synthesis of prostaglandins[9] also abolish the carrageenin hyperthermia, while hydrocortisone is inactive in both respects. It has been reported that prostaglandin $E_2$ increases body temperature in rats when it is administered into lateral cerebral ventricles[10], but when it is injected i.p., a dose-dependent decrease of body temperature occurs. Therefore, if prostaglandins play any role in the carrageenin hyperthermia, an additional explanation is needed except for local generation of prostaglandins. In unpublished experiments we have found that healthy rats injected i.v. with the exudate (0.1 ml) from the carrageenin foot edema immediately develop a pronounced hyperthermia. A search for a hyperthermic principle in the carrageenin exudate seems to be promising.

We propose to use the carrageenin-induced hyperthermia for screening of antipyretic properties of potential aspirin-like drugs. Carrageenin produces in rats all 3 measurable defensive reactions: inflammation, pain and pyresis. All 3 reactions are abolished by anti-defensive[11] aspirin-like drugs, which inhibit prostaglandin biosynthesis[9].

*Zusammenfassung.* Nachweis, dass über subplantare Injektionen von Carrageenin eine allgemeine Hyperthermie bei Ratten zu erhalten ist und die pyretische Wirkung des Carrageenins durch nicht-steroidische Antiphlogistica gehemmt werden kann.

H. SOBAŃSKI, J. KRUPIŃSKA and R. J. GRYGLEWSKI

*Departments of Pharmacology and Pharmacodynamics, Copernicus Medical Academy, P-31-531 Cracow (Poland), 28 May 1974.*

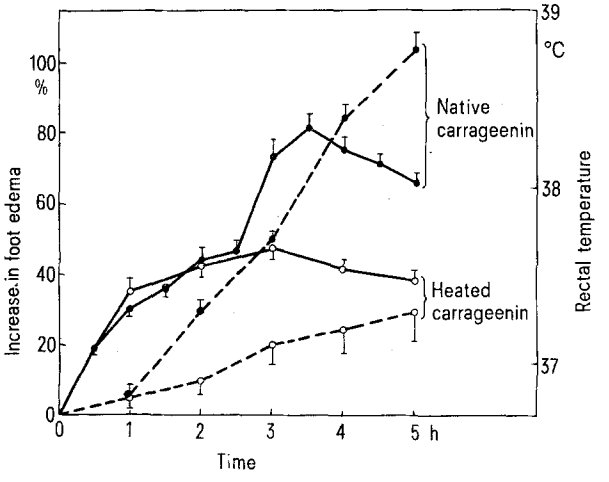



Fig. 3. Carrageenin paw edema (—) and carrageenin hyperthermia (---) induced by native carrageenin (●) or by heated carrageenin (○) injected at a dose of 1 mg s.p. Each point represents the mean of 16 experiments ± S.E.M. except for the group (○---○) consisting of 100 rats.

[9] R. J. FLOWER, R. GRYGLEWSKI, K. HERBACZYŃSKA-CEDRO and J. R. VANE, Nature New Biol. *238*, 104 (1972).
[10] W. J. POTTS and P. F. EAST, Archs int. Pharmacodyn. *197*, 31 (1972).
[11] H. O. J. COLLIER and C. SCHNEIDER, Nature New Biol. *236*, 141 (1972).

## 5-Hydroxytryptamine in the Blood Platelets of Cirrhotic and Hypertensive Patients

There is evidence of disturbed metabolism and storage of monoamines in the cirrhosis of the liver[1], as well as in various experimental and human hypertensive diseases[2]. The binding and uptake of 5-hydroxytryptamine (5HT) by blood platelets is similar to that of other monoamine storing cells[3,4]. Therefore the blood platelets should reflect the changes occurring in the monoamine storing cells of a diseased organism. This paper reports the concentration and uptake of 5HT by the platelets of patients with cirrhosis of the liver as well as that of patients with essential hypertension.

Cirrhotic patients all had typical signs and abnormal liver function tests. The patients with untreated essential hypertension were divided into 2 subgroups (Table). All hypertensive patients had normal liver- and renal functions. Healthy volunteers served as controls.

About 30 ml of blood was drawn from the antecubital vein with a siliconized needle into polypropylene tubes and mixed immediately with $^1/_{10}$ volume of 3.8% sodium citrate. Platelet-rich plasma was separated by centrifuga-

[1] P. PENTIKÄINEN, M. KEKKI and O. MUSTALA, Scand. J. Gastroenterol. *4*, Suppl. 4, 1 (1969).
[2] J. DE CHAMPLAIN, in *Perspectives in Neuropharmacology* (Ed. S. H. SNYDER; Oxford University Press, New York 1972), p. 215.
[3] M. K. PAASONEN, L. AHTEE and E. SOLATUNTURI, Progr. Brain Res. *34*, 269 (1971).
[4] J. M. SNEDDON, Progr. Neurobiol. *1*, 151 (1973).

Endogenous platelet 5HT content, and platelet count in control, cirrhotic and hypertensive subjects

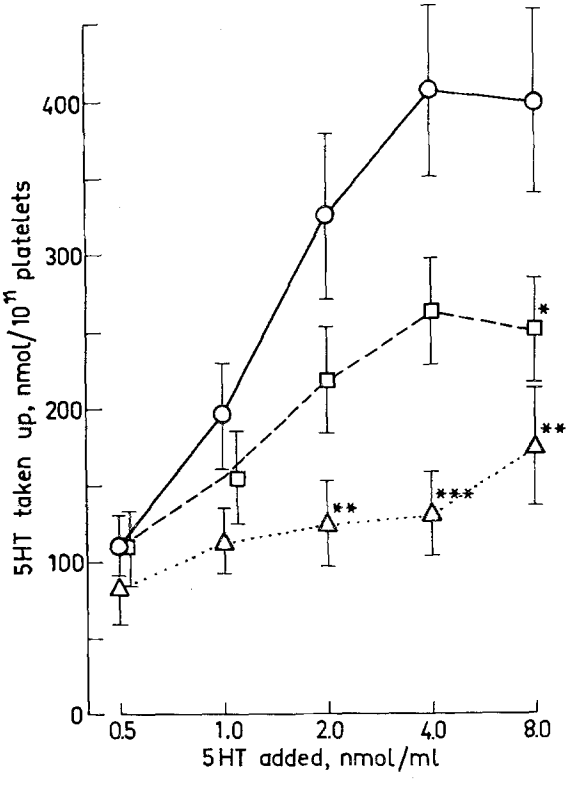
| Group (number of subjects) | Platelet 5HT content (nmol/$10^{11}$ platelets ± S.E.) | Platelet count (per ml × $10^8$ ± S.E.) |
|---|---|---|
| Control (4♂, 4♀) | 300 ± 45 | 3.4 ± 0.6 |
| Cirrhotic (6♂, 1♀) | 129 ± 22[a] | 2.2 ± 0.5 |
| Hypertensive Subgroup A (2♂, 3♀) | 346 ± 83 | 3.9 ± 0.2 |
| Hypertensive Subgroup B (1♂, 4♀) | 231 ± 51 | 4.1 ± 1.1 |

Subgroup A, diastolic blood pressure between 100–109 mmHg; subgroup B, diastolic blood pressure between 110–150 mmHg.
[a] Compared to control $p < 0.01$.

tion and incubated for 20 min at 37 °C with 5-hydroxytryptamine-$^3$H (G) creatinine sulphate, specific activity 0.5 Ci/mmol (The Radiochemical Centre, Amersham) mixed with 5HT creatinine sulphate (Fluka AG, Buchs). After incubation, the platelets were separated from plasma and the platelet pellets were solubilized. The radioactivity was counted in BRAY's solution[5] in a liquid scintillation counter (Decem NTL 314, Wallac Oy, Turku). The original 5HT content of the platelets was determined spectrophotofluorimetrically[6]. Platelets were counted in a phase contrast microscope.

As shown in the Table, the platelet count in the platelet-rich plasma of cirrhotic patients was lower than that in the plasma of the other groups, reflecting the thrombocytopenia known to occur in cirrhotic patients[7]. The endogenous platelet 5HT content of patients with cirrhosis was lower than the content of 5HT in the platelets of control subjects.

The uptake of 5HT into platelets of control and hypertensive patients increased linearly when the concentration of 5HT in the incubation medium was increased from 0.5 to 4 nmol/ml (Figure). These regression curves did not differ statistically significantly from each other. However, the platelets of hypertensive patients took up 5HT less than the platelets of control subjects at every 5HT concentration studied. Furthermore, the platelets of subgroup B hypertensive patients took up 5HT less than the platelets of subgroup A hypertensive patients. At 4 nmol/ml of 5HT the uptake of 5HT into the platelets of control subjects was 410 ± 60 nmol/$10^{11}$ platelets (mean ± S.E.), into the platelets of subgroup A hypertensive patients 300 ± 50 nmol, and into the platelets of subgroup B hypertensive patients 260 ± 40 nmol, respectively. At 8 nmol/ml of 5HT the platelets of subgroup B hypertensive subjects took up 5HT 37% less than the control platelets ($p < 0.05$).




The uptake of 5HT in the blood platelets of control (○— ○), hypertensive subgroup B (□---□), and cirrhotic (△.....△) subjects. 1 ml samples of platelet-rich plasma were incubated for 20 min with 0.5–8 nmol/ml of 5HT. Vertical bars indicate standard errors. Compared to control group * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

The platelets of cirrhotic patients took up 5HT distinctly less than the platelets of control or hypertensive patients. At 8 nmol/ml of 5HT the uptake (180 ± 40 nmol/$10^9$ platelets) into the platelets of cirrhotic patients was less than half of the uptake (400 ± 60 nmol/$10^{11}$ platelets) into the platelets of the controls ($p < 0.01$). Moreover, the uptake of 5HT into the platelets of cirrhotic patients differed from that into the platelets of subgroup B hypertensive subjects at 4 nmol/ml of 5HT ($p < 0.02$).

These results demonstrate that the content and uptake of 5HT into platelets of cirrhotic patients are clearly lower than those of control or hypertensive subjects. Moreover, the uptake of 5HT into the platelets of hypertensive patients is slightly less than into the control platelets and there is implication that the decrease in the uptake of 5HT into platelets is correlated to the increase of blood pressure. In addition, the plasma noradrenaline levels have been shown to be increased in essential hypertension[8]. Both the increased plasma noradrenaline concentration and the decreased 5HT uptake into platelets could be associated with decreased uptake and/or storage capacity for monoamines in hypertensive subjects. The decreased content and uptake of 5HT in platelets of cirrhotic patients could reflect defective binding of 5HT in cirrhosis. Hepatic uptake of 5HT is impaired in cirrhotic rats[1]. Defective binding of 5HT to tissues has been suggested to occur in cirrhotic patients[9], who have lower blood 5HT concentration than control patients[10].

If the storage and uptake of 5HT by blood platelets reflect these functions in other monoamine storing cells, the present findings with human platelets suggest a more generalized disturbance of these functions in hypertensive and cirrhotic patients[11].

*Zusammenfassung.* Die Konzentration und Aufnahme von 5HT in die Thrombozyten bei Patienten mit Leberzirrhose waren signifikant niedriger als bei Kontrollen. Die Aufnahme von 5HT in die Thrombozyten bei hypertensiven Patienten war eine Tendenz kleiner als bei Normotensiven, obgleich die endogenen Konzentrationen von 5HT bei beiden Gruppen ähnlich waren.

LIISA AHTEE, LEENA PENTIKÄINEN,
P. J. PENTIKÄINEN and
M. K. PAASONEN

*Department of Pharmacology, University of Helsinki, Siltavuorenpenger 10, SF-00170 Helsinki 17 (Finland), 1 July 1974.*

[5] G. A. BRAY, Analyt. Biochem. *1*, 279 (1960).
[6] D. F. BOGDANSKI, A. PLETSCHER, B. B. BRODIE and S. UDENFRIEND, J. Pharmac. exp. Ther. *117*, 82 (1956).
[7] H. HUBER, R. GMEINER, S. PLATZER and G. RICCABONA, Wiener klin. Wschr. *79*, 826 (1967).
[8] W. J. LOUIS, A. E. DOYLE and S. ANAVEKAR, New Engl. J. Med. *288*, 599 (1973).
[9] E. SCHMID, H. HAAS, N. HENNING, K. MEYTHALER JR. and H. SCHÖN, Klin. Wschr. *40*, 40, 86 (1962).
[10] E. SCHMID, I. SENG, N. HENNING and K. HEINKEL, Gastroenterologia *93*, 235 (1960).
[11] This work was supported by grants from the National Research Council for Medical Sciences, Finland and the Sigrid Jusélius Foundation. The blood samples were obtained through the cooperation of the Medical Staff of the Kivelä Hospital, Helsinki.