CENTRAL NEUROMODULATORY ROLE OF VASOPRESSIN IN ANTIPYRESIS AND IN FEBRILE CONVULSIONS

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REVIEW

Recent findings in our laboratories documenting a central role for vasopressin in the mammalian brain, in thermogenesis, fever and febrile convulsions are reviewed.

Vasopressin, administered to the lateral septal area of the brain reduced, in a dose-dependent manner, bacterial pyrogen-induced fevers. Conversely, increased release of endogenous vasopressin into the lateral septal area during the generation of fever was measured.

In other experiments repeated (intracerebroventricular) administration of vasopressin in rats induced progressive sensitization in the onset of convulsions. Exposure of rats to high environmental temperatures induced excessive release of vasopressin in the brain and in peripheral circulation and produced (sometimes fatal) convulsions at body temperatures of about 43°C. Brattleboro (congenital diabetes insipidus) rats and control animals passively immunized with vasopressin antiserum, convulsed or died at a higher (>44°C) body temperature.

INTRODUCTION

In recent years the likely involvement of vasopressin in modulation of brain function, in addition to its classical renal role as the antidiuretic hormone, has been documented in relation to a number of behavioural and physiological events.

DeWied and his colleagues have collected a great deal of information on the effects of vasopressin or of its analogues and fragments, on different parameters affecting memory (6). The role of vasopressin in memory consolidation, including attenuation of amnesia in experimental animals and man, is now well-established and therapeutical applicability of vasopressin in defective memory, including amnesia, is strongly indicated. Modification of various other spontaneous behaviour patterns by vasopressin and other peptides has also been described (28).

Other recent observations raise the fascinating probability that vasopressin may modulate other

central nervous system (CNS) functions. These include the mechanisms involved in the development of ethanol tolerance and of drug tolerance in general (28,22), the stimulation of ACTH release from the anterior pituitary (25) and the regulation of brain water permeability (23).

The projection of vasopressinergic neurons to many areas of the brain (additional to their classically held termination in the neurohypophysis) (2,24) coupled with alterations by vasopressin of catecholamine turnover in specific brain areas (26) strongly support a neurotransmitter-like role for vasopressin in the CNS.

The present report will review evidence obtained in our laboratories on yet another physiological function for vasopressin as a specific neuromodulator in the CNS, namely, the regulation of thermogenesis, fever and febrile convulsions.

MODULATION OF FEVER BY VASOPRESSIN

The observations that the newborn of many mammalian species and the parturient females of the same species fail to develop fevers under conditions when the adult, non-parturient, animals develop infection-related fevers, have led to the introduction of the term 'endogenous antipyresis' (13). Afebrile periods have been documented in newborn lambs, rabbits, guinea pigs and also in newborn humans (5). Parturient sheep (3) and newborn lambs (20) show reduced fevers to bacterial endotoxin or endogenous pyrogen from about 4 days before to 32 h after parturition although the ability of these animals to *thermoregulate* during this same period appears to be unimpaired (27). Conversely, the production of endogenous pyrogen by the white blood cells during this afebrile period remains unchanged. For those reasons, increased production of some centrally acting endogenous antipyretic substance during the afebrile period has been postulated (13).

By the use of a push-pull perfusion system which enables the administration of substances and the collection of the perfusing fluid in discrete and predetermined areas of the brain, evidence has been obtained indicating that vasopressin is such an endogenous antipyretic substance (9).

Stainless steel or push-pull cannulae were implanted stereotactically in various regions of female sheep hypothalamus and the septal area. Fever was induced by administration of bacterial pyrogen. Body temperature was measured by intravaginal thermistor probes and recorded continuously throughout the experiment on a pen recorder. Out of 14 hypothalamic and extrahypothalamic sites tested, with perfusions of 4 ng/ml vasopressin (AVP), only AVP perfusion of the lateral septal area, 2–3 mm anterior to the anterior commissure, reduced fevers in sheep made febrile with intravenous pyrogen. Vasopressin perfusion in the septum of normothermic animals did not change the body temperature appreciably. A clear dose-response relationship was demonstrated in successive experiments employing 0.8–4.0 $\mu\text{g/ml}$ of AVP in the perfusate (4).

In subsequent experiments, using the push-pull system, the same septal areas were perfused with vasopressin-free perfusing fluid, the perfusate being collected at 30 min intervals for radioimmunoassays (RIA) of AVP. The assay results revealed large quantities of AVP in the

perfusates of febrile sheep brains. Analysis of regression curves comparing the amount of AVP in the perfusate (*i.e.*, released into the extracellular space of the septal area) with the change in body temperature showed clearly that high levels of AVP in the perfusate (up to 790 pg AVP/ml) coincided with low fevers and low AVP levels were found in samples from animals with high fevers (4).

The antipyretic effects of vasopressin were found to be specific for this peptide, as perfusion of the same AVP-sensitive sites with other peptides (oxytocin, somatostatin, angiotensin II, substance P) did not affect the febrile response. Arginine vasotocin, which exhibits many of the peripheral actions of vasopressin, was partially effective in reducing fevers, as was bombesin (which is also known to act as a poikilothermic agent to lower normal body temperature) (1). Further support of the role of AVP as an endogenous antipyretic and for its specificity of action could be demonstrated by perfusion of the septal areas with an AVP-specific antiserum: the latency of fever production was decreased, the rate of rise and the maximum fever developed were enhanced as a result of sequestration of AVP by the AVP-antibodies (9).

While the experimental evidence as summarized above does not conclusively establish vasopressin as an antipyretic neurotransmitter, more recent experiments are strongly supportive of this view. Zeisberger *et al.* (29) have confirmed the antipyretic role of AVP in the guinea pig. Furthermore, they showed enhanced immunocytochemical staining for AVP in hypothalamic-septal and amygdaloid projections during antipyresis (16). A neurotransmitter-like antipyretic action of AVP at a specific brain locus is also supported by observations in the rat: AVP injection into the septal area of endotoxin-induced febrile rats decreased fever, but did not lower non-febrile body temperature (7). However, when AVP was administered intracerebro-ventricularly, it reduced body temperature non-specifically (11). Also, peripheral administration of AVP in rats was found to induce hypothermia; conversely, increased release of AVP was seen upon exposure of rats to heat (18).

While direct neurophysiological evidence to show the innervation of the septal fever-generating neurons by vasopressinergic projections is lacking at present, a proportion of the neurons of the paraventricular nucleus (PVN) has been demonstrated to project to the septal region (19). Moreover, afferent as well as efferent compo-

nents of such projections appear to exist. Electrophysiological evidence also favours the concept that different populations of PVN neurons project to different sites in the brain, *i.e.*, some PVN neurons project specifically to the lateral septal region. It remains to be established if such projections would (a) be vasopressinergic, and, (b) innervate the fever-sensitive septal neurons. If indeed vasopressin reaches the septal thermosensitive neurons through nervous pathways, the sites of origin of such vasopressinergic fibres need not be limited to the PVN. The presence of peptidergic fibres in the septal region has been described (2, 24). Sofroniew and Weindl (24) have shown with immunocytochemical studies that neurons of the suprachiasmatic nucleus (which contain vasopressin and no oxytocin) project to the septum and not to the neurohypophysis.

Increases in plasma AVP were found in the present experiments in the sheep during antipyresis, suggesting co-activation of central and neurohypophyseal pathways. If the hypothalamus-neurohypophyseal and septal AVP neuronal systems are subservient to two physiological mechanisms (water regulation and antipyretic function, respectively), excess stimulation of either of the two systems may, unspecifically, cause a stimulation of AVP secretion in the other system. Recent experiments in the awake rabbit support such a postulate: when blood osmolarity was raised by intravenous infusion of 3 M NaCl, AVP levels increased significantly not only in plasma but also in perfusates of lateral septum and amygdala. In sheep, haemorrhage lowered fever, presumably through central release of brain AVP (12).

VASOPRESSIN AND FEBRILE CONVULSIONS

Fever-related convulsions occur frequently in children, such convulsions being especially common in younger children in the age range of 1–7 years. Assuming that vasopressin may be secreted and released in the brain during fever, a possible involvement of vasopressin in the induction of febrile convulsions in children may be suspected. Several experimental approaches were used to investigate a hypothetical relationship between fever, vasopressin and convulsive behaviour, on the basis of a previous report of vasopressin-induced motor disturbances (15).

In a series of experiments in rats, repeated administration of vasopressin over 5 days into the lateral ventricles of the brain was found to

cause, firstly, lowered body temperature; secondly, progressively increasing severity of convulsive behaviour; and, thirdly, a lowered threshold dose (1/100 of initial amount) for vasopressin-induced myoclonic-myotonic convulsions on the second and third administration of vasopressin (11). Our recent experiments indicate that release of endogenous brain AVP may cause a similar sensitization of the brain to the combined effects of a subsequent intraventricular injection of vasopressin (3).

In a subsequent series of experiments the hypothesis that vasopressin may be involved in the etiology of febrile convulsions, was tested in different groups of rats rendered hyperthermic by exposure to high environmental temperature (50°C in an environmental chamber) (14). Four groups of rats ($n=5$ in each group) were used: 1) Long Evans (LE) animals; removed from the heat at body temperature of 42.7°C; decapitated, trunk blood collected for RIA of vasopressin, 2) LE rats kept in hot chamber until convulsions begun; after onset of convulsions removed, and treated as Group 1, 3) congenital diabetes insipidus (Brattleboro strain, DI) rats; in hot chamber until convulsions begun or death occurred; animals treated as in Group 1, 4) LE rats injected AVP antiserum ICV before placement in environmental chamber until convulsions or death occurred; animals treated as in Group 1.

The LE (Group 2) animals convulsed at a mean body temperature of $43.19 \pm 0.12^\circ\text{C}$; convulsions occurred after about 22 min heat treatment, mean blood AVP was 325.5 ± 124.6 pg/ml. In contrast, the blood AVP in the animals which were removed from heat chambers at a body temperature of 42.7°C (Group 1, no convulsions) was 56.1 ± 24.8 pg/ml. The DI rats convulsed or died at a mean body temperature of $44.4 \pm 0.12^\circ\text{C}$, blood AVP was not different from zero. The LE+anti-AVP immunized animals (Group 4) convulsed or died also at $44.00 \pm 0.20^\circ\text{C}$.

It may be concluded from these experiments (14) that animals without AVP (DI rats or those treated with AVP antiserum) had an increased threshold for convulsions, and that the extremely high plasma AVP in the convulsing normal animals, as compared with heated non-convulsive animals, support the view that AVP may indeed be a mediator in the induction of febrile convulsions (if high brain AVP levels occur as has been shown in febrile sheep and osmotically-challenged rabbits).

Further experiments will be required to establish the sites in the brain where vasopressin

acts to mediate induction of convulsive behaviour. It may be of significance to note that vasopressin may be closer to being a 'physiological' modulator of convulsive behaviour than other peptides. For example, enkephalins have been shown to induce convulsions in rats, however, at a 1,000 times higher concentration (8).

Received for publication 1 August 1981; and in revised form 5 November 1981

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