its predominantly hydrocarbon structure. If this feature of camphor is coupled with a general ability to decrease the membrane fluidity of cell plasma membranes it could be a useful agent for the modification of membrane related cellular functions in vivo. This kind of effect has been sought by membrane biophysicists[21,22] and it is hoped that the work described here may stimulate an investigation of the effect of camphor on the fluidity of cell membranes.

1 Acknowledgments. I thank Professor K. Marsh for his hospitality and assistance in the use of his microcalorimeter.
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0014-4754/83/090994-03$1.50 + 0.20/0

Ocular responses evoked by capsaicin and prostaglandin E_2 are inhibited by a substance P antagonist[1]

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Summary. Injection of capsaicin or prostaglandin E_2 into the vitreous chamber of the rabbit eye resulted in miosis and breakdown of the blood-aqueous barrier, manifested in aqueous flare. Pretreatment with the neuronal blocker tetrodotoxin or the substance P antagonist (D-Pro^2, D-Trp^{7,9})-SP_{1-11} greatly reduced the ocular responses to capsaicin and prostaglandin E_2. The results suggest a role for neuronal substance P in the ocular response to injury.

The response to ocular injury in the rabbit eye is characterized by miosis, vasodilatation and a breakdown of the blood-aqueous barrier. Among stimuli known to elicit one or more of these responses are chemical irritants, such as nitrogen mustard[3] and capsaicin[3,4], endogenous chemicals, such as bradykinin[5], prostaglandins[6] and substance P (SP)[7-9] and ocular trauma, induced, for instance, by IR-irradiation of the iris[10]. Following sensory denervation of the eye by diathermic destruction of the trigeminal nerve the miotic and hypertensive response to laser irradiation[11], capsaicin, bradykinin and prostaglandins is prevented[7,12,13] whereas that to SP remains[7,13]. It has therefore been proposed that all chemical irritants, except SP, act to release a mediator from sensory nerve endings[13]. It has also been suggested that the mediator is related to SP[13]. Recently, it was shown that the ocular response to IR-irradiation and to bradykinin can be prevented by pretreatment of the eye with a newly developed SP antagonist[14,15]. The present study is concerned with the mechanism behind the ocular injury evoked by capsaicin and prostaglandin E_2 (PGE_2).

Methods. Adult pigmented rabbits (1.5-3 kg) of mixed strain were anesthetized with methohexital sodium (Brietal®, Lilly; 5 mg/kg) when given intravitreal or retrobulbar injections. No anesthesia was administered during the rest of the experiments. The time course of the barrier damage was followed by photoelectric measurement[16] of the aqueous flare response (AFR). This response is a Tyndall phenomenon in the anterior chamber, reflecting protein leakage across the blood-aqueous barrier. A correlation between the AFR and the protein concentration has been established[17]. The method has the advantage of being atraumatic, permitting continuous recording of the AFR during the experiment. Furthermore, the method detects changes in AFR that cannot be observed by conventional focal illumination The results are expressed in arbitrary units with reference to a standard[17]. Unless otherwise indicated, the AFR and pupillary diameter were measured every 30 min. A potent blocker of nervous conduction, tetrodotoxin (TTX)[18], (10 µg in 20 µl bidest H_2O) was injected into the vitreous chamber of the left eye by means of a Hamilton precision syringe, 3-4 mm posterior to the limbus. The control (right) eye received 20 µl H_2O. These injections were made 4 h before the administration of either capsaicin or PGE_2 to both eyes. The SP antagonist (D-Pro^2, D-Trp^{7,9})-SP_{1-11} was applied topically in a volume of 50 µl to the left eye. The SP antagonist was given twice, 1 h and 30 min, respectively, before capsaicin or PGE_2. The right eye (control eye) received instead 0.9% saline topically. Capsaicin (150 µl of a 0.33% solution) was administered to both eyes by retrobulbar injection using a thin needle (0.4 mm diameter, 20 mm length), introduced through the center of the lower eyelid, near the lid margin, and around the interior aspect of the globe to a depth of 10 mm. Aspiration was invariably performed to make sure that the injection was not into the venous sinus. PGE_2 (0.85 µg in 5 µl) was applied topically onto both eyes. The doses of capsaicin and PGE_2 were selected because they produced small but consistent effects in the eye.

Capsaicin and PGE_2 were purchased from Sigma, St.Louis, Mo, USA. 50 mg of capsaicin was dissolved in 75 µl 99.5%

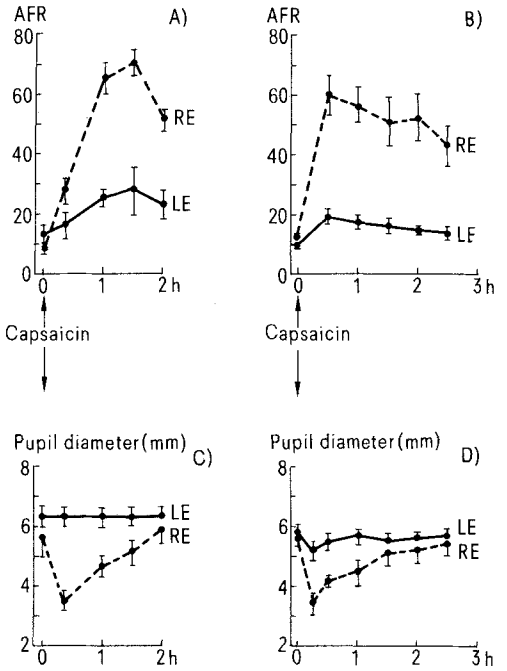

Figure 1. The AFR (A, B) and the pupil diameter (C, D) in response to retrobulbar injection of capsaicin to both eyes 4 h after the intravitreal injection of 30 nmoles (10 µg) of TTX (A, C) or 1 h after the 1st topical application of 300 nmoles (470 µg) of (D-Pro^2, D-Trp^{7,9})-SP$_{1-11}$ (B, D) onto the left eye (LE) and 0.9% saline onto the right eye (RE). Means ± SEM (vertical bars). Five rabbits received the SP antagonist and 3 rabbits received TTX. The difference between the left eye and right eye following injection of capsaicin was significant in both series of experiments (analysis of variance, $p < 0.001$ in A–D).

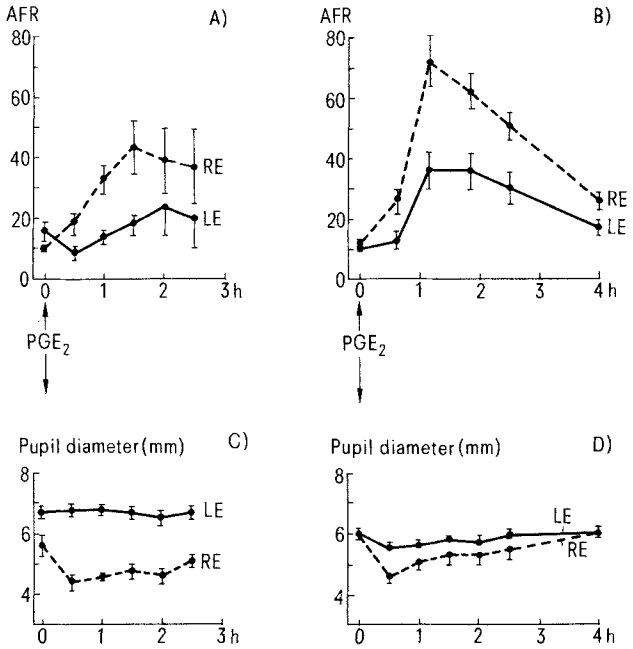

Figure 2. The AFR (A, B) and the pupil diameter (C, D) in response to topical application of PGE_2 onto both eyes 4 h after the intravitreal injection of TTX (A, C) or 1 h after the 1st topical application of 300 nmoles (470 µg) of (D-Pro^2, D-Trp^{7,9})-SP$_{1-11}$ (B, D) onto the left eye (LE) and 0.9% saline onto the right eye (RE). Six rabbits received TTX and 8 rabbits received SP antagonist. Means ± SEM (vertical bars). The difference between the left eye and right eye following application of PGE_2 was significant in both series of experiments (analysis of variance, $p < 0.001$ in A–D).

ethanol, 425 µl Tween 80 and 14.5 ml 0.9% saline to give a concentration of 0.33%. 1 mg of PGE_2 was dissolved in 0.1 ml ethanol and 0.9% saline was added to give a concentration of 0.17 mg/ml. The SP analogue was synthesized by techniques analogous to those described elsewhere[19,20]. Its purity was tested by HPLC and found to be better than 98%. It has previously been identified as a competitive antagonist of SP[21,22] with a selective action in that it antagonizes the smooth muscle contraction induced by SP and related tachykinins but not that induced by histamine, carbachol, 5-hydroxytryptamine, bradykinin, vasopressin, bombesin or prostaglandins[21]. 132 mg was dissolved in 14 ml 0.9% saline to give a concentration of 9.4 mg/ml. TTX was obtained from Sankyo, Tokyo, Japan, and dissolved in 0.9% saline.

Analysis of variance (2-way) was used for calculating the significance of difference between treated and control eyes.

Results and discussion. Injection of capsaicin produced AFR and miosis (fig. 1). Also PGE_2 evoked AFR and slight miosis (fig. 2). Pretreatment with either TTX or the SP antagonist greatly reduced the responses to both capsaicin and PGE_2 (figs 1 and 2).

The responses to ocular injury are thought to depend at least partly upon agents released from peripheral sensory nerve fibers[7,12–15]. Responses to intracameral administration of capsaicin, bradykinin and prostaglandin E_1 were greatly reduced or abolished after sensory denervation of the eye by diathermic destruction of the trigeminal nerve[7]. The response to SP was not abolished[7]. Hence, the response to SP does not depend upon the functional integrity of the sensory nerves, and it may be that SP bears some resemblance to the endogenous antidromic mediator[13]. In fact, SP has been put forward as a candidate mediator for the neurogenic response since: 1. Exogenous SP causes ocular hypertension and miosis[7,8,13,23]; in addition, disruption of the blood-aqueous barrier has been noted[23]. 2. SP is a constituent of sensory nerve fibers[24], including those of the trigeminal nerve[23,25–27]. 3. Sectioning of the trigeminal nerve lowers the SP levels in the uvea[28,29] and suppresses the responses to capsaicin, bradykinin and prostaglandins, but not to SP[7]. 4. Capsaicin, known to release SP[30], evokes signs of ocular inflammation[3,31]. 5. Capsaicin pretreatment prevents the ocular response to infrared irradiation and prostaglandins[31]. 6. Antagonists to SP suppress ocular responses to IR-irradiation, bradykinin and SP[14,15]. The results of the present study suggest that capsaicin and PGE_2 cause ocular irritation at least partly by a neurogenic mechanism, since the responses could be reduced by pretreatment with TTX. Conceivably, neuronal SP or a related peptide is involved as a mediator in the ocular response to both capsaicin and PGE_2 since a competitive SP antagonist greatly reduced the effects of these drugs.

1 This study was supported by the Swedish MRC (04X-1007, 14X-2321), The Medical Faculty of Lund, AB Ferring, Malmö, Sweden, Ferring Arzneimittel GmbH, Kiel, FRG, H. and L. Nilsson's Foundation and E. Henriksson's Foundation.

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0014-4754/83/090996-03$1.50 + 0.20/0

Differences in the content and turnover of noradrenaline in rat heart atria and ventricles and circadian-phase-dependency[1]

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Summary. In light-dark-synchronized male rats the levels of noradrenaline in heart atria were about 3 times that found in heart ventricles. Noradrenaline turnover rate which were about 8–9 fold greater for the atria than for the ventricles displayed a circadian-phase-dependency with increased rates in the dark period in both parts of the rat heart.

There is sound evidence demonstrating circadian variations in the level of various biogenic amines in different organs, especially the brains of mammals[2–5]. However, the endogenous level is in fact the resultant of a number of underlying phenomena: synthesis, storage, release and inactivation of the amine, and may not be a representative measurement of the dynamics of the respective transmitter substance. The turnover of a biogenic amine reflects its level of functional activity in a much better way[5–7]. Previous studies in light-dark-synchronized male rats have shown that the turnover rate of the cardiac noradrenaline was significantly greater in the activity period of the night-active animals, i.e. in the dark period, than in the resting period during light, even though the level of noradrenaline in whole hearts did not vary with the time of the day[7–9]. That this circadian ryhthm was triggered by central nervous activity was demonstrated in experiments in which ganglionic transmission was blocked by chlorisondamine, which abolished the rhythm in the turnover of the cardic noradrenaline[8].

It is well known that the neurones of the cardiac sympathetic nervous system terminate mainly in structures of the heart atria. Since no data were available concerning the noradrenaline turnover rate and its circadian-phase-dependency in different parts of the rat heart, it was the aim of this investigation to study separately the concentration and the turnover of noradrenaline in the atria and ventricles of the heart at different times of the day. In previous studies the turnover of cardiac noradrenaline was studied by inhibiting either the tyrosine-hydroxylase[7] or after injection of ^{3}H(–)-noradrenaline[7–9]. Since in the present experiment inhibition of the dopamine-β-hydroxylase by FLA 63 was used to determine the noradrenaline turnover, the results obtained under identical experimental conditions with both nonradioactive and radioactive techniques could be compared.

Material and methods. Male Wistar rats (TNO W. 74) of about 130–160 g were used. The animals were kept for at least 7 days under a controlled lighting schedule of 12 h light (07.00–19.00 h, 200 lx) alternating with 12 h darkness (19.00–07.00 H < 0.1 lx) with food and water ad libitum and at a room temperature of 23 ± 1 °C.

The noradrenaline contents of the atria and ventricles of the rat heart were determined by a spectrofluorometric method[10] using the procedures described by Schlumpf et al.[11] and Chang[12] with slight modifications. Briefly, the modifications mainly involved the extension of the miniaturized method of Schlumpf et al.[11] for 1.5–5 mg samples to tissue amounts of 15–250 mg (for details see Weimer[10]).

The turnover of noradrenaline in atria and ventricles was determined separately either during the light period (L) or the dark period (D). The parameters of the turnovers ($t^1/_2$ = half-life, k = rate constant, turnover rate) were determined from the logarithmic decline of the endogenous noradrenaline content after inhibition of the dopamine-β-hydroxylase with FLA 63 (bis-[4-methyl-1-homopiperazinyl thiocarbonyl]-disulfid, Labkemi AB, Göteborg, Sweden). FLA 63 has been shown to be a potent inhibitor of dopamine-β-hydroxylase[13], leading to a rapid and selective