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Modulation of substantia nigra self-stimulation by neuropeptides related to neurohypophyseal hormones

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Neuropeptides related to hypothalamic-neurohypophyseal hormones affect brain functions. Among these are learning, consolidation and retrieval processes[4,16]. Pathways with neurohypophyseal hormone immunoreactivity have been described originating from hypothalamic nuclei with endings in various brain structures[2,18], suggesting that these peptides may have direct effects on neuronal mechanisms in these structures. Behaviorally, a modulatory action of these peptides has been described using various test paradigms[4,16], including acquisition of heroin self-administration[15]. This particular behavior was attenuated by daily administration of desglycinamide[9], arginine[8] vasopressin (DG-AVP) and facilitated by that of prolyl-leucyl-glycinamide (PLG). It has been argued that the positively reinforcing characteristics of narcotics may be related to the action of these drugs on central reward structures[6,9]. Thus, determination of the reinforcing efficacy of reward structures through studies of intracranial electrical self-stimulation (ICSS) behavior may provide information about the mechanisms mediating the reward induced by narcotics.

The present study was performed to investigate the ability of DG-AVP and PLG to affect ICSS. The dopaminergic cell bodies in the substantia nigra-ventral tegmental area were selected as neuronal substrate for ICSS. Catecholaminergic, and in particular dopaminergic systems play a critical role in the rewarding quality of brain electrical stimulation[19] and of self-administered drugs[20]. Furthermore vasopressin and PLG affect catecholaminergic activity in various brain structures, including dopamine turnover in the nucleus caudatus[13,17].

Details of the materials and methods used, are presented elsewhere[5]. Briefly, 6 male Wistar rats were equipped with a twisted bipolar steel-wire electrode in the area of the substantia nigra (Pellegrino and Cushman[10] coordinates A 2.2, L 2.0, D 3.5.). After a recovery period of one week, the animals were shaped to self-stimulation in an operant conditioning chamber. Pressing the lever delivered an 0.5 sec biphasic square-wave train of impulses through the electrode on a continuous reinforcement schedule.

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Each train consisted of impulses of a frequency of 50 Hz, with a pulse width of 0.5 msec between the positive and negative pulses. Following training, a maximal current intensity for self-stimulation was established by increasing the stimulation intensity in 80 μA steps to a level which elicited the maximal number of responses. This current was used for daily training of the animals until stable response rates were obtained. Animals were then subjected to a biphasic test paradigm. Current intensity was gradually decreased from the maximal (training) level to zero by 80 μA steps (descending phase), and increased by the same steps to maximal current intensity again (ascending phase). The animals were exposed to each intensity for 4 min (sessions), but only the number of responses during the last 3 min of each session was recorded (responses per session). Based on the performance of the animals on 3 consecutive days, the current intensity at which more than 20 responses per session was achieved, was established and a current of 40 μA below it was inserted into the paradigm. Bar pressing at the inserted current and the current 40 μA below it was taken as the response rate at 'around threshold' currents.

The animals were exposed in succession to maximum and 'around threshold' current intensities and subsequently to 'around threshold' and maximum current again (day 1). On the next day (day 2), the animals were treated with 0.5 ml of 0.9% NaCl (saline) solution administered subcutaneously 30 min prior to testing. The following day (day 3), the animals were given 1.0 μg of prolyl-leucyl-glycinamide (PLG) dissolved in 0.5 ml saline subcutaneously 30 min prior to testing. Performance of the animals on the following day (day 4) without pretreatment was also examined. The animals were then trained daily in the threshold paradigm for 4 days and the above test procedure was then repeated except that 1.0 μg of des-glycinamide^{9}-arginine^{8} vasopressin (DG-AVP) was administered as the test peptide on day 3.

Current intensities which elicited maximal performance varied from 160 to 400 μA. Maximal response rates on day 1 were 45–230 responses per 3 min. Threshold current ranged from 80 to 200 μA which produced response rates on day 1 from 11 to 62 responses per 6 min (i.e. the sum of two 3 min periods). Subcutaneous administration of saline did not significantly modify response rates at either maximal or threshold current intensities (Figs. 1 and 2). Also the tested peptides did not alter the performance of the animals at maximal current intensities. However, at 'around threshold' current intensities PLG increased and DG-AVP decreased the number of responses over the 6 min periods of both the descending and ascending phase of the test paradigm as compared to performances following saline administration (Figs. 1 and 2). Neither peptide modified the behavior of the animals on the day after peptide treatment since performances similar to saline treatment were observed. Histological examination of the brains of the 6 animals revealed that all placements resided in or bordered on the very medial portions of the substantia nigra, and might have been in contact with cell bodies of the ventral tegmental area[5].

The ability of the neuropeptides to modify ICSS may be related to their interaction with catecholamine-containing systems of the brain. PLG has been reported to potentiate the behavioral effects of L-DOPA[12], and to reverse reserpine sedation[11]. This peptide also facilitates development of morphine tolerance[14], a process in which

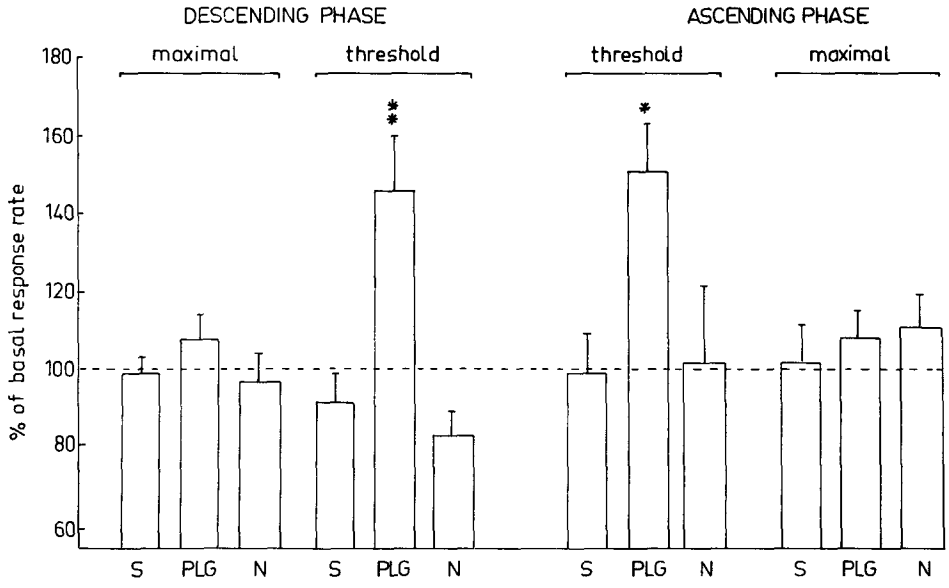

Fig. 1. Effect of PLG on self-stimulation behavior using the biphasic test paradigm. Performance of the animals at maximal and threshold current intensities during the descending and ascending phases of the test paradigm are shown. All values are mean ± S.E.M. of the response rate of the animals (n = 6) expressed as a per cent of basal (day 1) performance. The effects of subcutaneous treatment with 0.5 ml saline (S), 1 μg PLG in 0.5 ml saline (PLG), or no treatment on the day following peptide administration (N) are shown. Stars represent significant difference with respect to effects of saline treatment (* $P < 0.02$, ** $P < 0.01$, Student's paired t-test).

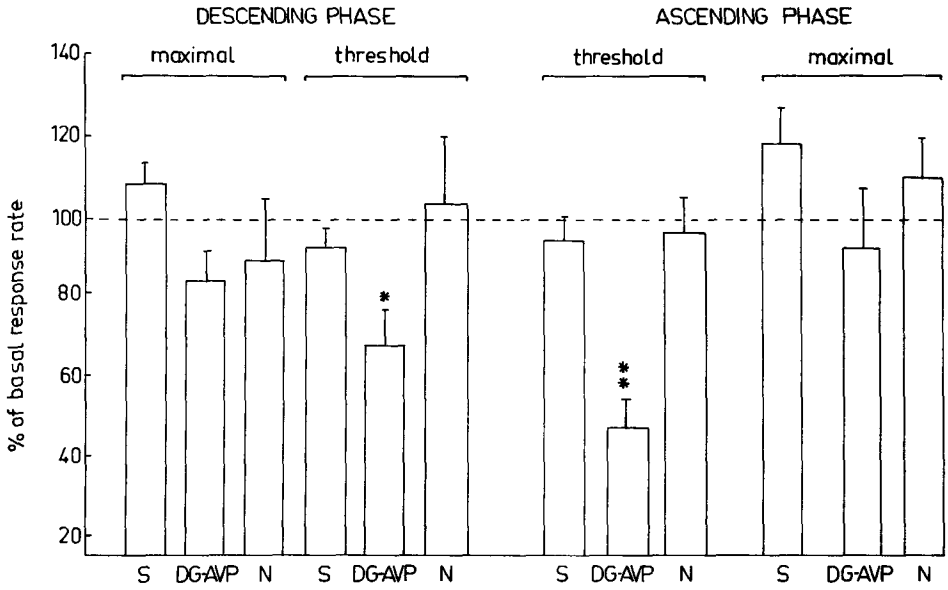

Fig. 2. Effect of DG-AVP on self-stimulation behavior in the biphasic test paradigm. As in Fig. 1, performance of animals (n = 6) on the day given 0.5 ml saline (S), 1 μg DG-AVP (DG-AVP), or no treatment (on the day after peptide testing, N) are expressed as a per cent of basal performance of the animals (day 1) (* $P < 0.01$, ** $P < 0.002$ with respect to saline treatment).

dopaminergic systems may be involved[3]. Versteeg et al.[17] have shown that intracerebroventricular administration of PLG promotes an increase in dopamine disappearance in the caudate nucleus following inhibition of its synthesis by α-methyl paratyrosine (α-MPT). Changes in noradrenaline disappearance in the A8 and A9 region were also noted. It is tempting to speculate that the facilitation of ICSS observed in the present study may be related to alterations of dopamine turnover observed after PLG administration[17].

Interactions of vasopressin-like peptides with catecholamine-containing systems of the brain have also been documented. Tanaka et al.[13] have reported that vasopressin increases dopamine disappearance (α-MPT-induced) in caudate nucleus, median eminence, dorsal raphe and A8 region. The similarity of effect of vasopressin and PLG on dopamine metabolism in the caudate nucleus makes it difficult to relate this effect to the modulation of ICSS noted in the present investigation. It is noteworthy, however, that vasopressin, in contrast to PLG, also has numerous effects on noradrenaline turnover in various brain regions. If the interaction of vasopressin with noradrenergic transmission is an important mediator of the effects of this peptide, then its suppressive effect on ICSS from the ventral mesencephalon would fit well with evidence which indicates that noradrenergic activity may be inhibitory to dopaminergically related components of ICSS[7,8].

The effects of PLG and DG-AVP on ICSS bear a striking similarity to their effects on heroin self-administering behavior[15]. In as much as ICSS and opiate self-administration may reflect an interaction with a common neuronal substrate of reinforcement mechanisms, the further study of the mechanisms by which neuropeptides and other drugs modify ICSS elicited from the ventral mesencephalon may provide valuable information on the nature of their effect on drug self-administering behavior. Furthermore, the ability of DG-AVP and PLG to modify ICSS at low and not at high current intensities provides further evidence of the function of these peptides as neuromodulators[1].

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