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The Effect of PGE_2 on Activity and Thermosensitivity of Hypothalamic Neurones in Rat Brain Slices

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Summary

Using brain slices the effect of prostaglandin E_2 (PGE_2) on neurones from different locations of the rat hypothalamus was analysed. PGE_2 (150 ng), when injected into the perfusion chamber, influences all hypothalamic neurones studied. The pattern of firing rate changes after PGE_2 is variable, but the depressive effect predominates – 72 % of neurones decrease their firing rate in long-term experiments. PGE_2 also lowers the thermosensitivity of warm sensitive neurones and increases the thermosensitivity of temperature insensitive neurones.

Key words

Neuronal thermosensitivity – Prostaglandin E_2 – Hypothalamus – Rat

The effect of PG E_2 on neural activity in hypothalamic slices has been studied by several authors (Boulant and Scott 1986, Watanabe *et al.* 1987, Ono *et al.* 1987, Morimote *et al.* 1988). The results obtained were inconsistent. Ono *et al.* (1987) observed that warm-sensitive neurones were inhibited more than the nonthermosensitive ones. Morimoto *et al.* (1988) found that PG E_2 inhibited neurones in the ventromedial hypothalamus, but stimulated neurones in the PO/AH. No final conclusions can be made from these data. The effect of PG E_2 on thermosensitivity of neurones has not yet been studied under *in vitro* conditions.

In this study, unit activity was recorded in tissue slices of the brain stem, prepared from Wistar strain rats, weighing 200 g. Several slices (400 μm thick) containing the anterior and posterior hypothalamus and the septal area, were obtained by using a razor blade slicer. The slices were allowed to recover for one hour in carbogene bubbled artificial cerebrospinal fluid (ACSF) at 37 °C. For extracellular recordings the slices were transferred to a small chamber (volume 0.5 ml), continuously perfused with carbogenated ACSF with a velocity of 2.5 ml/min. The temperature was measured at the slice surface by a small thermocouple and kept at 38 °C by means of a Peltier device. Periodical temperature stimulation between 35 and 41 °C at the slow speed of 0.02 °C/s (to minimalize possible dynamic temperature effects) were usually applied twice to test the temperature sensitivity of the recorded neurones. Temperature stimulation was repeated 15 and 45 min after drug administration. PG E_2 (Sigma) was applied as bolus injection (150 ng/0.15 ml) into the inlet of the perfusion chamber. Single unit activity was extracellularly recorded with glass covered platinum wire microelectrodes. Action potentials and temperature were recorded and/or stored on an oscillograph, a chart recorder and magnetic tape and also fed into a computer for on-line data evaluation.

Warm- and cold-sensitive neurones were defined by a minimal temperature coefficient (TC) of 0.6 imp/s/°C with a positive sign for warm sensitivity and a negative sign for cold sensitivity. The

temperature response curve of each neurone was evaluated by relating the firing rate to slice temperature. In case of nonlinearity of the frequency temperature relationship, ranges with different sensitivities were estimated by selecting those two subsets of data points for which piecewise linear regression analysis gave the minimum sum of least squares for the entire set of data points. The intersection of the two regression lines determined the threshold temperature for a given neurone.

Prostaglandin E_2 (PG E_2) administration (150 ng) into the perfusion medium influenced the firing rate at 37 °C (tonic activity) of all neurones, independently their previous spontaneous activity, thermosensitivity or localization in the brain.

The time course of changes in tonic activity at 37 °C in individual experiments after PG E_2 was highly variable. Fig. 1 summarizes schematically different patterns of changes in firing rate and their relative occurrence. Evidently, the depressive effect of PG E_2 predominated. Temporal increases in firing rate were recorded in 28 % of experiments, only.

The brain neurones studied (n = 28) exhibited different temperature sensitivity. 68 % of neurones showed a linear relationship between temperature and firing rate, while 32 % of neurones were "non-linear". About 55 % of "non-linear" neurones exhibited the "hockeystick" relationship between temperature and firing rates, with the "breaking point" between 38.1 – 40.6 °C, i.e. above the normal body temperature. At temperatures above the "breaking point", most of the neurones appeared to be warm-sensitive. At temperatures below the "breaking point" they exhibited low temperature sensitivity. Few "non-linear" neurones were warm-sensitive at temperatures below 36.5 – 39.9 °C and temperature insensitive, or cold sensitive, above this range of temperatures.

Out of 19 "linear" neurones, 42 % were warm-sensitive (0.6 imp./s/°C) and 58 % were temperature-insensitive. No cold-sensitive neurones were discovered among the "linear" neurones studied.

PG E_2 influenced the temperature sensitivity both of "linear" and "nonlinear" neurones. In warm-sensitive neurones, PG E_2 lowered the temperature coefficients, while in temperature-insensitive neurones PG E_2 tended to increase it (Fig. 2). Prostaglandin E_2 also influenced the character of the relationship between firing rate and temperature. About 50 % of "non-linear" neurones became "linear" after PG E_2, while PG E_2 induced a "non-linear" relationship between temperature and firing rate in 21 % of "linear" neurones.

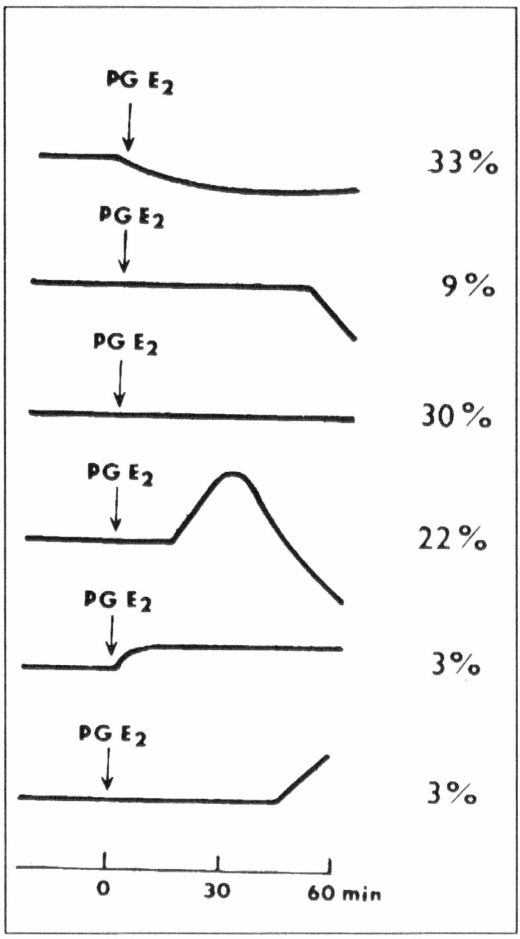

Fig. 1
The time course of changes in tonic activity of neurones at 37 °C before and after administration of PG E_2.

The final effect of PG E_2 is a general lowering of temperature sensitivity. Fig. 3 shows that among "linear" neurones 15 or 45 min after application of PG E_2 only 29 % or 12 % of neurones retained their warm-sensitivity, respectively, as compared to 42 % in the controls. A similar trend can be traced when all neurones ("linear" and "nonlinear") studied are considered.

These data indicate that not only the changes in tonic activity of neurones at 37 °C, but also changes in their thermosensitivity may be responsible for

elevation of the thermoregulatory "set point" during fever.

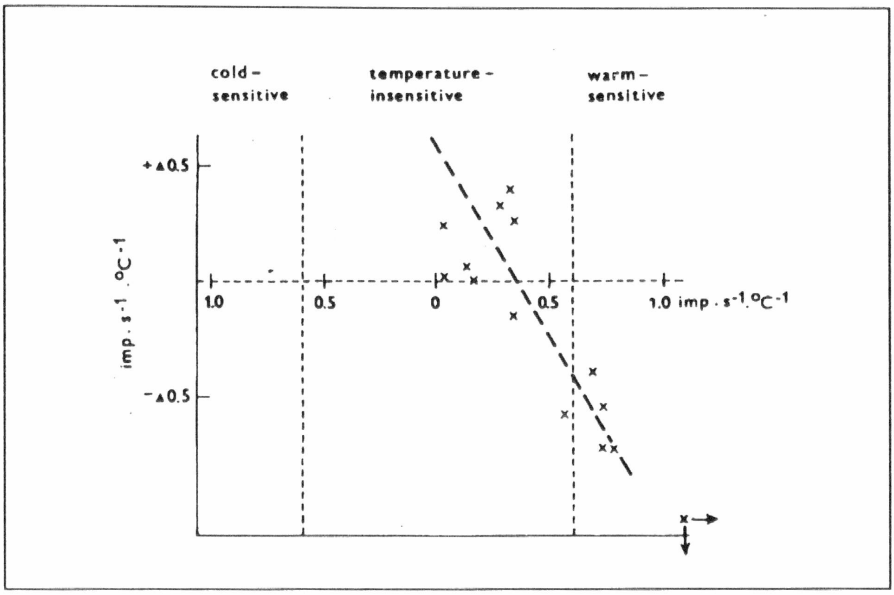

Fig. 2
Changes in temperature coefficients of "linear" neurones due to PG E_2 administration as related to their original thermosensitivity.

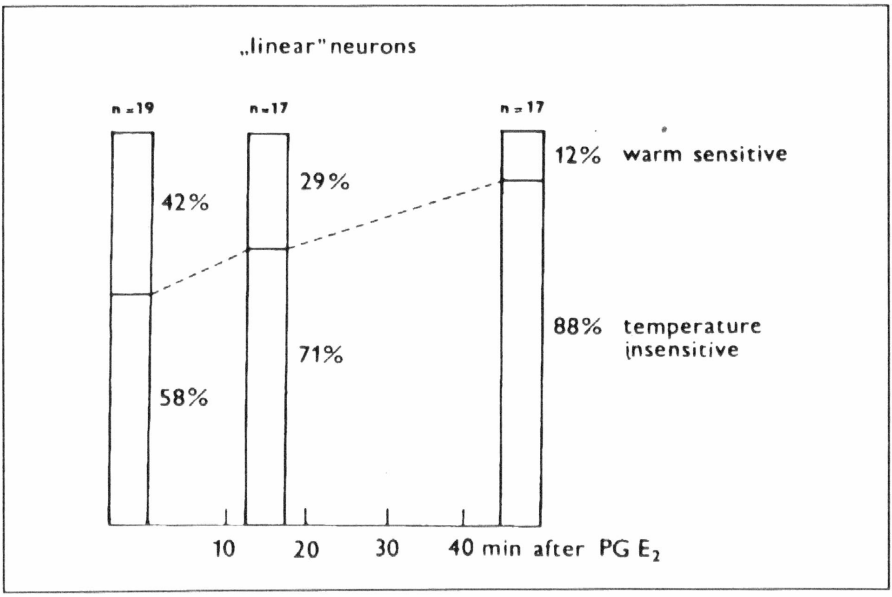

Fig. 3
Percentage of warm sensitive and temperature insensitive "linear" neurones before and 15 min and 45 min after PG E_2 administration.

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Reprint requests

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