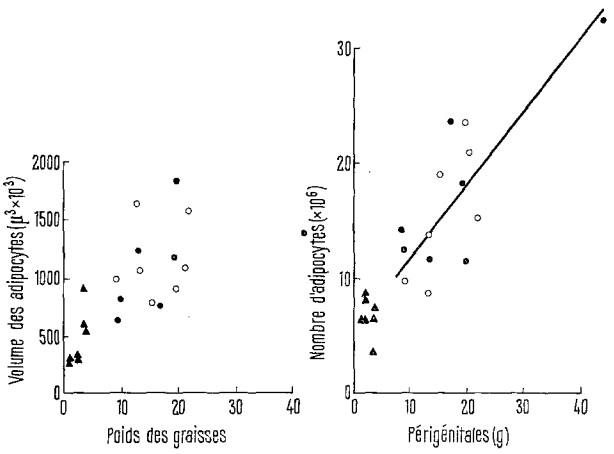
cellules chez les obèses, il n'y a donc de différence visible que dans la taille des cellules[4].

Les teneurs différentes en protéines, vitamines et sels minéraux des régimes riches en saindoux (+ 50% dans le régime S_3 par rapport au régime S_4) n'interviennent ni dans la taille ni dans le nombre des adipocytes; nous avons vérifié que les ingesta caloriques sont identiques avec ces deux régimes.

S'il n'y avait eu qu'hypertrophie, le poids du tissu adipeux des obèses aurait été de 2,84 g (poids du tissu des témoins) multiplié par 2,35 (facteur d'augmentation du volume, donc du poids, des adipocytes chez les obèses par rapport aux temoins) soit 6,67 g. Or le poids trouvé des graisses périgénitales des obèses est de 17,5 g soit une différence de 10,83 g, c'est donc que 60% environ du poids de ces dépots adipeux provient de la formation de nouveaux adipocytes eux-mêmes hypertrophiés. Chez le rat, rendu obèse par un régime hyperlipidique, l'hypertrophie rend compte à elle seule du triplement de poids des graisses epididymaires[3].

On sait, par ailleurs, que les rats et souris obèses, génétiquement ou par lésion hypothalamique, ne présentent pas d'augmentation du nombre des adipocytes mais seulement une hypertrophie[5,6]. Toutefois pour le cas des obésités expérimentales produites par un régime discontinu[7] ou par des injections d'insuline[8], il y aurait une hyperplasie. Chez l'homme[9,10], les résultats sont contradictoires[11].



Relations entre le volume, le nombre d'adipocytes et le poids du tissu périgénital des souris témoins (▲) et obèses qui ont été nourries avec les régimes hyperlipidiques S_3 (●) et S_4 (○).

Summary. Swiss mice became obese after administration of two 41% fat diets given, throughout life, ad libitum. The parametrial fat weights show a 6-fold increase in obese mice. The differences were accounted for in part by the adipose cell size enlargement and particularly by a 2,5-fold increase in their number.

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Oxidation of β-Hydroxybutyrate Infused Into the Cortical Subarachnoid Space[1]

Glucose is generally considered as the primary substrate for oxidative metabolism in the central nervous system. However, the oxidation of free fatty acids by the brain of cats and dogs has been demonstrated[2,3]. It has also been observed that the human brain removed both β-hydroxybutyrate (βOHB) and acetoacetate (AcAc) during prolonged starvation[4] and that βOHB was readily oxidized by the rat brain in vitro[5]. The physiological significance, however, of metabolites other than glucose in the energy supply of the brain remains uncertain.

The experiments described in this paper were undertaken to inquire if βOHB was oxidized when made available directly to brain tissue by infusion into the cortical subarachnoid space. This area was selected because it presents a relatively confined region of the subarachnoid space with a large underlying mass of nervous tissue.

Materials and methods. The experiments were performed on 4 male adult, mongrel dogs weighing 18–30 kg, after they had been fasted for 18 h. The animals were anesthetized with sodium pentobarbital (30 mg/kg) and received a continuous i.v. infusion of the same drug at the rate of 4 mg/kg/h. A tracheostomy was performed and artificial respiration was supplied by means of a Harvard respiration pump. A superficial branch of the femoral artery was cannulated for withdrawal of arterial blood samples. After exposing the parietal bone, a craniotomy was performed approximately 1 cm from the midline. A small polyethylene catheter was inserted through the dura and arachnoid, and passed laterally into the subarachnoid space toward the base of the temporal lobe. Through this catheter, colorless fluid could be obtained from the subarachnoid space throughout the experiment (referred to later as cortical sub-

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Table I. $^{14}CO_2$ counts (dpm/ml) during the infusion of Na DL-β-Hydroxybutyrate-3 ^{14}C into cortical subarachnoid space

	Dog No.	Time (min) 20	30	40	60	80	100	120
Cortical	1	–	3984	–	4988	6164	–	6140
Subarachnoid	2	1336	–	2064	1340	1812	2352	–
Fluid	3	–	1464	–	608	904	892	–
	4	3616	–	4428	3512	3696	5120	3924
Sagittal	1	–	392	–	526	699	683	920
Sinus	2	36	–	131	254	308	418	–
Blood	3	–	77	–	166	200	209	–
	4	100	–	181	242	287	348	–
Arterial	1	–	310	–	500	647	685	810
Blood	2	31	–	96	184	231	341	–
	3	–	56	–	119	158	178	–
	4	75	–	148	197	248	267	272

βOHB was infused throughout the experiments. Samples were removed at the times shown.

Table II. $^{14}CO_2$ specific activity during the infusion of Na DL-β-hydroxybutyrate-3 ^{14}C into cortical subarachnoid space

	Dog No.	Time (min) 20	30	40	60	80	100	120
Cortical	1	–	352.60	–	566.80	963.10	–	1096.40
Subarachnoid	2	82.47	–	132.31	85.90	119.21	168.00	–
Fluid	3	–	-	–	49.43	86.92	73.72	–
	4	354.51	–	442.80	481.10	506.30	731.43	622.86
Sagittal	1	–	23.76	–	33.08	47.55	47.76	59.35
Sinus	2	2.07	–	7.00	12.89	16.65	22.12	–
Blood	3	–	4.75	–	11.07	13.33	14.82	–
	4	6.13	–	11.31	16.03	18.64	21.48	–
Arterial	1	–	19.38	–	32.26	43.13	49.64	60.00
Blood	2	2.03	–	6.11	11.50	14.80	20.79	–
	3	–	3.86	–	8.81	11.13	13.38	–
	4	4.72	–	9.25	13.78	19.22	19.35	20.45

βOHB was infused throughout the experiments. Samples were removed at the times shown.

arachnoid fluid). A second catheter was inserted into the subarachnoid space for the infusion of βOHB. Cerebral venous blood was obtained through a polyethylene catheter introduced into the superior sagittal sinus and advanced toward the confluens sinuum.

An aqueous solution of βOHB was infused for 100 to 120 min at the rate of 0.194 ml/min using a Harvard constant infusion pump. The infusate provided 0.01 μc/kg/min of Na DL-3-hydroxybutyrate-3-^{14}C (Nuclear-Chicago) and 4.0 μmole/kg/min of Na DL-β-hydroxybutyrate (Calbiochem).

Each sample (2.5 ml) of cortical subarachnoid fluid was removed over a period of 4–5 min following the simultaneous arterial and sagittal sinus blood samples. CO_2 and $^{14}CO_2$ were analyzed as indicated previously[3], plasma glucose was determined by the Auto Analyzer, βOHB was estimated by enzymatic analysis[6].

Results. The concentration of $^{14}CO_2$ counts in arterial and sagittal sinus blood and in cortical subarachnoid fluid is shown in Table I. In each experiment the blood concentrations rose during the period of infusion. The counts in the cortical subarachnoid fluid were markedly higher than those in the sagittal sinus blood, and the latter counts were elevated over the arterial blood. Table II shows the specific activities of $^{14}CO_2$ in the same experiments. The trends are similar to those observed in the previous Table and indicate progressive increase in oxidation of the infused βOHB.

Table III shows the βOHB concentration in arterial and venous (sagittal sinus) blood and in the cortical subarachnoid fluid during βOHB infusion. A marked concentration gradient is apparent from the site of infusion to the venous blood and from there to the arterial blood.

The arterial and venous glucose values are shown in Table IV. No consistent change was observed in either the glucose levels or in the A–V difference of glucose during the experiments.

Discussion. Although glucose is the main source of energy for the central nervous system, other substrates may also be utilized under certain conditions. Thus, free fatty acids may be oxidized by brain tissue both in vitro[7,8] and in vivo[2,3]. The utilization of glycerol by the brain has also been reported[9]. More attention has been given in recent years to the utilization of ketones by the central nervous system. In addition to the oxida-

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Table III. βOHB concentration (μM/ml) following the infusion of βOHB into cortical subarachnoid space

	Dog No.	Time (min) 20	30	40	60	80	100	120
Cortical	1	–	114.8	–	107.6	–	123.8	–
Subarachnoid	2	68.4	–	102.5	73.8	62.7	77.3	–
Fluid	3	–	121.1	–	82.4	74.0	59.5	–
	4	83.8	–	104.2	88.4	82.0	95.6	88.8
Sagittal	1	–	0.078	–	0.200	–	0.446	0.420
Sinus	2	0.101	–	0.111	0.097	0.090	0.152	–
Blood	3	–	0.132	–	0.206	0.225	0.410	–
	4	0.856	–	0.850	0.710	0.500	0.514	–
Arterial	1	–	–[a]	–	0.140	–	0.027	0.137
Blood	2	0.027	–	0.057	0.046	0.078	0.050	–
	3	–	0.007	–	–[a]	0.017	0.032	–
	4	–[a]	–	–[a]	0.010	–[a]	–[a]	–[a]

βOHB was infused throughout the experiments. Samples were removed at the times shown. [a] Concentration too low to estimate.

Table IV. Glucose concentration (mg/100 ml) during the infusion of βOHB into subarachnoid space

	Dog No.	Time (min) 0	20	30	40	60	80	100	120
Arterial	1	116	–	122	–	129	126	128	127
Blood	2	130	132	–	136	132	126	124	–
	3	128	–	122	–	113	120	116	–
	4	111	116	–	121	–	128	126	–
Sagittal	1	106	–	116	–	115	118	118	118
Sinus	2	118	125	–	122	116	116	110	–
Blood	3	123	–	113	–	107	112	107	–
	4	107	110	–	117	–	122	114	–
A–V	1	10	–	6	–	14	8	10	9
Difference	2	12	7	–	14	16	10	14	–
	3	5	–	9	–	6	8	9	–
	4	4	6	–	4	–	6	12	–

βOHB was infused throughout the experiments. Samples were removed at the times shown.

tion of ketone bodies by the brain of experimental animals[5,10–13] it has also been shown that the human brain extracts ketones during prolonged starvation[4]. The demonstration of increased brain βOHB dehydrogenase activity during starvation[14] is of interest in this regard.

In the present study, the appearance of $^{14}CO_2$ in the cortical subarachnoid fluid and in the sagittal sinus blood during the subarachnoid infusion of labeled βOHB indicates a direct oxidation of this metabolite by the tissues of that region. The present data do not indicate the exact site of oxidation: in subsidiary experiments it was found that radioactive βOHB did not undergo significant oxidation to $^{14}CO_2$ when incubated with CSF. Because of the removal of $^{14}CO_2$ from the subarachnoid fluid by the venous blood and the unknown volume of distribution of the infused metabolites, it is not possible to estimate the fraction of βOHB that underwent oxidation. Nor is it possible to assess the physiological role of ketones in the cerebrospinal fluid in serving as oxidizable substrates for the brain under normal circumstances. It can be surmised, however, that under conditions accompanied by an elevation of cerebrospinal ketone levels, these metabolites may well serve as readily available oxidizable substrates for those portions of the brain that are in contact with CSF.

Résumé. Le βOHB, la concentration du $^{14}CO_2$ ainsi que l'activité specifique du $^{14}CO_2$ ont été determinées dans l'artère fémorale, le sinus sagittal supérieur et le liquid subarachnoïdal cortical. L'infusion du βOHB enregistré a amené la présence de $^{14}CO_2$ dans le liquide subarachnoïdal cortical. Les résultats indiquent que le βOHB du liquide cérébro spinal peut être oxydé par les tissus à proximité de l'espace subarachnoïdal cortical.

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