred to as hilar/CA3 complex-spike cells (n = 29). Fig. 1 provides examples of the analog signals recorded from different hippocampal cell types.

The preinjection spontaneous discharge rate was monitored for at least 15 min. This baseline rate was considered stable if it did not vary by more than about 15–20% across successive 2 min epochs. Rate determinations were based on a sampling bin size of 20 s (see Fig. 4). The effect of septal inactivation on unit discharge depended on the cell type recorded. Fig. 2 compares the mean (± S.E.M.) firing rates of cells before, immediately after, and 15 min after septal injection of lidocaine. The average firing rate of CA1 theta cells was significantly altered by septal inactivation (repeated measures ANOVA, $F_{2,24}$ = 3.32, $P < 0.05$). More than half of the theta cells (56%) showed rate changes of more than 30%. In contrast, the spontaneous rates of CA1 complex-spike cells did not change as a function of septal inactivation, $F_{2,42}$ = 1.10, ns. The firing rates of SG cells were significantly reduced following septal injection of lidocaine, $F_{2,53}$ = 6.90, $P < 0.01$. Scheffe analyses (α = 0.05) indicated that the firing rate of SG cells immediately after injection was significantly lower than the firing rate before injection or after recovery. The mean rates of hilar/CA3 cells declined by about 30% after septal inactivation.

Although the mean rates of certain hippocampal cells were reduced following septal inactivation, individual unit responses varied. Frequency distributions of the percent change in rate are provided in Fig. 2. CA1 complex-spike cells did not show the variety of responses shown by CA1 theta, SG, and hilar/CA3 cells. Indeed, only 21% of CA1 complex-spike cells showed rate changes of more than (plus or minus) one-third following septal inactivation. This contrasts with the finding that 56% and 65% of CA1 theta and SG cells, respectively, were temporarily altered by more than one-third. Hilar/CA3 cells exhibited a similar range of responses as SG and CA1 theta cells.

In order further to characterize the response changes of cells within the granular layer, 15 of the 56 SG cells were also subjected to physiological identification as basket or granule cells according to the criteria of Mizumori et al.[29]. Briefly, the identification tests involved assessing the relationship between perforant path-induced unit activation and the occurrence of a population spike in the field potential. This was accomplished by recording simultaneously the filtered unit activation through one wire of the stereotrode and the unfiltered field potential through the second stereotrode wire. When two pulses were delivered to the perforant path (25 ms interstimulus interval) at a stimulus intensity above the population spike threshold, basket cells discharged with equal probability during the first and second field responses. Granule cells, on the other hand, were much less likely to fire

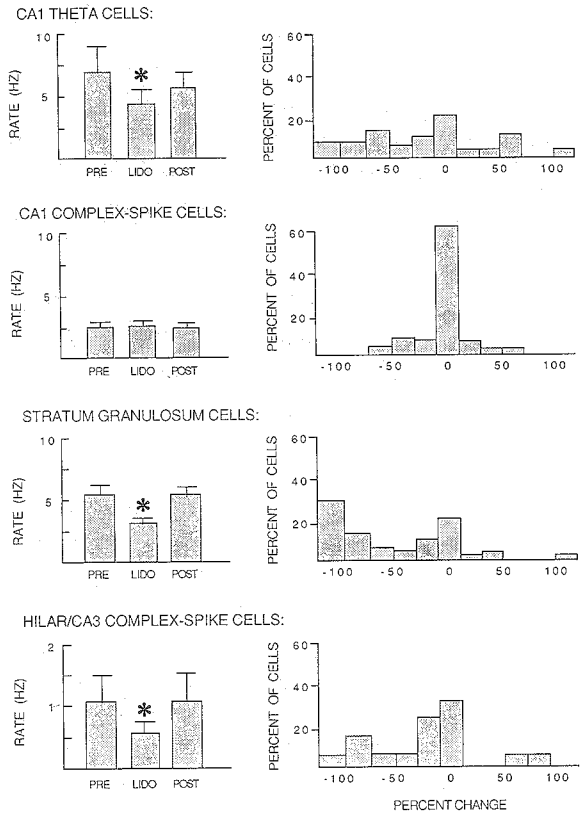

Fig. 2. The histograms on the left illustrate the mean (± S.E.M.) spontaneous discharge rates of different hippocampal cell types recorded before (PRE), immediately after (LIDO), and 15 min after (POST) lidocaine-induced inactivation of the medial septum. The average rates of CA1 theta cells, stratum granulosum cells, and hilar/CA3 cells were significantly reduced following septal inactivation. In contrast, CA1 complex-spike cells showed no change in rate. The frequency distributions on the right show the range of responses in terms of the percent change in rate. All cell types except the CA1 complex-spike cells exhibited a relatively wide range of effects. Asterisks indicate statistically significant changes (α = 0.05) in discharge rates following septal inactivation.

during the second field response. When the perforant path intensity was set below the threshold for a population spike, basket cells continued to be activated while granule cells were not. Examples of putative basket and granule cell responses to paired pulse stimulation of the perforant path are shown in Fig. 3. Fourteen of the cells tested were tentatively classified as basket cells, and one was classified as a granule cell. The firing rates of 7 of the presumed basket cells dropped by more than 30% after septal inactivation. The discharge rates of two basket cells increased by more than 30%. The spontaneous rate of the one SG unit identified as a granule cells was reduced by more than 90%.

Injection of lidocaine 1.0 mm above the medial septum never affected the firing rates of SG or hilar/CA3 cells that were altered if lidocaine was injected into the septum (n = 11). However, although the direct effects of lidocaine were localized, it is important to note that fibers of passage through the medial septal region were likely to have been inactivated. Injection of the vehicle solution alone did not alter the firing rates of any of the 8 SG cells tested.

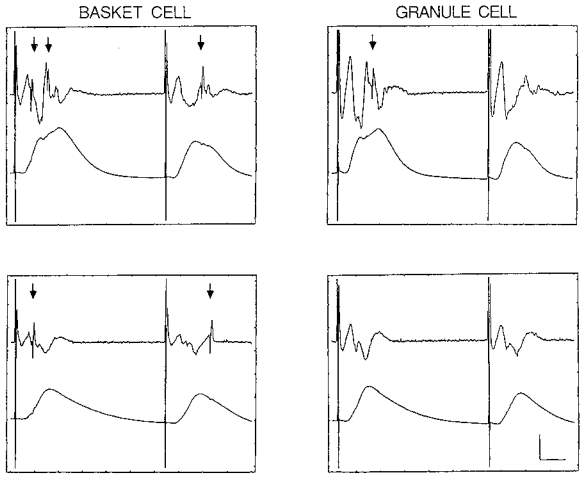

Fig. 3. Examples of perforant path-elicited basket and granule cell discharge. The unfiltered unit activation trace is shown as the upper trace in each panel. The filtered field potential is shown below the unit trace. Putative basket cells were activated during both field potentials elicited by paired stimulations of the perforant path if the stimulus intensity was above the threshold for a population spike (upper left). At stimulus intensities below the population spike threshold, basket cells continued to be activated (bottom left). In contrast, cells classified as granule cells discharge only once during the window of the population spike at high stimulus intensities (upper right), and not at all when the stimulus intensity was below population spike threshold (bottom right). Arrows identify unit activation in the filtered traces. Calibration: 4 ms; 250 μV for unit traces and 5 mV for field potential traces.

Ipsilateral entorhinal inactivation produced a similar pattern of unit effects as septal inactivation. The average firing rates of SG cells (n = 19) were significantly lower after lidocaine injection ($P < 0.05$). Overall, hilar/CA3 (n = 20) or CA1 complex-spike cells (n = 23) did not show a statistically significant change in rate. However, entorhinal inactivation reduced the rate of 43% of hilar/CA3 cells by more than 30%. This contrasts with only 4% of CA1 complex-spike cells showing a change in rate.

Supramammillary injections did not produce a significant change in the firing rate of any cell type (n = 40, cells recorded from 4 rats; $P > 0.10$ for all). Lidocaine injection into the contralateral hilus usually produced no clear change in the rate of SG and hilar/CA3 cells (n = 31 cells, recorded from 6 rats). However, rate increases of more than 60% were observed from 4 dentate units.

Although similar proportions of cells were affected by entorhinal or septal inactivation, sometimes a given cell responded differentially to injections in one or the other area. For example, 5 SG cells showed rate changes of greater than 30% following septal, but not entorhinal, inactivation. Six other SG units responded to lidocaine injection in the entorhinal area, while showing no clear response to septal inactivation. Examples of SG unit responses to lidocaine injection into different afferent nuclei are shown in Fig. 4.

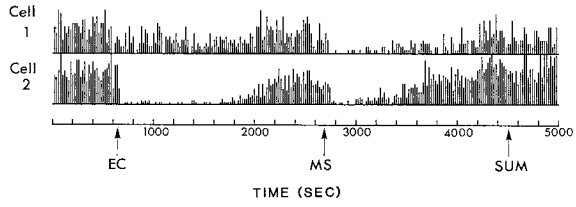

Fig. 4. A continuous record of two, simultaneously recorded SG unit responses to lidocaine injection into the ipsilateral entorhinal cortex (EC), the medial septum (MS), and then the supramammillary nucleus (SUM). The bin width is 20 s. The maximum number of spikes per bin was 47 for cell 1 and 37 for cell 2. These cells were differentially influenced by lidocaine inactivation of the 3 afferent nuclei.

DISCUSSION

Lidocaine-induced reversible inactivation of the medial septum selectively altered the spontaneous firing rates of SG, hilar/CA3, and CA1 theta cells (inhibitory interneurons). In contrast, the firing rates of CA1 complex-spike (pyramidal) cells were rarely altered. Results of anatomical investigations of the septohippocampal pathway suggest that the effects of septal inactivation are likely to be rather complex. Septal axons form both asymmetric and symmetric synaptic contacts onto granule, basket, and some pyramidal cells[9,16,35]. The different varieties of synapses do not necessarily correspond to afferents using a particular neurotransmitter. For example, the septohippocampal afferents that contain choline acetyltransferase, and thus are presumably cholinergic, form both asymmetric and symmetric contacts with granule, pyramidal, and nonpyramidal cells[16]. The septal afferents demonstrating glutamic acid decarboxylase immunoreactivity[18], and which are thus likely to be GABAergic, also form symmetric contacts with inhibitory interneurons in hippocampus[15]. Other neurotransmitters have been found in septohippocampal afferents (e.g. substance P[47], oxytocin, and vasopressin[42,43]). These also may have been involved in the modulation of hippocampal activity.

In addition to the direct effects of septal inactivation, hippocampal unit activity may have been affected by indirect mechanisms. For example, medial septal terminals have been identified in layer II of entorhinal cortex[1]. Cells from layer II provide an excitatory input to granule cell dendrites in the molecular layer[45] as well as to the apical tips of CA3 pyramidal cells[44]. Therefore, the possibility exists that medial septal inactivation compromised entorhinal cells that normally activate SG and CA3 cells. Of interest in this regard are the findings that layer III of entorhinal cortex preferentially innervates Ammon's horn[45], and layer III receives relatively few septal afferents[1]. These anatomical results are consistent with the finding that CA1 pyramidal cells were not affected by septal inactivation. In addition, part of the effects in CA3 may have been indirectly due to reduced mossy fiber activation.

The criticism might be raised that lidocaine spread to the recording sites in these experiments. Had this occurred however, one would have expected always to observe a reduction in firing rate. On the contrary, not only did we observe both increases and decreases in firing rates, but cells recorded simultaneously often responded differently to a single injection. Lidocaine injection into the contralateral hilus also resulted in increased dentate activity for some units. This increase in unit activity may be due to inactivation of the commissural input to dentate inhibitory neurons[7,11]. Furthermore, in agreement with quantitative analyses of the spread of effects of lidocaine performed by others[39,40], we found that injection of lidocaine 1.0 mm above the medial septum did not produce changes in the firing rates of units that were affected by injections directly into the septum. It should be noted, however, that septal injection of lidocaine probably inactivated fibers of passage, as well as cell bodies, in the septal region. Thus, although the overall pattern of unit effects is consistent with the known topography of septal terminals in hippocampus[46], determination of the specific mechanism(s) responsible for the observed changes in unit activity, a finding now verified in freely behaving animals[30,31], must await further investigation. It is possible that different mechanisms will be involved for different cell types.

Although the mechanisms underlying afferent inactivation effects on hippocampal unit activity are presently not certain, several tentative conclusions of some theoretical importance can nevertheless be offered. It is possible, for example, that the output of CA1 pyramidal cells remained unchanged despite reduced input from the hilar/CA3 region because of a proportional reduction of feedforward inhibition. This interpretation is consistent with the suggestion by Marr[21,22] that feedforward inhibition effectively divides the excitation of principle cells by an amount proportional to the number of afferents that are active. Such a mechanism was postulated to underlie associative recall and pattern completion in hippocampal circuitry (see McNaughton and Morris[24] and McNaughton and Nadel[25] for an elaboration of this hypothesis in terms of more recent neurophysiological data).

An alternative interpretation of the results of this study is that the physiologically most significant input to CA1 is not the CA3 Schaffer collateral system as commonly assumed (e.g. the 'trisynaptic

loop' of Andersen, Bliss, and Skrede[3]), but rather it is some other direct input from cortex. Indeed, several studies have demonstrated direct projections from the deep layers of entorhinal cortex to CA1[17,45,49]. Such projections may play a larger role in determining CA1 discharge rates than originally assumed.

In conclusion, as shown in investigations of the visual system[20,40], local reversible inactivation of afferents to the hippocampal formation appears to be a viable adjunct to the more traditional techniques of electrical stimulation and lesions in unravelling the details of functional connectivity. As the method is easily adapted to conscious, unrestrained animals[31], it should make a substantial contribution to understanding the nature of the role of these circuits in higher cognitive function.

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