ACTIVATION OF NEURONAL SYSTEMS WITH AGING AND IN ALZHEIMER'S DISEASE

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ABSTRACT

A central question in aging and Alzheimer's disease is why amidst degenerating cell groups some neurons in the brain remain remarkably intact. The hypothesis has been put forward that stimulation of neuronal systems might be a crucial factor in their survival during aging and in Alzheimer's disease.

The project concerns changes in the activity of peptidergic and monoaminergic systems in the human and rat brain during the process of aging and in Alzheimer's disease (AD).

In the rat hypothalamus vasopressin (AVP) and oxytocin (OXT) cells were studied in the supraoptic (SON) and paraventricular nucleus (PVN). These cells project to the posterior lobe of the pituitary from where the peptides are released into the blood stream. Using radioimmunoassay, an increase in the 24-h urinary excretion of AVP and OXT was observed in 34-month-old Brown-Norway (BN) rats as compared with young animals (Goudsmit et al., 1988a). This increase was related to a decrease in concentrating ability of the kidney, one of the peripheral target organs of AVP. Since the number of AVP binding sites was biochemically shown to decline with aging in this strain (Herzberg et al., 1989), it is proposed that the AVP and OXT cells in the rat hypothalamus are activated in senescence in order to compensate for the reduced sensitivity of the aging kidney to AVP and the corresponding tendency to develop a (renal) diabetes insipidus.

The AVP and OXT neurons in the SON and PVN were also studied in the human hypothalamus during normal aging and in AD. Determination of cell numbers in these nuclei using morphometric techniques showed that these nuclei remain remarkably stable in human senescence and in AD, in contrast to the suprachiasmatic nucleus, another AVP cell containing nucleus in the hypothalamus, which showed a marked degeneration in senescence, which was even more pronounced in AD (Swaab et al., 1985). Since previous research had shown that the AVP cells in the human SON and PVN are activated in senescence, as they are in the rat (Fliers and Swaab, 1983; Hoogendijk et al., 1985), these findings are consistent with the hypothesis that degenerative changes in senescence might be
postponed or even prevented by neuronal activation. Current research to further investigate this hypothesis concerns determination of the numbers of immunocytochemically identified AVP and OXT cells in the human SON and PVN with aging and in AD.

In addition to the SON and PVN, AVP and OXT cells which project to central brain regions where the peptides act as neurotransmitters were investigated in the rat brain. Previous research had shown that the integrity of central AVP projections depends on plasma levels of sex steroids (De Vries et al., 1985). Since plasma testosterone levels decline progressively with aging in the male rat the effects of aging and of testosterone supplementation were studied in the male BN rat using immunocytochemistry. The results of this study showed a decline in AVP fibre density in several brain regions including the locus coeruleus in senescence, which could be restored by elevating plasma testosterone levels to the level of young animals for a period of one month (Goudsmit et al., 1988b). A subsequent study using micro-punches and radioimmunoassay showed an elevation of AVP levels in the medial amygdala, one of the areas containing centrally projecting AVP neurons, in male rats up to 32 months of age following peripheral testosterone administration (Goudsmit et al., 1990b).

Further studies focused on the effects of testosterone administration on other transmitter systems, such as the monoaminergic projections from the locus coeruleus, an area containing noradrenergic neurons which have been shown to be activated following local AVP injection. Monoamine metabolism was determined in a number of brain regions of sham- and testosterone-treated young, middle-aged and aged male BN rats using high pressure liquid chromatography. The results indicated diverse reductions in the activity of nigrostriatal, mesocortical and coeruleo-hippocampal systems with aging. Changes indicating an activation of monoamine metabolism following testosterone administration were observed in young animals only, suggesting a reduced sensitivity to testosterone in aged animals in this respect (Goudsmit et al., 1990c). Choline acetyltransferase activity, a marker for cholinergic innervation which had also been shown to depend on sex steroids was shown to decline in senescence in the medial preoptic area, but not to be restored following testosterone administration (Goudsmit et al., 1990b).

Behavioral effects of testosterone administration to senescent rats were studied using a Morris water maze. The results of this experiment showed a decline in spatial memory in senescent male rats as compared to young ones. Testosterone administration failed to restore this deficit. A surprise finding was the impaired spatial memory of young and middle-aged animals following testosterone administra-

The general conclusion from these studies was that changes in neuronal activity differ from system to system in both the rodent and human brain with aging and in AD, and that neuronal activity does not necessarily decline with aging, but may in some cases even increase in senescence and AD. The possibility to stimulate
specific neuronal systems in senescence, e.g., by peripheral administration of sex steroids, might be of interest in view of the search for therapeutical strategies for age-related neuro-degenerative diseases such as AD.

REFERENCES


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