Tissue angiotensinase activity is shown in the Table. No differences were found between the total tissue angiotensinase activity per unit mass in any of the tissues studied, nor was tissue angiotensinase activity more variable in the guinea-pig than in the other 2 species. The rat stomach displayed a significantly higher rate of angiotensin destruction, exceeding the level in vascular tissues by a factor of 4, in approximate proportion to the larger mass utilized. It has also been suggested that the rate of relaxation of a contracted vascular strip represents a valid index of overall drug inactivation[11]. The development of tachyphylaxis in some preparations makes such an interpretation suspect, but examination of the Figure makes it clear that relaxation of the rat aortic strip after washout of aqueous phase angiotensin was considerably more rapid than that of the rabbit.

A parallel between total tissue angiotensinase levels in a number of vascular tissues and their propensity to develop angiotensin tachyphylaxis could not be demonstrated in this study. Such a parallel is a requisite of the hypothesis elaborated by KHAIRALLAH et al.[6]. The much more rapid degradation of angiotensin by the rat stomach makes it clear that the assay system could detect differences. In addition, the more variable propensity to develop tachyphylaxis of the guinea-pig aorta was not associated with a more variable angiotensinase activity in that tissue. It thus seems unlikely that total tissue angiotensinase is the critical determinant in angiotensin tachyphylaxis. There is also debate concerning the role of plasma angiotensinases in tachyphylaxis in a number of systems[4], but the considerable washing carried out on the tissues prior to study makes it unlikely that they could have influenced the results. If tissue angiotensinase is critical, and attractive evidence supports that concept[6], specificity must be applied either through the differences in the metabolic products of enzymes in various tissues or in the specific distribution of the enzymes in the tissues. The possibility exists that the location of angiotensinases in the tissue, specifically their precise relationship to the receptor site, may be an important factor. It is important to recognize, however, that saturation of receptors with an agonist can only account for a failure of response if PATON's[7] concept of receptor activation as a rate rather than occupation phenomenon provides an adequate description of receptor activation, a matter of continued debate[1,12-14].

Zusammenfassung. Die Auffassung, dass die Gewebsangiotensinase-Aktivität entscheidend sei, ob sich eine Gewebs-Tachiphylaxie gegenüber Angiotensin entwickelt oder nicht, konnte durch Versuche an verschiedenartigen Geweben keine Bestätigung finden.

N. K. HOLLENBERG[15], LINDA R. BARBERO and K. P. J. HINRICHS

Harvard Medical School and Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston (Massachusetts 02115, USA), 29 March 1971.

[11] S. KALSNER and M. NICKERSON, Can. J. Physiol. Pharmac. *46*, 719 (1968).
[12] R. F. FURCHGOTT, Ann. N.Y. Acad. Sci. *144*, 869 (1967).
[13] B. BELLEAU, J. med. Chem. *7*, 776 (1964).
[14] B. BELLEAU, Adv. Drug Res. *2*, 89 (1965).
[15] Supported by grants from the John A. Hartford Foundation, Inc., and the U.S. Army R and D Command No. DA-49-193-MD 2497.

The Oxygen Uptake of the Developing Brain in the Rat with Intra-Uterine Growth Retardation

Our previous studies on body composition of the fetus with intra-uterine growth retardation (IUGR) and about somatic development of these animals until adulthood point out the importance of low blood glucose level and decreased total liver glycogen stores in the experimental rats[1-4]. The formation and oxidation of amino acids constitutes a main pathway of glucose metabolism in the brain[5], and it is probable that most of the liver glycogen which is mobilized after birth is utilized by the brain rather than the body as whole. These findings led us to suggest that the glucose requirements for brain of IUGR rats are higher than the amount available by synthesis, and partly explain the hypoglycemia of the stunted rats.

This report deals with oxygen consumption of cerebral cortex of IUGR and control rats during perinatal development.

Methods. Female rats of Sherman strain are mated overnight; they were fed ad libitum on pelleted diet. After birth only 6 newborn are left per litter. The growth retardation was induced in pregnant rats by artery clamping of 1 horn at 17th day after mating. All the IUGR animals had a reduction of weight of more than 15% as compared to controls. This criterion was determined in a previous work[1].

On the 21th day of gestation, the mother was killed by decapitation and the fetuses were extracted immediately by Caesarean section. After the birth, the animals were killed by decapitation and brains were quickly removed, dissected and the cerebral cortex weighed and kept for chemical analyses.

Oxygen consumption was determined by the conventional Warburg technique. Homogenates (10% W:v) were prepared in 'an isotonic NaCl solution' according to ELLIOT et al.[6]. This solution was prepared freshly each day. All manometric experiments were carried out in duplicate at 37 °C. Air was used as the gaseous phase. After 10 min of thermal equilibration, oxygen consumption was measured for 30 min. The results were expressed as μmoles O_2/H/g wet tissue.

At each age, dry weights were obtained by heating the tissue in an oven to a constant weight. Aliquots were used for the subsequent determinations: a) Protein with Folin/Ciacalteu reagent by the LOWRY procedure. b) Des-

[1] C. TORDET-CARIDROIT, J. M. ROUX and C. CHANEZ, C. r. Soc. Biol., Paris *163*, 1321 (1969).
[2] C. CHANEZ, J. M. ROUX and C. TORDET-CARIDROIT, C. r. Soc. Biol., Paris *163*, 2272 (1969).
[3] J. M. ROUX, C. TORDET-CARIDROIT and C. CHANEZ, Biol. Néonate *15*, 342 (1970).
[4] C. CHANEZ, C. TORDET-CARIDROIT and J. M. ROUX, Biol. Néonate *17*, 355 (1971).
[5] M. K. GAITONDE, D. RICHTER and R. VRBA, Biochem. J. *84*, 105 (1962).
[6] K. A. C. ELLIOT and B. LIBET, J. biol. Chem. *146*, 227 (1942).

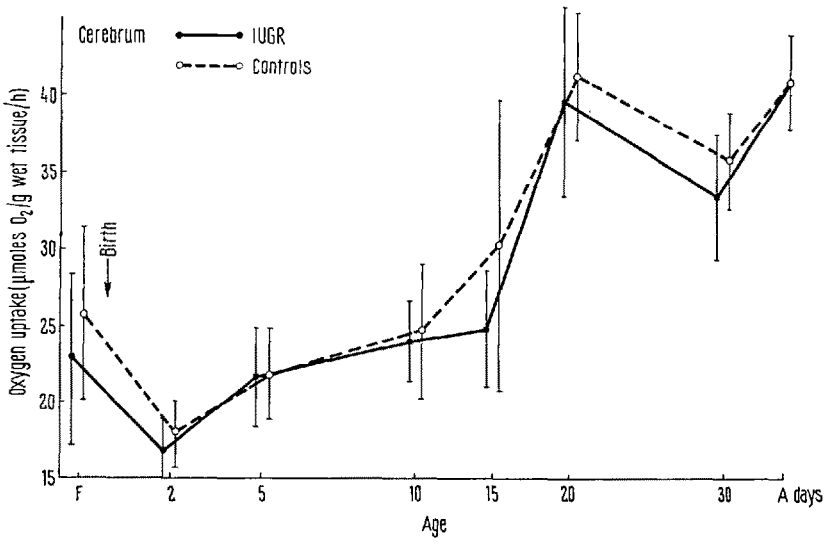
oxyribonucleic acid by the colorimetric technique described by BURTON[7].

Results and discussion. In Table I, the average cortex weight as well as the total solid, the protein and DNA content are shown. The differences in fresh or dry weights of the cerebrum between IUGR and control were never significant. The DNA concentration and its rate of decrease were the same in the stunted and control rats. Likewise, the pattern of protein content was no different.

The Figure shows oxygen uptake of cerebral cortex expressed in relation to wet weight from birth to weaning. The results related to DNA or protein content do not indicate other information. We found it more suitable for the nature of our experiments to express oxygen consumption per g tissue, as shown by MOUREK et al.[8] in recent publication. As seen on the Figure, the patterns of respiration are the same in both groups of animals during suckling.

The fetal brain of IUGR and control rats had a rather high oxygen uptake. As shown by some authors[9-11], the endogenous respiration of cerebral cortex is at its lowest level during the first week of post-natal life. A light fall in respiration occurs between the birth and the 5th day. At 10 days, the oxygen uptake is still low. At 15 days of age, the consumption increases in both groups; and at 20 days, it reaches the adult level. This rise in respiration coincides with the beginning of myelinization of the rat's brain. It is noteworthy that the respiration of cortex of the IUGR rats is not modified. Some of our preceding results (weight, DNA and protein content), and now the oxygen uptake, led us to belief that the growth retardation spares the developing brain. In human infants, the brain seems also to be preserved in the growth retardation syndrome[12].

[7] K. BURTON, Biochem. J. *62*, 315 (1956).
[8] J. MOUREK, H. C. AGRAWAL, J. M. DAVIS and V. PRUZKOVA, Physiologia bohemoslov. *17*, 104 (1968).
[9] D. B. TYLER and A. VAN HANEVELD, Am. J. Physiol. *136*, 600 (1942).
[10] J. MOUREK, Physiologia bohemoslov. *14*, 79 (1965).
[11] J. MOUREK and M. TROJANOVA, Physiologia bohemoslov. *18*, 79 (1969).
[12] A. MINKOWSKI, *Entretiens de Bichat, Médecine* (1967), p. 169 (Expansion Scientifique, Paris).



Oxygen uptake plotted in µmoles O_2/h/g wet weight against age in days. —●—, IUGR. —○—, control. Standard deviations are indicated by bars.

Table I

Age (days)	No. of rats		Cortex weight (g)	Total solids (% wet weight)	Protein (mg/g wet weight)	DNA (mg/g wet weight)
1 ante-partum	IUGR	13	0.102 ± 0.013	11.48	67 ± 17.5	6.81 ± 1.16
(foetus)	Control	12	0.121 ± 0.018	11.43	72 ± 10	6.74 ± 0.90
2	IUGR	11	0.148 ± 0.015	12.49	76 ± 7.0	4.58 ± 0.83
	Control	11	0.181 ± 0.020	12.49	71.6 ± 5.5	4.15 ± 0.18
5	IUGR	8	0.267 ± 0.033	11.76	57.6 ± 7.0	3.26 ± 0.15
	Control	7	0.325 ± 0.047	11.64	61 ± 5.4	3.21 ± 0.32
10	IUGR	11	0.581 ± 0.095	12.43	68.6 ± 15.7	2.05 ± 0.25
	Control	11	0.654 ± 0.131	12.70	67.4 ± 13.9	1.91 ± 0.27
15	IUGR	15	0.664 ± 0.102	15.60	88 ± 10.8	1.64 ± 0.11
	Control	13	0.750 ± 0.060	15.78	92 ± 7.4	1.61 ± 0.12
20	IUGR	7	0.778 ± 0.038	16.80	84 ± 11.9	1.69 ± 0.21
	Control	8	0.850 ± 0.091	17.30	92 ± 9.4	1.62 ± 0.23
30	IUGR	9	0.838 ± 0.080	21.10	88 ± 10	1.50 ± 0.17
	Control	9	0.882 ± 0.085	21.40	89 ± 10	1.53 ± 0.14

Table II

Age (days)		Cortex weight (g) / Body weight (g) × 100	Cortex weight (g) / Liver weight (g) × 100
1 ante-partum (fetus)	IUGR	3.0	55
	Control	2.2	33
2	IUGR	2.8	74
	Control	2.3	59
5	IUGR	3.1	88
	Control	2.4	69
10	IUGR	3.4	107
	Control	2.6	99
15	IUGR	2.7	84
	Control	2.1	72
20	IUGR	2.0	54
	Control	1.6	42
30	IUGR	1.5	25
	Control	0.9	19

Table II shows the brain/body weight and brain/liver weight ratios from fetal to adult age. It is noteworthy that these ratios are always higher in the stunted animals. We could therefore assume that the severe hypoglycemia found in the IUGR new-borns would be the consequence of the discrepancy between the needs of their developing brain (normal oxygen uptake) and the diminished potentialities of the liver metabolism.

Résumé. Les hémisphères cérébraux des rats normaux et des rats ayant subi un retard de croissance intra-uterin ont une consommation d'oxygène identique à tous les stades du développement. Ces résultats confirment que le cerveau est épargné par l'hypotrophie provoquée pendant la vie fœtale tant au point de vue pondéral que métabolique.

C. TORDET-CARIDROIT

Centre de Recherches Biologiques Néonatales, Hôpital Port Royal, F-75 Paris 14e (France), 9 March 1971.

Influence of Various Intracranial Pressure Levels on the Concentration of Certain Arylethylamines in Rabbit Brain

Impairment of the cerebrospinal fluid outlow from the ventricular system increases the ventricular fluid pressure (VFP) and results in hydrocephalus. The condition is accompanied by thinning of the brain mantle, atrophic changes in the brain tissue, and often distinct neurological symptoms. However, little is known about the extent of damage to the cerebral neuron systems and about such associated chemical disturbances as may be responsible for the neurological symptoms. Dopamine (DA), noradrenaline (NA) and 5-hydroxytryptamine (5-HT) in brain are located in neurons[1] and seem to have a transmitter function[2–4]. Information about changes in the brain concentration of these amines during different intracranial pressure conditions would offer a measure of the neuronal involvement as well as additional possibilities for an interpretation of functional disturbances seen in hydrocephalus.

Material and Methods. 22 rabbits of either sex (2–3 kg body weight) were used. They received standard pellet food (SAN-bolagen, Sweden), turnips, carrots and tap water ad lib. throughout the experiment. Intracranial hypertension was induced in 18 rabbits by intracisternal injection of 0.5 ml kaolin (30 g/100 ml concentration) as previously described[5]. The VFP was recorded in the conscious animals during $^1/_2$–1 h via a pressure cannula inserted into the left lateral ventricle of the brain[5] at different time intervals after the kaolin injection. Control recordings were obtained from 4 non-injected animals.

After recording was completed, the animals were killed by i.v. air and the brain was immediately removed. The concentrations of DA, NA and 5-HT were measured fluorometrically[6–8] in one tissue preparation comprising the telencephalon, mesencephalon and diencephalon (except cerebellum) and one (brain stem) consisting of pons and medulla oblongata. The different amines were determined on one and the same tissue sample, one animal being used for each determination (Figure).

Results. The mean VFP during the recording period was 5 mm physiological saline in the non-injected animals (Figure). 2 days after kaolin injection the VFP had increased to about 50 mm saline (Student's t-test: $p < 0.05$). At 7 days the VFP returned to a level that was not significantly different from that of the controls. The pressure was of about the same magnitude also 30 days after the injection.

As illustrated in the Figure, the concentration of DA in brain (brain stem not analyzed) was continuously reduced upon kaolin injection to a level about 30% below that of the controls ($p < 0.01$). The pattern of changes in the amount of NA and 5-HT in the brain and brain stem preparations resembled each other, but differed from that of DA in the brain. Thus, 2 days after kaolin treatment (i.e. when VFP was increased) the amine concentrations were 23–38% lower than in the untreated controls. The differences in the mean concentrations were significant except for 5-HT in the brain stem tissue (Figure). 5 days later (i.e. when the VFP had normalized) the amine concentrations had returned almost to the control values. The concentrations were similar also 30 days after the injection (Figure).

Discussion. The results have shown that kaolin-induced intracranial hypertension reduces the concentration of DA, NA, and 5-HT in the brain and the brain stem. It can be assumed that these changes selectively illustrate the influence of intracranial hypertension on the neuronal component in the brain. Several explanations to the changes can be offered. They can be the direct results of the mechanical pressure effect on the neurons, or they can be associated with changes such as in the oxidative meta-

[1] N. E. ANDÉN, A. DAHLSTRÖM, K. FUXE, K. LARSSON, L. OLSSON and U. UNGERSTEDT, Acta physiol. scand. *67*, 313 (1966).
[2] P. J. PORTIG and M. VOGT, J. Physiol., Lond. *204*, 687 (1969).
[3] U. BANERJEE, T. F. BURKS, W. FELDBERG and C. A. GOODRICH, Br. J. Pharmac. *38*, 688 (1970).
[4] J. R. COUCH, Brain Res. *19*, 137 (1970).
[5] CH. OWMAN and K. A. WEST, Brain Res. *18*, 469 (1970).
[6] Å. BERTLER, A. CARLSSON, E. ROSENGREN and B. WALDECK, K. fysogr. Sällsk. Lund Förh. *28*, 121 (1958).
[7] J. HÄGGENDAL, Acta physiol. scand. *59*, 242 (1963).
[8] Å. BERTLER, Acta physiol. scand. *51*, 75 (1961).