VESTIBULAR PROJECTIONS TO HYPOTHALAMIC SUPRAOPTIC AND PARAVENTRICULAR NUCLEI

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INTRODUCTION

In a previous paper it was shown that a volume receptor outside the thorax is located within the inner ear (7). Pressure changes in the inner ear were able to modify vasopressin (ADH) release, thus representing an additional controlling system. The release of the ADH from neurons localised in the hypothalamic supraoptic (SON) and paraventricular (PVN) nuclei depends upon the homeostatic control which is modulated by the osmoreceptors and by the afferent branch of volume receptors located in the walls of large thoracic vessels and in the right atrium (24, 34, 35, 39, 42, 45). Variations of the inner ear pressure were followed by an inverse response: increase in the inner ear pressure produced a decrease in ADH secretion and *vice versa*. These results are consistent with the hypothesis that the inner ear has a functional role in the release of ADH. The volume receptors have an elastic structure contained within a rigid structure. Thus, a large excursion of pressure could easily be induced by small variations in the volume of inner ear fluids which are in dynamic equilibrium. The aim of the present research was to study the characteristics of the neuronal connections between the inner ear structures and the hypothalamic nuclei which are responsible for ADH release.

METHODS

The experiments were carried out on 60 guinea pigs of both sexes weighing 400-500 g, bought commercially (Morini, San Polo D'Enza, Italy), kept in an appropriate animal environment and maintained on a standard diet. After an overnight fast, with only drinking water allowed ad libitum, the animals were anesthetised with ketamine (50 mg/kg) and diazepam (10 mg/kg) and tracheotomized. Plastic catheters were inserted into the jugular vein for fluid infusion and into the femoral artery for pressure measurements. The animals were then fixed to the stereotaxic frame. EKG and internal temperature were monitored throughout the experiment. Additional doses of anesthetic were periodically added. Under microscopic dissection, the right eighth nerve was reached within the inner meatus via a translabyrinthine approach, along the facial nerve, which was removed. The eighth nerve was left intact as well as its branches. Bipolar stainless steel electrodes (intertip distance: 0.7-0.9 mm), lacquered except for the tips, were placed on the vestibular nerve trunk, which was protected by applying a mixture of paraffin and mineral oil. Stimulation of

the eighth nerve was performed by means of single or double electric impulses (interval: 1 msec): duration 0.1 msec, frequencies ranging from 0.5 to 10 Hz, intensity just above the threshold for inducing ocular jerks. This intensity was constant throughout the experiment. In control experiments, this adjustment of the level of stimulation was proved to be 2.2 times the threshold for the N_1 response and adequate for generating a clear P_1-N_1-N_2 wave sequence by recording from the ipsilateral vestibular nuclear complex (2, 3, 31). Furthermore, the results of previous researchers using the same technique exclude possible contamination from responses arising from structures not related to the labyrinth, in particular the 7th nerve which in any case was removed (2, 8, 17, 25, 26, 36, 44). A craniotomy was performed in order to expose a zone of the cerebral cortex wide enough to introduce stimulating and recording electrodes. The animals were then paralyzed and artificially ventilated with the respiratory gases under control. Field potentials and single unit activity were recorded from the SON or the PVN by means of tungsten microelectrodes (0.8-1.2 MOhm) advanced by an electronic microdrive. The stimulating electrodes were bipolar stainless steel electrodes, lacquered except for the tips, positioned in the neurohypophysis in order to elicit antidromic responses according to the method of Poulain and Wakerly (30, 41). Analysis of spontaneous and evoked electrical activity of neurons localized in both hypothalamic nuclei was performed by computer using the Computerscope EGAA by R.C. Electronic Inc. software for electrophysiological data. Evoked potentials and post-stimulus-time-histograms (PSTH) of the neuronal responses elicited by vestibular nerve stimulation were analyzed. In a second group of 10 animals the experimental design was the same except for the preparation of the labyrinth which was exposed by opening only the epitympanic recessus in order to perform caloric stimulation by using warm (45° C) or cold (15°C) water. At the end of the experiments an electrolytic lesion marked the recording spots.

RESULTS

The results are based on the analysis of 62 responding neurons out of 98 (63%). Thirty-eight responsive cells out of 53 (71.7%) were localized in the SON and 24 out of 45 (53.3%) in the PVN. Their position was ascertained not only by means of histologic control (Fig. 1 A and B) but also by antidromic activation performed by stimulating the neurohypophysis. In addition, changes in the discharge rate of single units were induced by hypotonic or hypertonic fluid infusion. Fig. 2 shows the expected effects on the spontaneous firing rate of a SON neuron during the infusion of hypotonic (250 mosmol/kg) (A) and hypertonic (360 mosmol/kg) (B) solutions at a rate of 1.5 ml/min during 180 sec.

Fig. 3 shows the responses of a neuron located in the SON to electrical stimulations of the ipsilateral vestibular nerve. The cell exhibited excitation followed by inhibition. This pattern of response is typical for all the neurons recorded from the SON. In all the 38 units, the excitation started at 6.8 ± 0.9 (mean $\pm$S.D.) msec and was characterized by a mild increase in the discharge probability, while the inhibition was more pronounced starting at 11.1 ± 1.2 msec and lasting up to 27 msec. As shown in Fig. 3 A, this inhibitory effect was interrupted by a disinhibition period which was suppressed by increasing the frequency of stimulation (B, C).

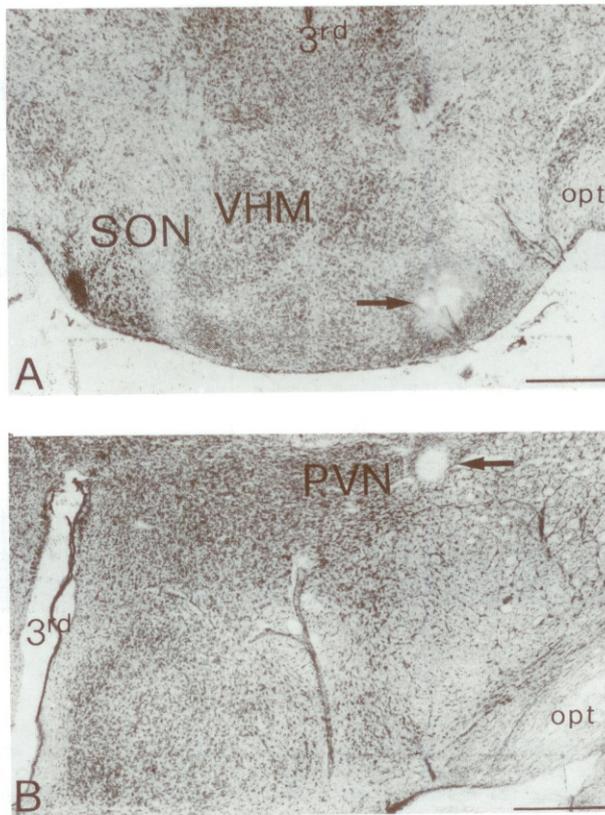The responses recorded from the 24 PVN neurons were different in type. Fig. 4

Fig. 1 – *Labyrinth and ADH release.*

The arrows point to electrolytic lesions in the hypothalamic SON (A) and PVN (B). SON: supraoptic nucleus; PVN: paraventricular nucleus; VHM: ventromedial hypothalamic nucleus; 3rd: 3rd ventricle; opt: optic tract. Calibration: 0.5 mm.

illustrates the more frequent patterns of response observed during these experiments. Fig. 4 A shows early inhibition followed by excitation (7 units, 29.2%), while in Figs. 4B and 4C excitation followed by late inhibition (11 units, 45,8%) and pure excitation (6 units, 25%) can be seen. The characteristics of the responses recorded from the PVN differed from those of the SON also in the response latencies. Early inhibition (7 cells) started at 5.1 ± 0.6 msec, excitation at 7.9 ± 0.9 msec in all the 24 units and late inhibition (11 cells) at 18 ± 2.1 msec.

Further evidence of the influence of the impulses travelling along the eighth nerve on the neurons located in both SON and PVN was observed in the second group of animals. In this case the responses of SON and PVN neurons during caloric stimulation of the labyrinth were studied. A total of 19 cells (10 in SON and 9 in PVN) was analysed. Seven cells (70%) of SON and 5 cells (55.5%) of PVN were responsive. Fig. 5A illustrates the increase in the discharge rate of a neuron located in the PVN following caloric stimulation of the ipsilateral
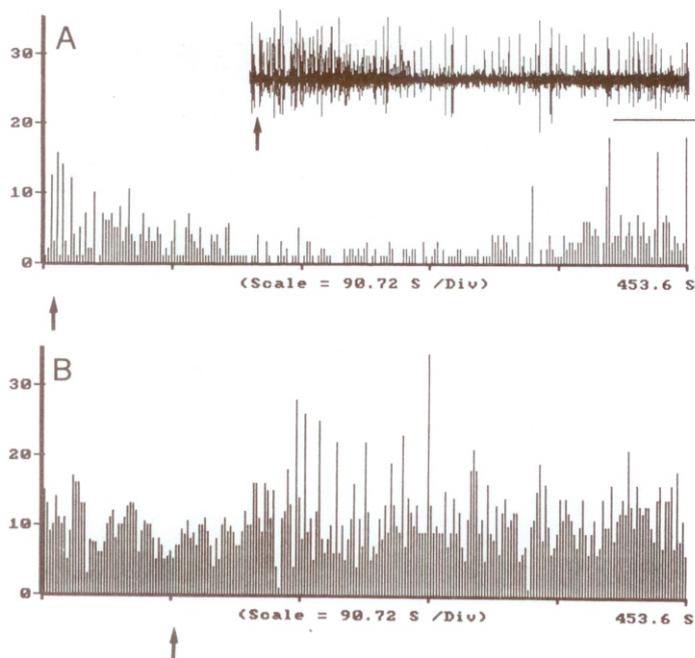
Fig. 2 - *Labyrinth and ADH release.*

Unitary discharge frequency of a neuron located in the SON during dripping with hypotonic (A) and hypertonic fluid (B). The arrows indicate the beginning of 180 sec of infusion. In this as well as in the Fig. 5, the ordinates indicate the discharge rate of the units expressed as number of counts per time units (2.016 sec) and the abscissas indicate time in seconds. The inset in A reports the respective raw data; horizontal calibration: 90.72 sec, vertical calibration: 150 μV.

labyrinth with cold water and the decrease in the discharge rate (Fig. 5B) during warm water stimulation. This pattern of responses was similar in both nuclei for ipsilateral vestibular stimulation, but one cell of SON which responded with an opposite pattern. These effects usually lasted up to 30-60 sec and gradually disappeared within 90 seconds.

DISCUSSION

The results of the present experiments have clearly shown that impulses travelling along the eighth nerve are capable of modulating the electrical activity of single units located in the magnocellular part of the SON and PVN. The final effect would be that eighth nerve volleys contribute to the release of ADH. The fact that receptors controlling vasopressin secretion are located within the inner ear is not surprising. The labyrinthine and acoustic formations are both contained in an elastic structure which is surrounded by a rigid capsule. As reported in our previous study (7) showing that pressure changes in the inner ear modulate ADH release, the relation between volume and pressure within the inner ear de-
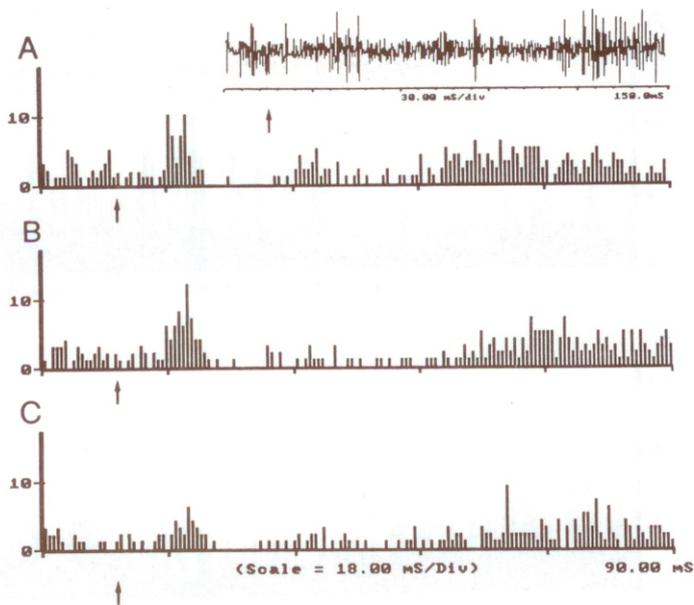
Fig. 3 – *Labyrinth and ADH release.*

PSTHs of the responses of a cell, localized in the SON, following 100 stimuli applied to the ipsilateral eighth nerve. The arrows indicate the time of the stimulus application at 1 Hz in A, 4 Hz in B, 6 Hz in C. In this as well as in Fig. 4, the ordinates indicate the number of spikes/bin and the abscissas indicate the time in msec. The inset shows the raw data of A.
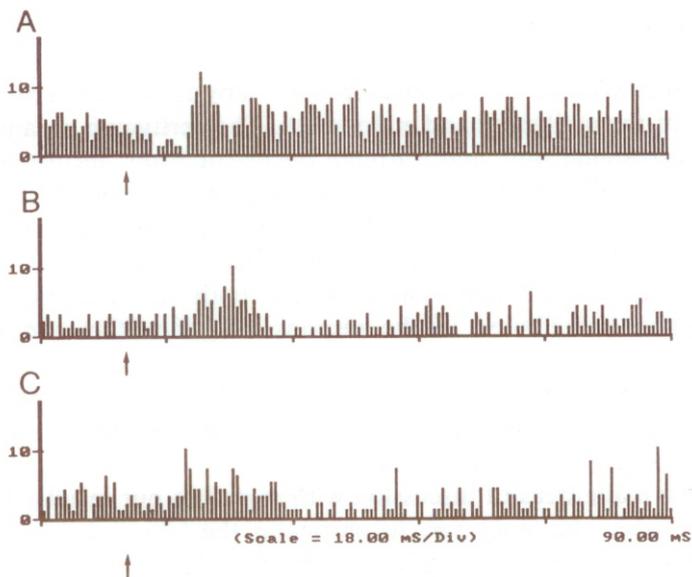
Fig. 4 – *Labyrinth and ADH release.*

PSTHs of the responses of three cells, localized in the PVN, following 100 stimuli applied to the ipsilateral eighth nerve. The arrows indicate the time of the stimulus application at 1 Hz.
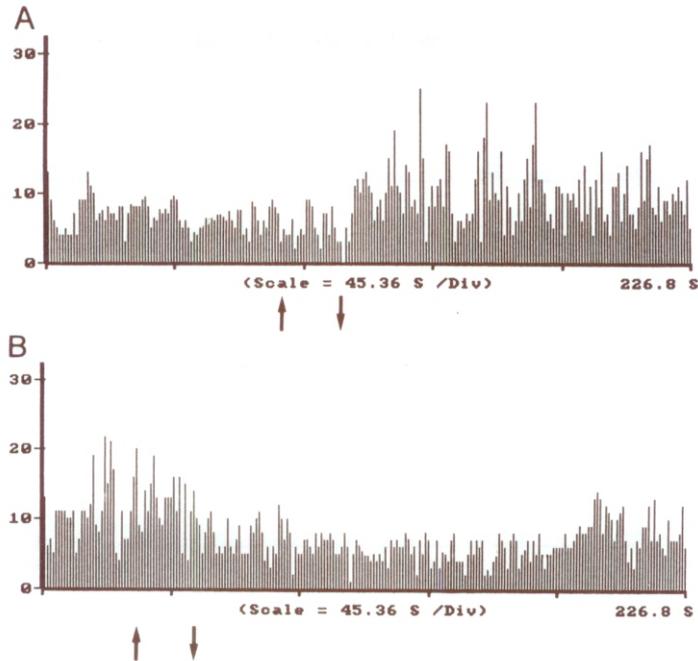
Fig. 5 - *Labyrinth and ADH release.*

Unitary discharge frequency of a neuron located in the PVN during caloric stimulation of the ipsilateral labyrinth with cold (14°C, A) or warm (46°C, B) water. The upward and downward arrows indicate the beginning and the end of the stimulation.

pends on the compliance of the membranous labyrinth. This structure balances the variations of the perilymph and endolymph. The perilymph parallels the dynamics of the cerebro-spinal fluid and, through the elastic walls, influences the pressure of the endolymph. Thus, it is likely that volume receptors located within the inner ear respond to these changes and represent an additional controlling system for ADH release. The results of the present research suggest that these receptors are located in the labyrinthine system. While both the acoustic and vestibular fibers might have contributed to the responses of the SON and PVN units to electrical stimulation of the eighth nerve trunk, it was clearly shown that neurons of the same hypothalamic nuclei, driven by fluids infusion, were influenced by the caloric stimulation of the labyrinth. We could then prove the influence of the vestibular system on these neurons.

There are two main areas of discussion with regard to our results: 1) the neuronal connections between the inner ear, in particular the labyrinth, and the SON and PVN; 2) the functional role of this sensory system. As to the first point, it should be noted that no direct connections have been traced so far from the vestibular nuclei to the SON and PVN. However, it is possible to trace many indirect connections. The two hypothalamic nuclei may, in fact, receive synaptic inputs from

different sources. Ascending fibers to the hypothalamus leaving the reticular formation at the level of the A_{10} cell group (12) have been traced by Carpenter and Strominger (10). Noradrenergic fibers reach the two nuclei from the nucleus of the solitary tract (A_2 cell group), while non-noradrenergic projecting fibers arise from the neurons lying just dorsal to the lateral reticular nucleus (A_1 cell group) (12, 19, 37, 39, 41). In addition, the A_2 cell group send an indirect projection to SON and PVN through fibers contacting the A_1 cell group (40, 45). These fibers run within the so-called ventral noradrenergic bundle (37). Moreover, ascending fibers through the dorsal noradrenergic bundle connecting the locus coeruleus (A_6 cell group) with SON and PVN have also been described (24, 39, 40, 45).

Different linking pathways can, therefore, be established. The labyrinthine volleys may reach the SON and PVN through bulbopontine reticular ascending projections. A different route that transmit labyrinthine volleys to SON and PVN is represented by the connection between the cerebellar fastigial nucleus and the A_1 and A_6 cells groups (13, 14, 15) since strong vestibulo-fastigial projections are well established (10). The cells lying dorsally to the lateral reticular nucleus and the locus coeruleus may also represent a source for labyrinthine projections to SON and PVN. These structures receive in fact large vestibular inputs (9), and there is evidence that reticular neurons can be affected by the ampullar and macular stimulations (18, 27). Moreover, recent investigations have shown that the locus coeruleus neurons respond to sinusoidal stimulation of labyrinth receptors (29) and intervene in the gain regulation of the vestibulospinal reflexes (28). Therefore these structures may represent an important relay station conveying labyrinthine inputs to the hypothalamic nuclei. Although it is known that norepinephrine acts in the central nervous system by modulating the responses of target neurons to excitatory and/or inhibitory neurotransmitters (cf. 1 for ref.), it has also been reported that norepinephrine released from the brainstem neurons controlling the vasopressin secretion is excitatory in nature (32, 33). A further path transmitting labyrinthine volleys to SON and PVN could also be taken into account. It has been shown that the area postrema may influence the emetic center to drive the SON and PVN (40) and that the labyrinth is able to modulate the neurons of the area postrema (22).

In conclusion, neuroanatomical and electrophysiological investigations show that clear, though indirect, connections exist between the vestibular system and the SON and PVN.

With regard to the functional role of the labyrinthine control of vasopressin release, it is likely that this system represents a finer bias of homeostatic balance not only towards volume but also sodium excretion. This assumption is also supported by the fact that the inner ear derives from the lateral organ of the fish, which is sensitive to water composition (20). Furthermore, it has been observed that water deprivation provokes in the gerbil modifications of the inner ear morphology (4, 5, 6, 23) and that the inner ear of the guinea pig contains receptors for the atrial natriuretic peptide, which is involved in natriuresis (16, 21, 38). On the other hand, it is likely that hypothalamic responses to labyrinthine stimula-

tion might serve for vasopressin release at brainstem level and intermediolateral gray column of spinal cord for controlling somatic as well as visceral functions (11, 43). Microinjection of vasopressin in the locus coeruleus and the neighbouring dorsal pontine reticular formation controls posture and the vestibulospinal reflexes (1). Thus, the labyrinth can be also regarded as the site for the modulation of hormone release.

S U M M A R Y

The effects of electrical stimulation of the eighth nerve and caloric stimulation of the labyrinth were tested on the spontaneous or evoked electrical activity of single neurons located in the hypothalamic supraoptic (SON) and paraventricular (PVN) nuclei.

It was found that these neurons responded to both kinds of stimulation. In particular, the neurons of the SON showed a predominant response pattern characterized by a sequence of excitation-inhibition, whereas the neurons of the PVN showed different patterns of response with various combinations of inhibition and excitation sequences. The latencies of these neuronal responses to the electrically induced eighth nerve volleys were compatible only with a polysynaptic connection. The possible pathways involved in this vestibulo-hypothalamic relation as well as their functional role are discussed.

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