cervical vagus. Platinum electrodes were connected to AC preamplifiers (Grass Model P511) with a band width of 10 c/s to 10 Kc/s. Nervous activity and all variables recorded on the polygraph were fed into a tape recorder (Hewlett-Packard 3900). Five of these variables could also be photographed from a slave cathode-ray tube arranged in parallel with a Tektronix 565 oscilloscope.

We isolated 31 afferent cardiac vagal fibers which were excited during ischemia produced either by stopping the coronary inflow pump or by transient occlusion of the main left coronary artery using a snare (Table). The receptors were identified as atrial or ventricular according to their pattern of discharge[8,9]. They were judged to be either in the left or right heart by their response to separate occlusions of pulmonary artery and aorta. They were further localized by direct probing of the cardiac chamber in which they were thought to be located. As shown in the Table receptors from each cardiac chamber were activated during ischemia (69 trials, 31 fibers, 100% success rate).

The discharge of a right atrial receptor is shown in Figure a. 3 min after cessation of left coronary inflow, the arterial pressure fell to 0 mm Hg, the heart was markedly dilated and contracting weakly, while its electrical activity was barely discernible (Figure b). A clear increase in disharge of the receptor was then present. If at this time the heart was manually emptied by cardiac massage, a temporary reduction or cessation in discharge occurred. After the pump was turned on, the pattern of discharge returned to normal in about 30 min.

When the coronary pump was stopped, the mean latency for excitation of all fibers was about 42 sec. At this time, aortic pressure had begun to fall, atrial pressures were rising, and the heart was failing. The stimulus to these receptors might therefore have been mechanical due to enlargement of the failing heart, or chemical due to ischemia. The reduction in discharge produced by emptying the heart manually indicated that the stimulus to these receptors was mainly mechanical although a chemical component due to ischemia could not be ruled out.

To distinguish further amongst these possibilities, we attempted to produce myocardial ischemia by acute, severe hemorrhage since this event is associated with a marked reduction in coronary flow[10]. In this case atrial pressures are reduced[11,12], while myocardial contractility is still relatively well-preserved[13]. Therefore, any possible myocardial ischemia that may occur would not be associated with an increase in cardiac size. However, these experiments suffer from the limitation that ischemia is probably both general and regional. In Figure c, the discharge of the fiber was clear reduced following removal of 60 ml of blood. The ECG was markedly altered, and the arterial pressure had fallen to about 20 mm Hg. When the blood was reinjected, the discarge increased as the atrial pressure began to rise (Figure d). 4 atrial and 2 ventricular fibers that were excited during myocardial ischemia produced by reduction of coronary flow were inhibited during acute hemorrhage (14 trials, 100% success rate). A decrease in firing of vagal atrial receptors during hemorrhage has already been reported[14].

Cardiac vagal receptors located in each of the cardiac chambers were activated during myocardial ischemia produced by reduction of left coronary flow. The effective stimulus to these receptors is likely to be the attendant increase in heart size while ischemia per se seems to be of little or no importance. This would account for the excitation of right atrial receptors whose blood supply is probably largely independent of left coronary flow. Such receptors are known to be highly responsive to changes in atrial volume[8,14]. By contrast, cardiac receptors whose afferent fibers run in the cardiac sympathetic nerves respond to myocardial ischemia after a much shorter latency (10–20 sec) and ischemia appears to be the effective stimulus[7].

It is reasonable to speculate that excitation of cardiac vagal receptors may initiate depressor reflexes[4,5] when myocardial ischemia is accompanied by cardiac failure.

Résumé. La décharge de fibres vagales d'origine cardiaque est augmentée au cours d'une réduction du flux sanguin dans l'artère coronaire de gauche. Toutefois cette excitation n'a lieu que lorsque le coeur est déjà défaillant à cause de l'ichémie. La stimulation effective paraît être de nature mécanique.

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Summary of afferent cardiac vagal fibers excited during myocardial ischemia

Method used to produce ischemia	No. of fibers	Location of the receptors R.A.	R.V.	L.A.	L.V.
Cessation of pump inflow	21	13	–	4	4
Transient occlusion by snare	10	4	2	4	–

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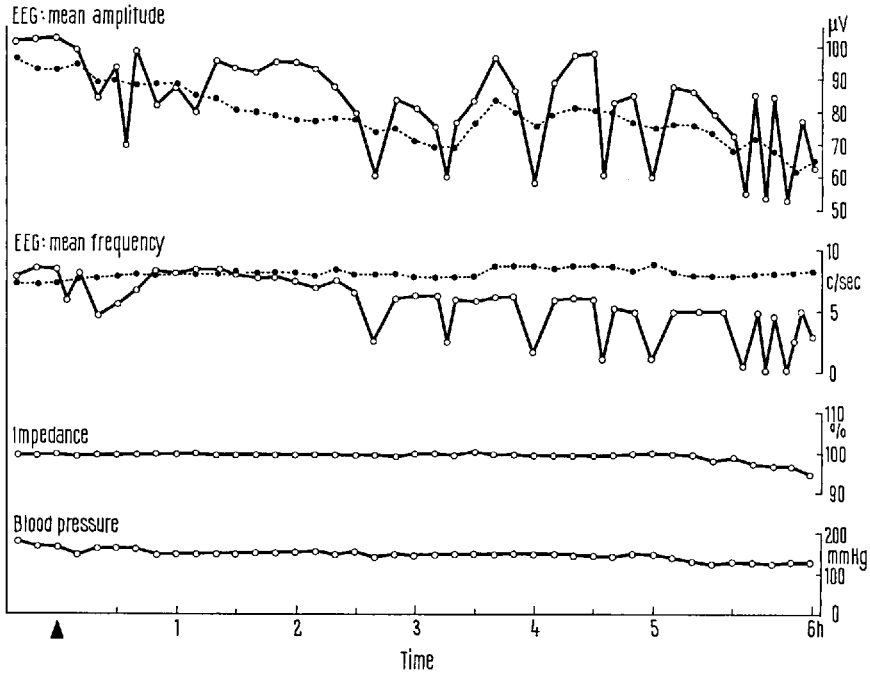
Periodic Depression by N-Methyl-N-nitrosourea of Electrocortical Activity in the Cat Brain

N-Methyl-N-nitrosourea (MNU) is an alkylating agent which has been widely used in the experimental production of brain tumors[1,2]. Early biological effects of MNU include methylation of nucleic acids[3], inhibition of DNA synthesis[4] and pathological changes in proliferating cells. Recent observations of episodes of tonic seizure activity after systemic application in mice suggest that MNU also exerts an acute neurotoxic effect[5].



Periodic depression of EEG activity after infusion of 60 mg N-Methyl-N-nitrosourea into the right carotid artery (duration of infusion is marked by the horizontal bar). EEG was recorded with bipolar electrodes from the dura over the right and left suprasylvian gyrus. Mean amplitude (µV) and mean frequency (cycles/sec) were computed during periods of 10 min (right hemisphere: solid line; left hemisphere: dotted line). Cortical impedance (as percentage of the control) was measured in the right ectosylvian gyrus, and systolic arterial blood pressure in the right femoral artery. EEG changes are markedly pronounced on the side of the infusion, and not related to changes in cortical impedance or blood pressure.

We have investigated the influence of MNU on electrocortical activity in the cat brain. Animals (2.3–3.5 kg) were anaesthetized with pentobarbital (30 mg/kg), immobilized and placed under artificial respiration. A dose of 60 mg MNU (1% in physiological saline – 3 *m M* citrate buffer, pH 6) was infused into the right carotid artery over a period of 12 min, and EEG (with automatic frequency analysis), cortical impedance, and arterial blood pressure were continuously recorded for 3–5 h.

Immediately after the application of MNU, EEG changes were observed which were markedly pronounced on the side of the injection. The least noticeable change consisted in the transient suppression of spontaneous barbiturate spindles for up to 20 min. In other experiments periodic episodes of EEG changes occurred which lasted 5 to 20 min, and during which 8–10/sec spindles appeared, separated by isoelectric periods or low voltage slow waves. Between such episodes the EEG almost completely recovered. In one such case the first episode occurred immediately after the infusion, the second afer 2.5 h, and others periodically at shorter time intervals for several hours (Figure). In a third group of animals EEG activity was completely suppressed immediately after the infusion and remained isoelectric, with the exception of one experiment in which low voltage spindles reappeared temporarily for a period of 10 min.

Continuous recording of cerebral impedance and systemic blood pressure did not reveal any major changes even in those experiments in which the EEG was completely suppressed. Consequently, the depression of electrocortical activity seems to be a direct effect of MNU on the brain and not the result of a reduced cerebral blood flow or of brain edema. A systemic effect of MNU can be ruled out as the depression was definitely more pronounced on the side of the injection and i.v. injection of an equal dose of MNU did not produce any changes in control experiments.

The present study substantiates the previous suggestion of an acute neurotoxic effect[5]. MNU readily passes the blood-brain barrier[6], it decomposes rapidly in vivo[7], and it seems to effect its biological actions by alkylating intermediates which are released during its metabolization[1]. Further investigations are necessary to reveal the mechanism of action of MNU on electrocortical activity, in particular the possible effect of MNU-induced reduction of nicotinamide adenine dinucleotide concentration in the brain[5]. The repetitive character of EEG changes may reflect periodic changes due to MNU of brain metabolism or it may represent a prolonged functional response by cerebral neurons to the short lasting impact. In the latter case periodic EEG depression could be related to cyclic changes in neuronal activity[8].

Zusammenfassung. An Katzen wurden die Auswirkungen von N-Methyl-N-Nitrosamin auf das EEG untersucht. Die intracarotidale Injektion von 60 mg dieser Substanz bewirkt einseitige zyklische Depressionen des EEGs, die über mehrere Stunden anhalten können.

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