Stress-Related Plasma Catecholamine and Corticosterone Responses and Psychotropic Drug Action

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LONG-TERM SUPPRESSION OF VITAMIN K DEPENDENT ENZYME SYSTEMS IN THE RAT - BIOCHEMICAL AND BIOLOGICAL EFFECTS -

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Vitamin K dependent proteins and enzyme systems are not only found in the liver but also in several non-hepatic tissues like kidney and testis. The function of hepatic vitamin K dependent systems is clear; less is known about the function of extrahepatic vitamin K dependent systems. S-Acenocoumarol (AC), a 4-hydroxycoumarin derivative, was infused directly into one testis of the rat, to circumvent effects on the hepatic clotting systems and to elucidate more of the relation of testicular vitamin K dependent systems to male fertility. An AC solution of 1 mg/ml or saline (n=5/5) was delivered, via a silastic tube protruding into the testis, by an osmotic minipump at a constant rate of 1 ul/hr. Minipumps were changed every week. The infusion lasted for 8 weeks. The contralateral testis was removed. Each experimental rat was housed with 5 female rats during the last 6 days of infusion. At the 6th day of infusion, all male rats were euthanized and blood, liver and testis removed. The offspring of the female rats was counted and checked up. In the testis vitamin K epoxide reductase activity and vitamin K dependent carboxylase activity was reduced to 26% of control. Plasma coagulation activity was not affected. The quantity and mobility of sperm cells in the cauda epidydimis was equal in both groups. Morphological analysis of sperm cells and testis tissue revealed no differences between the 2 groups. The litter size in the AC treated group was 9.9±1.0 and 11.0±0.6 in the control group (mean ± SEM), a statistically non-significant difference.
Our experiments show that direct delivery of acenocoumarol to the testis of the rat has profound effects on biochemical parameters without interrupting the hepatic clotting system. Effects on fertility parameters, however, could not be detected.

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COMPARISON OF THE M_1-CHARACTERISTICS OF SOME MUSCARINIC AGONISTS

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Traditionally McN-A-343 (4(m-chlorophenylcarbamoyloxy)-2-butynyltrimethylammmonium-chloride) is the currently selective M_1-agonist. However, its usefullness as a tool may be subject to debate, because of its low efficacy (Eglen and Whiting, 1985) and the fact that McN-A-343 may act allosterically with the receptor (Birdsall et al., 1983). It was the aim of the present study to compare the characteristics of three muscarinic agonists in vivo and in vitro.
In vivo the pithed rat model was used to investigate the agonist-mediated bradycardia (M_2) and their ganglionic activity of the same agonists (M_1). In vitro radioligand binding studies were performed. The following agonists were used: pilocarpine, aceclidine and McN-A-343. The muscarinic antagonists atropine, pirenzepine, dicyclomine, 4-DAMP and AF-DX 116 (11-2[[2-[(diethylamino)methyl]-1-[piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3,-b][1,4]benzodiazepine-6-one) were also used. The order of potency of the agonists in vivo with respect to their increase in blood pressure (M_1) and bradycardiac activity was as follows: McN-A-343 > pilocarpine > aceclidine. All of the three compounds studied showed higher potency for the sympathetic ganglia, and no preference for the M_1 or M_2 binding sites in the in vitro studies. Besides pirenzepine, also 4-DAMP and dicyclomine show high affinity for M_1-binding sites, compared to those in the heart (De Jonge et al., 1986). However, 4-DAMP and dicyclomine proved to be non-selective in vivo when McN-A-343 was used as an agonist for the M_1-receptor present in the sympathetic ganglia. This is in contrast to the results obtained when pilocarpine or aceclidine were used as agonists for this M_1-receptor, but this finding is in agreement with the binding experiments. The present results indicate that aceclidine and pilocarpine might be better tools for the investigation of M_1-receptors in vivo.

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STRESS-RELATED PLASMA CATECHOLAMINE AND CORTICOSTERONE RESPONSES AND PSYCHOTROPIC DRUG ACTION

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In chronically catheterized rats, we have demonstrated that the environmental demand of exposure to auditory stimulation (10 min, 95 dB) leads to specific temporal patterns of plasma noradrenaline (NA), adrenaline (A) and corticosterone (CS) responses. Manipulation of subtle psychological attributes of this event, predictable (regular) versus unpredictable (irregular) repetitive exposures, affects the specific characteristics of the biochemical responses (i.e. magnitude, temporal pattern and ratio). Upon predictable stimulation, the NA response accelerated whereas the CS response diminished in magnitude. Subsequent presentation of the noise stimulus after 24 h differentially affected the sympathetic and adrenocortical responsivities depending on prior predictability. Rats previously exposed to unpredictable noise showed higher CS and lower NA responses than those exposed to prior predictable stimulation. A responses were not different in these conditions.
These observations indicate that changes in sympathetic neural (NA) and adrenomedullary (A and NA) activity as well as adrenocortical activity (CS) are independently modulated by brain mechanisms. This also applies to the effects of extinction of appetitive operant behavior.
Additionally, data will be discussed indicating that measurements of plasma NA, A and CS profiles in stressed and undisturbed rats could serve as a sensitive biochemical index for the assessment of presence, nature and potency of psychotropic drugs known to affect behavioral adaptation mechanisms.

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GONADAL HORMONES AND HEART RATE AS AN ACUTE EMOTIONAL STRESS RESPONSE

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Heart rate is a sensitive parameter of acute emotional stress. Radiotelemetry[1] permits registration in freely moving Wistar rats subjected to a step through passive avoidance conditioning paradigm using electric footshock as an unconditional stimulus[2]. During forced exposure to the shock compartment heart rates of intact male rats are lower than in a control group of animals not conditioned by foot shock. The same observation has been made for intact females in di-oestrus although the difference might be slightly less. Females in oestrus do not show this difference and also the corresponding control group shows slightly lower heart rates. Substitution experiments in castrated males and females point to a role of oestradiol in causing these effects in the female. Its ineffectiveness in males, however, suggests an organizational gender difference. In connexion with the literature the conclusions are drawn that oestradiol decreases vagally mediated bradycardia during a type of emotional stress which is strongly related to the orienting response. It also reduces sympathetic drive during exploration. Dose-response relationship and the effects of progesterone suggest a neurophysiological connexion with the generation of sexual behaviour located in the ventromedial nucleus of the hypothalamus with a possible permissive role for progeny in reducing arousal during oestrus.

1. B. Bohus Biotelemetry 1974, 1: 193-201.
2. R. Ader et al. Psychon Sci 1972, 26: 125-8

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