the $Na^+, K^+$-pump, rather than a decreased $K^+$-conductance out of the atrial cell. However, the possibility should not be excluded that a stimulating effect of taurine on the $Na^+, K^+$-pump was a plausible explanation for the finding reported.

Taurine alone, at the doses used, did not affect contractility of the heart and amounts of intracellular $K^+$ in both media. Since it has been shown that, at the stage at which development of contracture was induced by large doses of ouabain, there were an increase in $Ca^{++}$ contents and a decrease in $K^+$ contents in hearts[19], the possibility should also not be excluded that taurine might prevent the increase of the intracellular $Ca^{++}$ content at the toxic stage (the decrease in the inotropism after the large doses of ouabain). On the other hand, the present authors[12] reported that a combined treatment of taurine at the dose of 3.0 mM, and ouabain at doses ranging from 0.5 μM to 2 μM under the same experimental conditions as the present, resulted in both potentiation of the positive inotropic effect and an increase in intracellular $Ca^{++}$ contents. Other authors have also reported that taurine promoted a myocardial uptake of $Ca^{++}$[13] and slowed a rate of myocardial loss of $Ca^{++}$[20]. Consequently, the inhibitory effect of taurine on the decrease of the inotropic action of ouabain at the doses used might not be concerned in movement of intracellular $Ca^{++}$.

19 K. S. Lee, M. R. Shin, D. H. Kang and K. K. Chen, Biochem. Pharmac. *19*, 1055 (1970).
20 R. Huxtable and R. Bressler, Biochim. biophys. Acta *323*, 573 (1973).

## Effect of harmaline on the cerebello-rubral system

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*Summary.* Harmaline induces synchronous rhythms in both the cerebellum and the red nucleus of the rabbit. The level of synchronization is lower in the red nucleus than in the cerebellar cortex, probably because the cerebello-rubral pathway and the red nucleus neurons only participate poorly in the harmaline-induced olivo-cerebellar rhythm.

Previous investigations[2–7] have shown that under the influence of central depressants (barbiturates in particular), strychnine and tetanus intoxication, synchronous frequencies can always be recorded from the cerebellum (CB) and red nucleus (NR), whereby NR-neurons fire in bursts that are correlated with the respective cerebello-rubral rhythm. Evidence has been presented that the synchronous firing of these neurons and the NR-rhythm are initiated by cerebello-rubral pathway[2,5]. The discharge pattern of NR-cells is so distinctly correlated with the cerebellar rhythm, as if these units were under the synaptic drive of the cerebellar pathway only.

In studies on tremor mechanisms, Lamarre et al.[8,9] have proved that the harmaline-induced 6–12 Hz tremor is generated by rhythmic firing of olivary neurons; these impulses are transmitted to spinal levels mainly by the

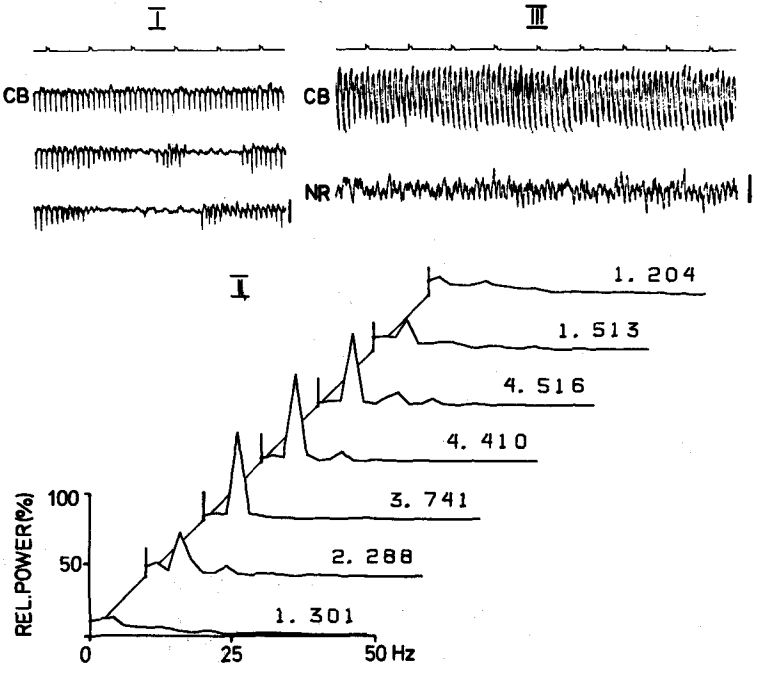


Fig. 1. Effect of harmaline on the electrical activities of the cerebellum (CB) and red nucleus (NR). *I* Continuous record (EEG) from the CB; calibrations: 0.2 mV and 1 sec. *II* Power spectra of the electrocerebellogram. Each spectrum represents the analysis of a 10-sec recording sample with a frequency resolution of 2 Hz. Numbers: total power ($\mu V^2$) in arbitrary units. *III* Simultaneous records from the CB and NR; calibrations: 0.2 mV and 1 sec.

cerebellar cortex. In addition, rhythmic activity of the same frequency was recorded from the cerebellar vermis by means of gross electrodes[10,11]. Since our investigations[2–7] have suggested that under various experimental conditions rhythmic impulses of the cerebellar output induce rhythmic discharge patterns of NR-neurons, these cells might be expected to be influenced also by the harmaline-induced olivo-cerebellar rhythm.

*Material and methods.* Surgical procedures were performed on male rabbits, weighing between 2.8 and 3.6 kg, under propanidid anesthesia, and all wounds and pressure points were carefully infiltrated with 2% procaine hydrochloride. Following surgery, the rabbits were immobilized by gallamine triethiodide and kept under artificial respiration. Gross electrode recordings were made bipolarly from the CB (mainly from the vermal part of the anterior lobe), and in some experiments also from the NR. The activity of NR-units was recorded extracellularly by means of steel microelectrodes. Details of these methods have been described in previous publications[2,5]. A HP Signal Analyzer System (a 2108 A computer and a 5480 Signal Analyzer) was used for computational procedures. Harmaline hydrochloride and hexobarbital sodium were injected intravenously in doses of 5 mg/kg and 20 mg/kg respectively.

*Results and discussion.* 2–4 min after the administration of harmaline, the low-voltage cerebellar activity of the awake immobilized animal is replaced by high-voltage rhythms, the frequency of which remains roughly stable in the individual experiments, but ranges from 6 to 10 Hz between the experiments. The harmaline-induced rhythm lasts 15–40 min. During this period the rhythm can repeatedly be interrupted for several seconds by low-voltage fast activity (figure 1, I). Electrocerebellograms of 10-sec-duration were taken for spectral analysis at 10-min-intervals, beginning with the first minute after harmaline administration and carried on to the first interruption of the rhythm (figure 1, II). This figure shows the stability of frequency and the 'waxing and waning' character[12] of the harmaline-induced rhythm. Simultaneous EEG-recordings of both the CB and NR have shown that under the influence of harmaline, rhythms of identical frequency appear in both structures (figure 1, III). The stability, synchrony and amplitude are much lower in the NR- than in the CB-rhythm. Moreover, while highly synchronized harmaline-induced rhythm can be recorded from the CB, the NR-neurons do not fire in such a uniform pattern as, for instance, they do under the influence of barbiturates. Figure 2, I, depicts the cerebellar EEG and the simultaneously recorded activity of a NR-cell. In comparison with the outstanding

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2 G. Gogolák, G. Liebeswar, Ch. Stumpf and H. L. Williams, Electroenceph. clin. Neurophysiol. *29*, 67 (1970).
3 G. Gogolák, F. Krijzer and Ch. Stumpf, Naunyn-Schmiedebergs Arch. Pharmak. *272*, 378 (1972).
4 G. Gogolák and Ch. Stumpf, Naunyn-Schmiedebergs Arch. Pharmak. *272*, 387 (1972).
5 G. Gogolák, Naunyn-Schmiedebergs Arch. Pharmak. *267*, 249 (1970).
6 G. Gogolák, S. Huck, P. Porges and Ch. Stumpf, Arch. int. Pharmacodyn. Ther. *207*, 322 (1974).
7 S. Huck, G. Gogolák and Ch. Stumpf, Naunyn-Schmiedebergs Arch. Pharmak., suppl. to *282*, R36 (1974).
8 C. De Montigny and Y. Lamarre, Brain Res. *53*, 81 (1973).
9 Y. Lamarre and M. Weiss, Brain Res. *63*, 430 (1973).
10 Y. Lamarre and L. A. Mercier, Rev. Can. Biol. *31*, 181 (1972).
11 G. C. De Trujillo, A. Scotti de Carolis and V. G. Longo, Neuropharmacology *16*, 31 (1977).
12 J. A. Fuentes and V. G. Longo, Neuropharmacology *10*, 15 (1971).

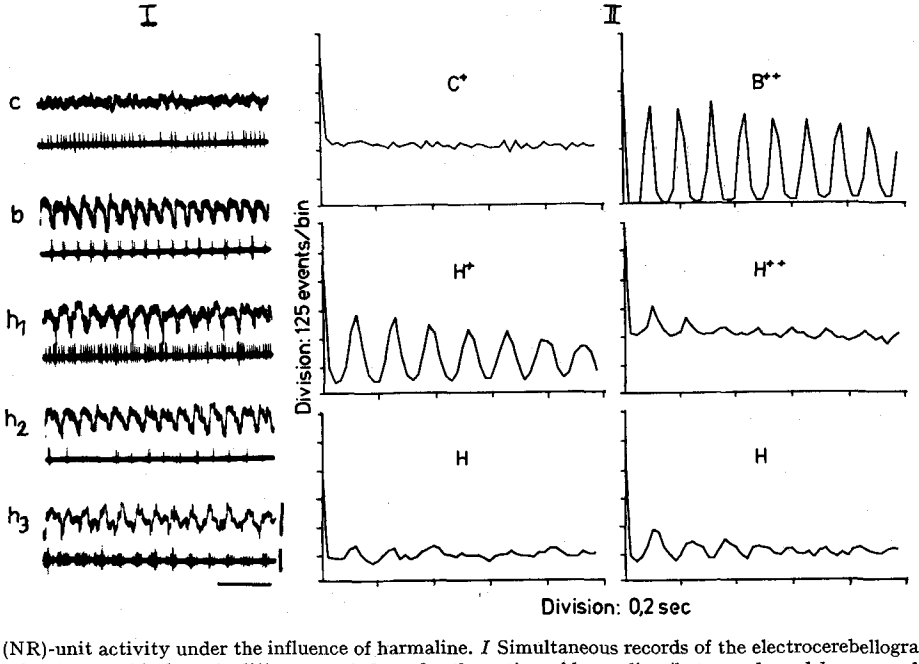


Fig. 2. Red nucleus (NR)-unit activity under the influence of harmaline. *I* Simultaneous records of the electrocerebellogram and the activity of a NR-cell. *c* Control; *b* hexobarbital; $h_1$–$h_3$ different periods under the action of harmaline (between $h_2$ and $h_3$ a second NR-unit with low amplitude spikes appeared). Calibrations: 0.2 mV and 1 mV for the EEG and the unit activity respectively; 0.5 sec. *II* Autocorrelograms of discharges of NR-units. Each of the 4 harmaline records (H) is derived from a different NR-unit. $C^+$ is the control for $H^+$; $B^{++}$ represents the barbiturate-induced activity of the same unit as $H^{++}$. Estimates of correlation functions were calculated on 10-sec-periods of recording using a bin width of 20 msec. Abscissa: time. Ordinate: number of events.

regular burst firing pattern induced by hexobarbital (figure 2, Ib), the synchronization level of cell discharges seems to be lower under harmaline: In the course of the harmaline action, the same unit may change its discharge pattern from irregular firing (figure 2, $Ih_1$) to silent periods (figure 2, $Ih_2$) or to a regular burst firing pattern (figure 2, $Ih_3$). When spikes of 2 different cells are recorded simultaneously (for example: figure 2, $Ih_3$), the level of the harmaline-induced synchronization seems to be different for each unit.

Autocorrelation functions of NR-unit activities obtained from periods of highly synchronized cerebellar rhythms show that harmaline does induce NR-cells to fire rhythmically (figure 2, IIH; compare also $C^+$ and $H^+$ of this figure); these discharge patterns, however, never reach that uniform regularity which can always be observed under the influence of barbiturates (compare $B^{++}$ and $H^{++}$ in figure 2, II).

It has been suggested[5] that the NR-rhythm induced by barbiturates, and other agents acting like barbiturates, is formed by synchronous membrane oscillations of many NR-units, which is due to their synchronized cerebellar input. Additional findings[6] have indicated that a positive correlation exists between the synchronization level of NR-cells and the amplitude of NR-rhythm. This assumption also seems to be supported by the present experiments which show low synchronization levels of cell discharges and unstable low-amplitude rhythms in the NR under the effect of harmaline.

The harmaline-induced rhythmic olivary impulses reach the spinal cord via the cerebellar cortex, fastigial and reticular nuclei[13]. Along this pathway, neurons were found to discharge in rhythmic sequences and in correlation with the tremor frequency. The cerebellar input via interposed nuclei to the NR seems to be only partly involved in these rhythmic discharges, since low synchronization levels of NR-neurons have been found to co-occur even with periods of highly regularized cerebellar rhythms. This conclusion is in accordance with that of Lamarre et al.[13] who proved that structures in the brain stem rostral to the pons are not essential for the induction and maintenance of the harmaline-induced tremor.

According to other authors[13,14], harmaline induced a synchronization of Purkinje cell activity mainly in the median area of the cerebellar vermis; the synchronization decreases rapidly with increasing distance from the midline. On the other hand, those Purkinje cells which project to the NR, via interposed nuclei, are known to be located preferentially in the intermediate zone of the vermis[15,16]. Thus, the cerebellar area projecting to the NR will be only marginally affected by the synchronizing action of harmaline. This may explain the low degree of synchrony between the electrical activities of the CB and NR under the influence of harmaline.

13 Y. Lamarre and L. A. Mercier, Can. J. Physiol. Pharmac. *49*, 1049 (1971).
14 R. Llinás and R. A. Volkind, Exp. Brain Res. *18*, 69 (1973).
15 A. Brodal, Prog. Brain Res. *18*, 135 (1967).
16 C. C. Bell and S. R. Dow, Neurosci. Res. Prog. Bull. *5*, 121 (1967).

## Metaraminol uptake by human thrombocytes: A poor model for neuronal noradrenaline uptake

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*Summary.* The $IC_{50}$ of a number of antidepressants and related drugs on the uptake of l-metaraminol and serotonin into human thrombocytes, and of noradrenaline and serotonin into rat midbrain synaptosomes were compared. In accordance with previous reports, it was found that platelets provide a good model for the study of neuronal uptake of serotonin. Platelet uptake of l-metaraminol, although correlated to some extent with noradrenaline uptake into synaptosomes, seems to be an unsatisfactory model for the neuronal uptake of the latter amine.

The uptake of serotonin (5-HT) into thrombocytes is a good model of the neuronal re-uptake of this amine[1-3]. This is especially important for the study of the inhibitory effects of antidepressants on 5-HT uptake in man, where the neuronal uptake of this transmitter cannot be estimated directly.

However, many antidepressant drugs inhibit the neuronal re-uptake of noradrenaline (NA)[4-7]. According to the catecholamine hypothesis of depression[8], it is this property of the tricyclic drugs which is crucial for their antidepressants effects[7,9].

Blood platelets take up catecholamines, especially NA, slowly and only to a limited extent[10,11], and are therefore not well suited as a model for the study of the inhibition of neuronal re-uptake of these amines[2]. It has recently been suggested that metaraminol (MR), which can be substituted for NA in the study of its uptake in sympathetic nerves[12-14], could serve a similar purpose in the platelet model[15], though very little evidence was adduced to support this theory. Since it would be a great advantage to have a model for the study of NA uptake in man, we have therefore investigated the suitability of metaraminol uptake into platelets for this purpose in more detail.

*Materials and methods.* C-49802-B-Ba (1-(1-methyl-amino-2-hydroxy-3-propyl)-dibenzo[b,e]bicyclo[2,2,2]octadiene-HCl) and CGP 6085 A (4-(5,6-dimethyl-2-benzofuranyl)piperidine-HCl) are experimental drugs synthesized in the laboratories of CIBA-GEIGY which selectively inhibit the uptake of NA and 5-HT respectively inhibit the uptake of NA and 5-HT respectively (manuscripts in preparation).

The uptake of $^3$H-5-HT (12.5 Ci/mmole, Radiochemical Centre, Amersham, England) into human thrombocytes and of $^3$H-5-HT and $^3$H-NA (4–6 Ci/mmole, Radiochemical Centre) into rat midbrain synaptosomes was determined as described earlier[16]. The uptake of $^3$H-MR (dl-$^3$H-MR, 6.5 Ci/mmole, New England Nuclear, Boston, Mass.) was determined by a modification of the procedure for 5-HT[16]. 0.1 ml of a $2.4 \times 10^{-4}$ M solution of l-MR (Merck, Sharpe and Dohme N.V., Haarlem, Holland) containing 5 μCi/ml dl-$^3$H-MR was added to 1.1 ml platelet-rich plasma pre-incubated for 5 min with the drugs to be tested, and incubation was continued for a further 45 min. The tubes were cooled in ice, the platelets sedimented by centrifugation at $3{,}000 \times g$ for 10 min, the supernatants discarded and the pellets resuspended in 1 ml ice-cold 0.9% NaCl. The platelets were spun down again and the