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Circadian and seasonal rhythm in stimulation-produced analgesia

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Summary. The antinociceptive effect induced in mice by peripheral electrical stimulation has been shown to exhibit both circadian (24 h) and seasonal (1 year) rhythms. These findings contribute to an explanation of the variability reported for stimulation-produced analgesia.

In both animals and man it is known that many physiological and pharmacological effects due to endogenous substances and exogenous compounds are under circadian control[2], as well as in many instances being subject to rhythmic influences of much longer duration[3]. It has recently been demonstrated that electrical stimulation-induced analgesia of short duration (ESPA)[4] in mice may represent an endogenous pain control system[5] which is called into play in the face of noxious stimuli, thus permitting the taking of aversive action under antinociceptive cover. This paper provides evidence to show that ESPA in mice is a phenomenon which displays both circadian and seasonal rhythms.

Methods. CD1 female albino mice (20–25 g b.wt) from Charles River, France were housed 20 per cage at 22 °C with a 12-h light cycle commencing at 06.00 h and were allowed rodent diet and water ad libitum. Not less than 1 week after arrival animals were randomly allocated to groups of ten and placed in new cages 4 h before testing. ESPA was induced by caudal stimulation of lightly restrained animals with a bipolar surface electrode (3 mm diameter, P-P-E, Hugo Sachs KG) using a Grass S-48 stimulator and SIU-5 isolation unit. Rectangular wave pulses of 15 msec pulse width were passed at 20 Hz for 30 sec at the threshold voltage for vocalization. ESPA was then measured by immediate transfer within 5 sec of the animals to a hot-plate (22.5 × 11.0 cm surface at 52 °C, with 10 cm high enclosure) and recording the escape latency in seconds. Each mouse was used only once.

Results. Analysis of the results obtained over a 24-h period

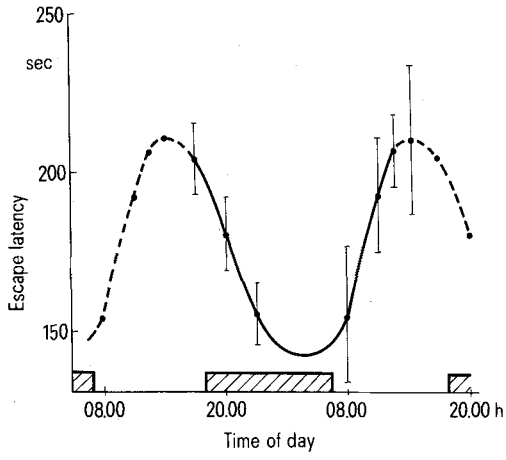

Fig. 1. Circadian rhythm in escape latencies of mice on a 52 °C hot-plate after induction of electrical stimulation-produced analgesia (ESPA). The latencies (mean ± SE, N = 20) in sec are shown against time of day in h. The graph represents mean data from 2 experiments carried out during February and several points are repeated byond 24 h (broken line) so as to emphasize the rhythm. The shaded areas on the abscissa represent the dark phase of the cycle.

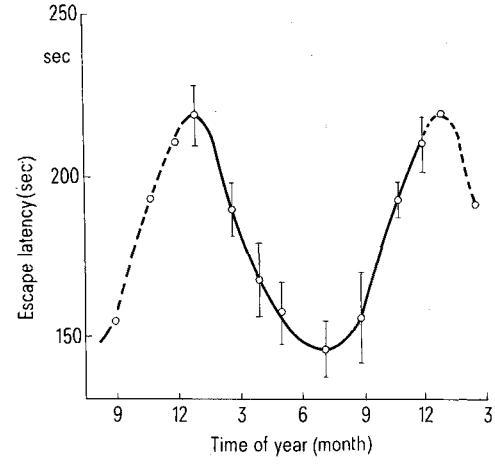

Fig. 2. Seasonal rhythm in escape latencies of mice on a 52 °C hot-plate after induction of electrical stimulation-produced analgesia (ESPA). The latencies (mean ± SE, N = 20–60) in sec are shown against the time of year in months. The graph respresents mean monthly data from experiments carried out from 13 to 17 h during 1 year and several points are repeated (broken line) in order to clearly illustrate the rhythm.

during the month of February (fig. 1) showed that ESPA fluctuated rhythmically throughout this time. A circadian rhythm was clearly demonstrated and the maximum latency to escape i.e. least sensitivity, could be seen in the early afternoon. A retrospective study of results obtained in afternoon experiments conducted over a year (fig. 2) revealed that ESPA was also altered in a rhythmic manner on an annual basis. The maximal effects were observed during the winter months. Significant ESPA could not be induced on summer mornings suggesting that this annual rhythm was probably not artefactual as a consequence of a circadian phase shift, although it cannot be excluded on the basis of this evidence alone.

Discussion. These findings clearly demonstrate the existence of rhythmic influences upon which ESPA depends. They may therefore account for some of the variability obtained with various types of electro-analgesia in both animals and man[6]. The variability is also due in part to biological variation between individuals contributing to the spread of results. The seasonal effect could be expected to be consequent to a phase shift of the circadian rhythm, but this may not be the case because ESPA was not readily induced on summer mornings. However only further extensive experiments in that season can finally validate this point. Some of the characteristics of ESPA are similar to those of morphine analgesia, for example antagonism of the antinociceptive effect by naloxone[4] and modulation by serotoninergic manipulations[7]. It is therefore of interest to note the close parallel between the circadian pattern of the analgesic effect of morphine in mice tested on the hot-plate[8] and the circadian dependence of the induction of ESPA as reported here. The escape reaction of mice on the hot plate has been associated more with an emotional component of the reaction to continued perception of a noxious stimulus and as such is prolonged both by morphine and by ESPA. At the present time the precise mechanism of ESPA is not fully elucidated, but it probably involves the enkephalins in a functional role as short-acting[9] endogenous antinociceptive substances released in response to harmful stimuli[10]. The rhythmic influences should also be of functional importance. In relationship to the circadian rhythm, recent studies[11] have shown that whole brain levels of methionine-enkephalin in mice subjected to noxious stimuli are significantly increased in the afternoons at the peak time of ESPA and of the analgesic activity of morphine, whereas in the mornings no changes are apparent. Similarly a circadian rhythm in rat brain opiate receptor has recently been reported[12] using [^{3}H]-naloxone binding, in which the number of recognition (binding) sites was maximal in the first half of the dark phase and minimal in the early morning hours correlating with minimal ESPA at this time.

Pharmacological studies in relationship to the seasonal control of ESPA remain to be explored, although difficulties with regard to serotoninergic mechanisms are anticipated in view of annual rhythms associated with that monoamine itself[13]. However the seasonal rhythm reported here is the first indication of such control within an antinociceptive system and, like the circadian rhythm, may partially contribute to an explanation of the varying results with regard to the pharmacology of stimulation-produced analgesia.

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Effects of centrophenoxine, piracetam and hydergine on rat brain lipid peroxidation

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Summary. The cerebral insufficiency improvers centrophenoxine, piracetam and hydergine were tested for their effect on lipid peroxidation of rat brain homogenates, both in vitro and in vivo. There was no effect either in vitro or after chronic 8 week dosing of animals.

There has been much discussion in recent years regarding the role of lipid peroxidation and its consequences in cellular deterioration. Thus, lipid peroxidation has been implicated as a causative agent in the ageing process, hyperbaric oxygen toxicity, ozone damage, the radiation syndrome and CCl_4 and $BrCCl_3$ toxicity[2-9]. Peroxidation of lipids or other molecules as a common aetiological factor in the above states is an attractive hypothesis, because for many years there has appeared to be a relationship between these diverse forms of cellular damage. However, as pointed out in the review by Plaa and Witschi[10] most of the evidence for such a relationship is indirect. The experimental evidence for a role of increased lipid peroxidation in the aging process is controversial with results ranging from significant increases in peroxidation[4,11,12] to no significant change or even decreases in peroxidation with increasing age[13,14].

Recently, there has been a resurgence of interest in a class of compounds loosely classified as cerebral insufficiency improvers. Compounds such as piracetam, hydergine and centrophenoxine have been used clinically in geriatric patients who present with symptoms such as confusion,