'[Poster 37]'

Behavioral and neurochemical observations of streptozotocin-treated rats: effects of chronic treatment with acetyl-L-carnitine

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Treatment of middle-aged rats with an i.c.v. injection of streptozotocin (STREP) may provide a relevant model of neurodegeneration that could be induced by a decrease in the central metabolism of glucose. Acetyl-L-carnitine (ALCAR) has been found to enhance the utilization of alternative energy sources, such as lipid substrates or ketone bodies. Via such a mechanism of action ALCAR could antagonize the effects of STREP treatment. This study was designed to evaluate the behavioral and biochemical effects of chronic treatment with ALCAR in the middle-aged STREP-treated rat. Spatial discrimination learning in the Morris task was affected after STREP treatment and this cognitive impairment was related to hippocampal choline acetyltransferase (ChAT) activity. ChAT activity in the frontal cortex, striatum and septum was not affected after STREP treatment. Chronic treatment with ALCAR attenuated the STREP-induced impairment in spatial bias during the probe trial and attenuated the STREP-induced decline in hippocampal ChAT activity. These findings suggest that, in this animal model, chronic treatment with ALCAR had a beneficial effect on the behavioral as well as on the biochemical level. Presently histological, neurochemical, and behavioral studies are in progress to elucidate the effect of STREP on the neurodegeneration of certain brain structures and transmitter systems.

'[Poster 38]'

Transplantation of the suprachiasmatic nucleus (SCN); first steps to increase functional response by ex vivo gene transfer methods.

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The SCN of the hypothalamus is the major component of the biological clock in mammals. SCN-lesioned -and thus arhythmic- rats can recover their circadian drinking rhythm upon homotopic transplantation of a fetal SCN in only 40% of the cases. These studies suggested that the recovery of drinking rhythm is only seen when the outgrowth of vasopressin- and vasoactive intestinal polypeptide-containing fibers from the transplanted SCN neurons reach the host brain. Stimulation of these sparse outgrowing fibers might therefore result in a higher percentage of recovered rats. One possibility to achieve this, is to place the transplanted SCN nearer to one of its target areas so that fibers can more easily make functional contacts. However, SCN transplantation near the paraventricular nucleus of the thalamus resulted in recovery of drinking rhythm in 33% of the rats. A second possibility to enhance fiber outgrowth is to provide the transplant with an additional gene encoding for either growth factors or growth-associated proteins. Preliminary results show that it is possible to introduce the marker gene encoding for ß-galactosidase into fetal SCN tissue by means of infection with a replication-defective adenoviral vector. The foreign gene is expressed for at least 8 days after transplantation both in neural and non-neural cells.

'[Poster 39]'

A COMPARISON BETWEEN IN VITRO AND IN VIVO EFFECTS OF THIOPENTAL.

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The aim of this study was to gain insight into the molecular mechanism underlying the in vivo effects of thiopental. We compared the dose-response curve of thiopental on the withdrawal reflex to transcutaneuos stimulation in rats [1] to the dose-response curve of thiopental on the binding of [^{3}H]TBOB to the $GABA_A$ receptor complex in rat brain homogenates [2]. The sigmoid E_{max} model was fitted to both datasets.
In vivo thiopental suppressed the withdrawal responses with an ED_{50} of 4.5 mg/kg corresponding to 9.2 µmoles/kg brain, and a slope factor of 1.60.
In vitro thiopental inhibited [^{3}H]TBOB binding with an IC_{50} of 28 µM and a slope factor of 1.65.
The results of this study show a remarkable similarity between the in vivo curves and the in vitro curves, concerning both the effective concentrations and the shape of the curves. Based on this similarity we hypothesize that:
1) an interaction of thiopental with the $GABA_A$ receptor complex can account for the inhibition of the withdrawal effect; this relationship is linear. 2) two thiopental molecules bind to the $GABA_A$ receptor complex with a positive cooperative effect on the (negative) modulation of the [^{3}H]TBOB binding site. This can account for the high slope factors found.
[1] Dirksen, R. et al. Eur. J. Anaesth., 7, 1990, 285.
[2] Van Rijn C.M. et al., Epilepsy Res., 12 (1992) 163.

'[Poster 40]'

EFFECTS OF CHRONIC DIAZEPAM ON EEG AND MOTOR BEHAVIOR OF THE RAT

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We evaluated the effect of chronic diazepam during 21 days on motor behavior and on the spectral content of the EEG of the WAG/Rij rat.
The animals subcutaneously received silastic tubes either empty or filled with diazepam (50 mg/kg/day) resulting in constant blood concentrations (± 200 ng/ml). EEG's were filtered between 1-100 Hz and sampled with a frequency of 200 Hz. Two baselines were recorded. During the treatment we registered the EEG 5 times. A post-drug recording was taken 9 days after tube removal. The spectral content was determined by FFT for 10 periods of 3.2 s of EEG accompanying passive wakefulness. Motor coordination was determined using an accelerod. The muscle tone was blindly scored on a two point scale via direct palpation.
Diazepam induced an increase in the power of the higher frequencies of the EEG (12-50 Hz) and a decrease in the power of the lower frequencies (1-8 Hz). No tolerance developed to this effect of diazepam. Diazepam induced a decrease in the accelerod performance. Tolerance to this effect was found on the 3rd day. The drug induced a decrease in muscle tone. No tolerance to this effect was found.
We conclude from these observations that functional tolerance is present. Our data exclude as a cause global decremental processes. We therefore hypothesize that the animal invokes oppositional processes in order to compensate for those effects of diazepam which impair its normal functioning.