

Synthesis and regulation of lipoprotein lipase in the hippocampus

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Abstract Lipoprotein lipase (LPL) expression was determined in adult rat hippocampus and compared to enzyme expression in other brain regions. Hippocampus LPL mRNA levels were at least 2.5-fold higher than those detected in the cerebral cortex, cerebellum, and remaining brain regions. Enzyme mass and activity levels in the hippocampus were also increased to a similar degree. De novo synthesis of LPL in the hippocampus was confirmed by [³⁵S]methionine-labeling of the tissue and identification of a 57 kDa protein obtained by immunoprecipitation. Addition of an excess amount of bovine LPL completely prevented the immunoprecipitation of this protein. The effect of nutritional modulations on brain LPL activity was determined after a 12-h fast. While no significant changes were observed in other regions of the brain, hippocampus LPL activity in fasted rats increased by 60% compared to the fed control group. Simultaneously, fasting reduced adipose LPL activity by 60%. Intraperitoneal injection of ACTH over a 5-day period had no effect on hippocampus LPL activity, while adipose LPL levels increased 2.3-fold and heart LPL levels decreased 1.4-fold. **■** We conclude that LPL is synthesized, active and regulated in a tissue-specific manner in the adult rat hippocampus. — Ben-Zeev, O., M. H. Doolittle, N. Singh, C. H. Chang, and M. C. Schotz. *J. Lipid Res.* 1990. 31: 1307-1313.

Supplementary key words brain • cerebral cortex • cerebellum • fasting • ACTH

Lipoprotein lipase (LPL, EC 3.1.1.34) is a critical enzyme in the metabolism and transport of lipids. It is essential for triacylglycerol hydrolysis of chylomicrons and very low density lipoproteins, thus providing fatty acids for storage (in adipose tissue) or oxidation (in heart and other tissues) (1). In addition, studies in vitro have shown that the enzyme has phospholipase activity (2, 3) and capability to act as a transfer protein for cholesteryl esters (4) and vitamin E. In this latter context, LPL may be a principal mediator for transfer of dietary tocopherol to the tissues (5). LPL activity and mRNA are present in a variety of tissues and cell types, notably in heart, skeletal

muscle, adipose tissue, adrenal, and lactating mammary gland (6, 7). Smaller, yet detectable, amounts of LPL have been found in other tissues, such as testes, spleen, lung, small intestine, and brain (8).

The existence of brain LPL activity has been documented in brain microvessels of the rabbit (9) and rat (10), and in hypothalamus and pituitary gland of the monkey (11). The finding of enzyme activity in rat hypothalamic cell cultures indicated that these cells are capable of LPL synthesis (12). An ontogenic study of LPL from a variety of rat tissues revealed that in brain, as in muscle, neonatal LPL activity was about fourfold higher than in the respective adult tissues, with peak activities at day 4 postpartum (13). Recently, in situ hybridization studies in 5-day-old rats showed an intense signal, indicating the presence of LPL mRNA, in the pyramidal neurons of the hippocampus. A weaker but detectable signal was noted in the cerebral cortex (14). The significance of these findings in terms of LPL function in the neonatal brain remains unclear.

The present study attempts to determine whether the adult rat hippocampus also displays higher levels of LPL mRNA compared to other brain regions, and, if so, whether the predominance in enzyme message extends to the translated protein and its activity. In addition, since variations in nutritional and hormonal states are known to cause tissue-specific changes in LPL activity (1, 6, 15), it was of interest to determine whether brain LPL in general, and hippocampus LPL in particular, are also modulated by these factors.

Abbreviations: LPL, lipoprotein lipase; SDS, sodium dodecyl sulfate; BSA, bovine serum albumin; SSC, 0.45 M NaCl-0.045 M trisodium citrate; Staph A, crude insoluble Protein A from lyophilized *Staphylococcus aureus* cells (Cowan strain); PMSF, phenylmethylsulfonyl fluoride; PAGE, polyacrylamide gel electrophoresis; ELISA, enzyme-linked immunosorbent assay.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (Hilltop), weighing between 180 and 200 g were used. Unless otherwise stated, the animals were fed ad libitum. For the feeding-fasting experiment, the fasted group was deprived of food overnight (9 PM to 9 AM). The fed group was refed for 12 h (9 PM to 9 AM) with rat chow supplemented with 15% glucose in the drinking water after a 24-h fast. In the ACTH study, rats were injected with 5 units of repository corticotropin (Armour Pharmaceutical Co.) subcutaneously twice daily for 5 days. Control rats were injected with normal saline in a similar manner.

After decapitation and removal of the brain, the cerebral cortex, cerebellum, and hippocampus were isolated by blunt dissection; the remaining brain, containing the brain stem and associated regions, was also included in the analysis. In some cases, hearts and epididymal adipose tissue were also collected. Tissues were utilized immediately for [³⁵S]methionine labeling, or they were frozen rapidly in liquid nitrogen and stored at -80°C.

Northern blot analysis

Total RNA was isolated by the single-step method of Chomczynski and Sacchi (16). For Northern analysis, 10 µg of brain RNA and 1 µg of adipose RNA were electrophoresed in 1% formaldehyde-agarose gels, transferred to nylon, and crosslinked by exposure to ultraviolet light for 3 min. The blot was prehybridized (17) in 0.5 M sodium phosphate, pH 7.0, 1 mM EDTA, 7% SDS, and 1% BSA at 65°C for several hours. cDNA probes of mouse LPL clone mL5 (7) and rat α tubulin (generous gifts from T. Kirchgessner) were labeled with [³²P]dCTP by random oligonucleotide priming (18). Hybridization was carried out at 65°C overnight, followed by washing the blot to a final stringency of 1 × SSC, 0.1% SDS at 45°C. The blot was exposed to Kodak X-AR film with an intensifying screen for 1–11 days at -80°C. Autoradiographic signals for LPL and α tubulin were quantitated with the aid of an LKB 2202 Ultrascan Laser Densitometer.

Tissue labeling

Tissues were labeled with [³⁵S]methionine (200 µCi/ml) at 37°C for 20 min in a metabolic shaker (19). Incorporation of radioactivity was stopped by the addition of cycloheximide to a final concentration of 10 µg/ml. The labeled tissues were homogenized (100 mg/ml) in ice-cold lysis buffer (Tris 0.2 M, pH 7.5, 0.15 M NaCl, 3% Triton X-100, 0.1% N-lauroyl sarcosine, 0.3% SDS, 1 mM EDTA, and protease inhibitors: 0.2 mg/ml soybean trypsin inhibitor, 45 µg/ml aprotinin, 1 mM benzamide, 10 µg/ml leupeptin, and 1 mM phenylmethylsulfonyl fluoride).

Heparin-Sepharose chromatography

One ml adipose lysate or 2 ml hippocampus lysate was incubated with 0.5 ml heparin-Sepharose for 90 min on ice on a rotary shaker. After incubation, the slurry was loaded onto a 0.5 × 6 cm column. The gel was washed with 5 ml barbital buffer (5 mM sodium barbital, pH 7.2), followed by 5 ml of 0.5 M NaCl in the same buffer. The salt concentration was increased to 1.2 M NaCl and fractions of 0.6 ml were collected. Fractions containing the highest amount of radioactivity were pooled and used for immunoprecipitations.

Immunoprecipitations

A detailed description of the LPL immunoprecipitation procedure has been described (19). Briefly, 200 µl of the partially purified tissue lysates was adjusted to 3% Triton X-100, 0.1% N-lauroyl sarcosine, 0.3% SDS, and 1 mM PMSF in a final volume of 450 µl; 2.4 µg of affinity-purified chicken anti-bovine LPL was added and the incubation was carried out for 16–20 h at 4°C. SDS polyacrylamide electrophoresis and fluorography were performed as described (20) utilizing 9% polyacrylamide, 0.25% bisacrylamide in the separating gel.

Other methods

For LPL activity and mass determinations, tissues were homogenized (100 mg/ml) in extraction buffer (50 mM NH₄OH adjusted with HCl to pH 8.1 containing 0.125% Triton X-100) at 4°C and centrifuged for 20 min at 12,000 g. Supernates were removed and stored at -80°C until use. For activity/mg DNA determinations, the centrifugation step was omitted and crude homogenates were employed.

LPL activity was assayed with a serum-activated tri[9,10(n)-³H]oleoylglycerol substrate (21) and expressed as mU. One mU represents release of 1 nmol free fatty acids/min. Lysates were diluted at least 50-fold in the assay system to prevent inhibition of the activity by the presence of detergent. Protein was determined by the Coomassie blue assay (22) or by the Lowry et al. procedure (23). DNA concentrations in tissue extracts were measured by the fluorescent H33258 (Hoechst) dye-binding assay (24).

Statistical significance was determined by the two-tailed Student's *t* test.

RESULTS

Northern blot analysis

Northern blot analysis of adult rat brain RNA showed the presence of LPL mRNA in all four brain regions examined. A single mRNA species was detected, co-migrat-

ing with adipose tissue LPL mRNA at 3.6 kb (**Fig. 1**). The analysis also indicated that adult rat hippocampus contained higher levels of LPL message compared to the other brain regions. The same blot, hybridized with α tubulin cDNA as an internal control, was quantitated by densitometry; when normalized against α tubulin, LPL mRNA levels were at least 2.5-fold higher in the hippocampus compared to the other brain regions (**Table 1**).

LPL activity and mass

To ascertain that the elevated levels of LPL mRNA in the hippocampus resulted in an increased concentration of the enzyme in this area, activity and mass were determined in the various brain regions. In accord with the mRNA distribution, enzyme activity levels in the hippocampus exceeded those observed in the other brain regions, based on mg tissue protein (**Table 1**). Further, when DNA was measured as an indicator of cell number, the hippocampal predominance of LPL activity expressed per DNA was even more pronounced (**Fig. 2**). Since LPL activity is characterized by its unique sensitivity to NaCl inhibition, lysates from the various brain regions were assayed for lipase activity in the absence and presence of 1 M NaCl. The reagent inhibited the assay by $91\% \pm 4$ (hippocampus), $80\% \pm 4$ (cerebellum), $78\% \pm 3$ (cerebral cortex), and $91\% \pm 3$ (remaining brain) ($n = 6$, \pm SEM). This salt inhibition indicates that the lipase activity observed is LPL.

A similar result, indicating that the enzyme was concentrated in the hippocampus, was obtained when LPL mass in the various brain regions was determined (**Table 1**).

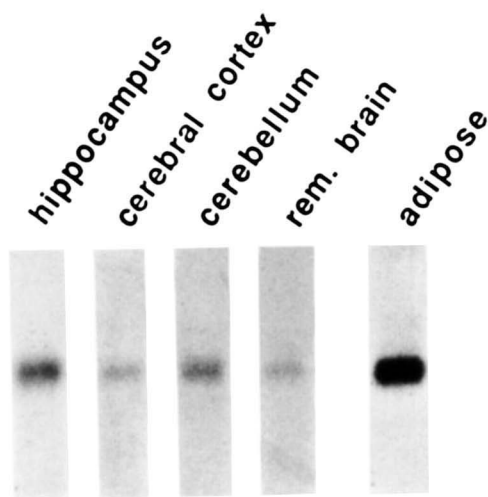


Fig. 1. Northern blot analysis of brain mRNA. Ten μ g RNA isolated from various rat brain regions and 1 μ g RNA from rat epididymal adipose tissue were electrophoresed in a 1% agarose gel, transferred to a nylon membrane, and hybridized with 32 P-labeled mouse LPL cDNA. The blot was exposed to film for 1 day (adipose) or 11 days (brain regions).

TABLE 1. LPL expression in various brain regions

	Lipoprotein Lipase		
	mRNA	Activity	Mass
	LPL/ α tubulin	mU/mg protein	ng/mg protein
Hippocampus	0.72	2.35 ± 0.14	4.48 ± 0.30
Cerebral cortex	0.13	0.86 ± 0.06	1.28 ± 0.06
Cerebellum	0.29	0.60 ± 0.04	1.84 ± 0.14
Remaining brain	0.20	0.99 ± 0.10	2.43 ± 0.27

Total RNA was isolated from pooled tissues of four animals. LPL and α tubulin mRNA levels were quantitated by scanning densitometry of a Northern blot hybridized with the respective probes (see legend to Fig. 1), and are expressed as LPL/ α tubulin (mean of two determinations). For activity and mass measurements, tissues were homogenized in 50 mM ammonia buffer, pH 8.1, containing 0.125% Triton X-100 and centrifuged for 20 min at 12,000 *g*. Both activity and mass results are the mean \pm SEM of six animals.

Immunoprecipitation of hippocampus LPL

To demonstrate enzyme synthesis de novo in the hippocampus and to confirm the identity of the lipase protein as LPL, hippocampus and adipose tissue were pulse-labeled with [35 S]methionine. The labeled lysates, after partial purification by heparin-Sepharose chromatography, were immunoprecipitated and subjected to SDS-PAGE. As described previously (19), adipose LPL appeared as a single band with molecular weight of 57 kDa (**Fig. 3**). Although the hippocampal immunoprecipitate contained several bands, the most intense band comigrated with adipose LPL at a molecular mass of 57 kDa. In addition, prior incubation of the antibody with excess unlabeled bovine LPL prevented the appearance of only this 57 kDa labeled band, while the other protein bands remained unaffected (**Fig. 3**).

Regulation of LPL activity in rat brain

As shown above, the adult rat brain contains active LPL, which is particularly concentrated in the hippocampus. However, does the enzyme in hippocampus respond similarly to effectors that are known to regulate LPL in peripheral tissues?

A fasting period of 12 h causes an increase in heart LPL activity and a decrease of the same magnitude in adipose tissue (19). We compared the response of LPL in the various brain regions to similar nutritional changes. Although there was no significant effect on cerebral cortex, cerebellum, and the remaining brain, hippocampus LPL activity increased by 60% ($P < 0.001$). This response of LPL activity to fasting was opposite in direction to that seen in adipose tissue, which showed a 60% decrease ($P < 0.02$) (**Fig. 4**).

Since LPL regulation during feeding and fasting is hormonally controlled (1, 6), the response of brain LPL to another hormone, ACTH, was also examined. ACTH

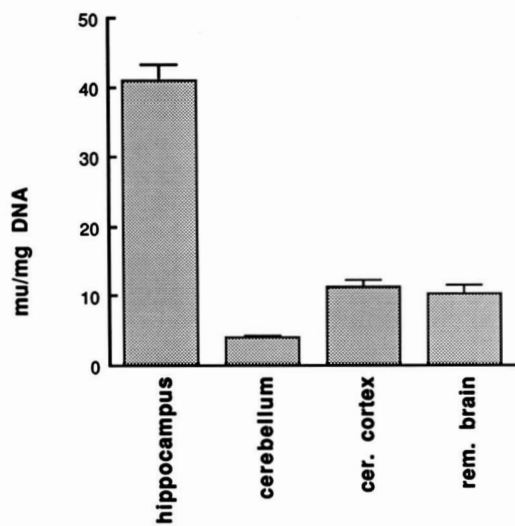


Fig. 2. LPL activity in various brain regions. Tissues were homogenized (100 mg/ml) in 50 mM ammonia buffer, pH 8.1 containing 0.125% Triton X-100. LPL activity and DNA concentration were determined as described in Materials and Methods. Results are the mean \pm SEM of six animals.

greatly enhances circulating glucocorticoid levels, which are known to affect LPL activity in heart and adipose tissue (25). Although administration of the hormone caused a 2.3-fold increase in adipose LPL activity and a 1.4-fold decrease in heart activity, no significant change in any of the brain regions, including the hippocampus, was

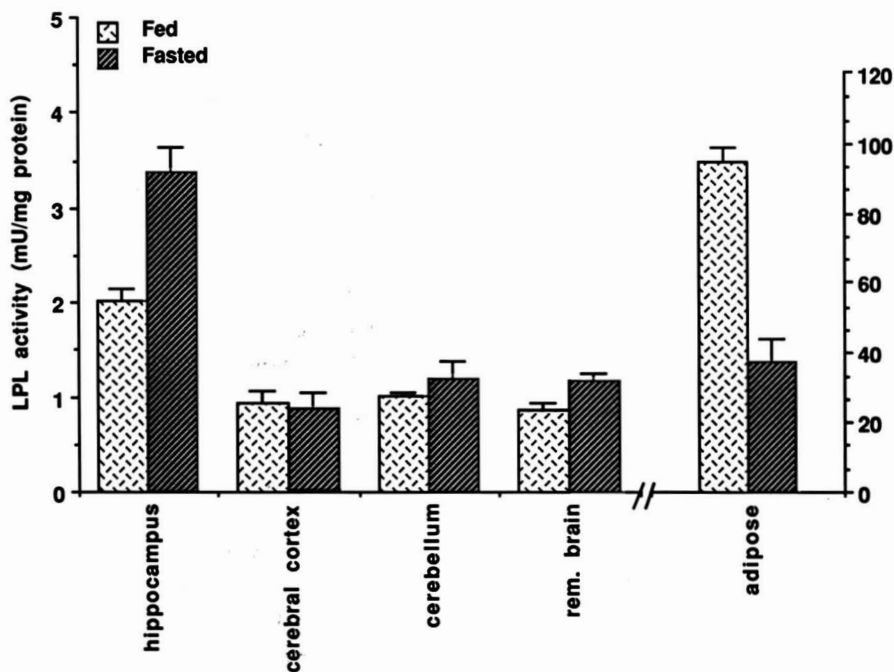


Fig. 4. Response of brain LPL and adipose tissue LPL to 12 h feeding and fasting. Tissues of animals fed or fasted for 12 h were homogenized in 50 mM ammonia buffer, pH 8.1, containing 0.125% Triton X-100, and centrifuged for 20 min at 12,000 *g*. Supernatants were diluted 50-fold and assayed for LPL activity. Results are the mean \pm SEM of six animals (hippocampus) or three animals (all other tissues).

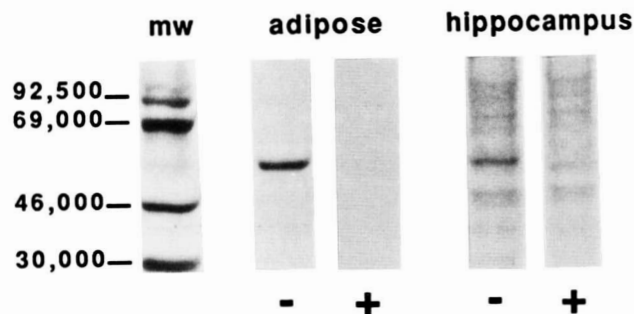


Fig. 3. LPL immunoprecipitation. Hippocampus and epididymal adipose tissue were labeled for 20 min with [35 S]methionine, homogenized in the presence of detergents and protease inhibitors, and LPL was partially purified by heparin-Sepharose chromatography. Immunoprecipitation (-) was carried out as described in Materials and Methods. For competition experiments (+), samples were preincubated for 4 h with 10 μ g bovine milk LPL prior to immunoprecipitation. All immunoprecipitated samples were electrophoresed on a 9% polyacrylamide gel. Note that preincubation of the hippocampus sample with excess unlabeled LPL exclusively prevents the appearance of the 57 kDa band.

observed (Fig. 5). These results suggest that LPL in the various brain regions is independently regulated.

DISCUSSION

Our study focuses for the first time on the localization of lipoprotein lipase message, mass, and activity in the adult rat hippocampus. The presence of LPL message

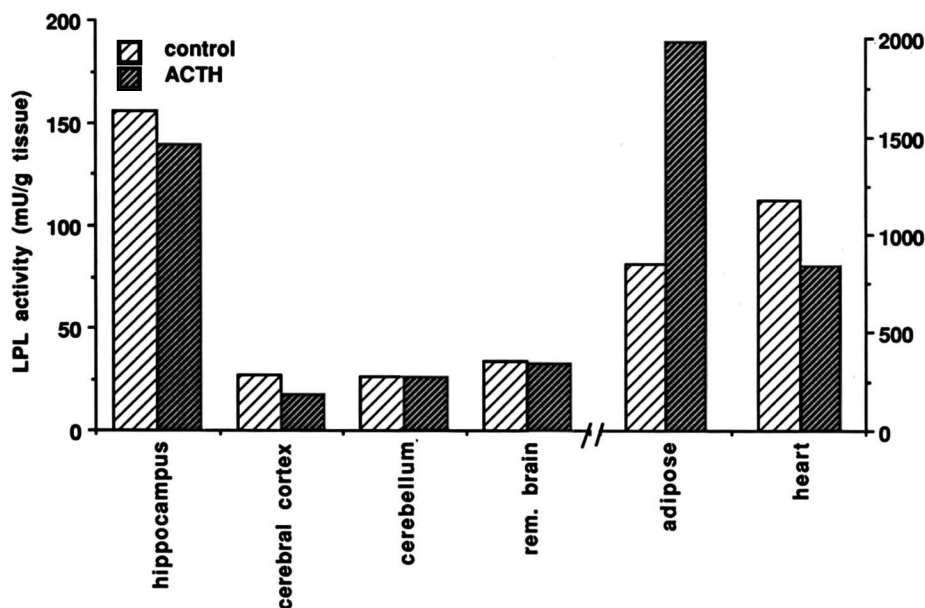


Fig. 5. Response of LPL activity to ACTH treatment. Rats were injected with 5 units of ACTH subcutaneously twice daily for 5 days. Brain tissues, heart, and adipose tissue were homogenized and assayed as described in the legend to Fig. 4. Results are the mean of two concentrations assayed in duplicate from pooled homogenates of five rats. Activity is expressed as mU/g wet weight.

was identified by Northern blot analysis, where a single 3.6 kb species, co-migrating with adipose tissue LPL mRNA, was observed (Fig. 1). This finding is in agreement with the concentration of LPL message seen in the hippocampus of the neonate rat, as detected by *in situ* hybridization (14). *De novo* synthesis of LPL in the adult hippocampus was demonstrated by the incorporation of [³⁵S]methionine into a 57 kDa immunoprecipitable protein. Identification of this protein as LPL was confirmed by its selective competition with purified bovine milk LPL (Fig. 3).

Although LPL was significantly higher in the hippocampus, all regions of the brain examined showed the presence of enzyme mRNA, mass and activity (Table 1, Fig. 2). The primary role of LPL in the brain might be similar to that played in extracranial tissues, i.e., supplying triglyceride fatty acids from circulating lipoproteins to the tissue. Although the brain does not effectively utilize fatty acids for β -oxidation (26), more than 50% of its dry weight consists of lipids (27). Since the central nervous system has a mechanism for lipid transport and homeostasis similar to that of other tissues (28), the enzyme, anchored to the luminal surface of the capillary endothelium, has the ability to hydrolyze circulating lipoproteins (10) and supply the brain with fatty acids. Indeed, Eckel and Robbins (12) have shown that LPL in hypothalamic cell cultures is responsible for incorporation of label for [¹⁴C]triolein into cellular triglycerides, phospholipids and sphingomyelin.

Adaptive changes in LPL occur in different tissues in response to variations in the nutritional and hormonal state of the animal. For example, dietary-induced variations in LPL activity result in the preferential uptake of circulating triglyceride fatty acids by adipose tissue for storage in the fed state, and by the heart and muscle for oxidation during periods of fasting (1). Within this context, we examined the effect of a 12-h fast on LPL activity in various brain regions. No dietary effect on LPL activity was seen in the cerebral cortex, cerebellum, or the remaining brain, whereas enzyme activity in the hippocampus increased significantly compared to the refeed group. The effect was in the opposite direction to that seen in adipose tissue after fasting, where a more pronounced change in activity was observed (Fig. 4).

Other investigators examined the effect of longer fasting periods on the fraction of LPL activity released from brain tissue by heparin. Thus, a 72-h fast showed no effect on heparin-releasable LPL from rat cerebral cortex, cerebellum, and midbrain, but a 44% decrease was observed in the hypothalamus (12). The authors suggest a role for hypothalamic LPL in the control of food intake and body-weight regulation. Prolonged fasting (96 h) showed a slight decrease in the heparin-releasable component of LPL activity in the whole brain (29). It would be difficult to compare these findings to our results, which show the effect of an overnight fast on tissue homogenate activity rather than on the heparin-releasable component. Besides, as mentioned, the LPL-enriched hippocampus

was isolated in our study from the remaining brain regions, allowing us to determine nutritionally induced changes specifically in this tissue.

In an attempt to determine whether brain LPL in general, and hippocampus LPL in particular, responds to hormonal-induced changes other than feeding and fasting, the effect of adrenocorticotropin (ACTH) was studied. The hormone is known to influence behavior and to exert direct neurochemical and physiological effects of the brain (30). Specifically, adrenal steroids bind to hippocampal neurons, and may contribute to hippocampal cell loss during aging (31). In addition, ACTH stimulation results in excessive production of glucocorticoids (32), which has been shown to increase both adipose and cardiac LPL activity (25). Injection of corticotropin twice daily for 5 days resulted in a 2.3-fold increase in adipose LPL activity, a 30% decrease in heart LPL activity, but had no discernible effect on LPL in hippocampus, nor on any other of the brain regions studied (Fig. 5). The lack of response of brain LPL activity to ACTH stimulation, compared to the significant change observed in adipose tissue, shows that LPL in the hippocampus specifically, and in brain in general, is independently regulated. As in the case of heart and adipose LPL activity, which have been shown to be under independent genetic control (33), hippocampal LPL expression probably conforms to separate, tissue-specific, regulatory mechanisms.

We have shown the concentration of enzymatically active lipoprotein lipase in the adult hippocampus and its unique response to physiological changes. The biological importance of LPL presence in this selected region is not clear. In addition to hydrolysis of circulating lipoproteins in the brain microvessels, it is possible that LPL performs specific functions in the neuronal-rich hippocampus. Thus, for instance, it has been shown that when vitamin E-enriched lipoproteins are added to neurons in vitro, the longevity of the cells is markedly increased (34). Since LPL appears to function as the mechanism by which vitamin E (tocopherol) is transferred to tissues, it is possible that the enzyme plays an essential role in providing a lipid-enriched and/or antioxidant-supplemented milieu for neuronal survival.

Underlining the possible importance of LPL in neuronal function, LPL deficiency has been linked to a number of neurological disorders. An example most pertinent to our discussion is the association observed between people affected by hyperchylomicronemia, which in most cases is caused by LPL deficiency, and neurological disorders directly linked to the hippocampus; it is reported that these patients suffer from memory loss, especially for recent events, and some of them experience inability to think clearly, with difficulty in problem solving (35, 36). All of these functions have been specifically associated with the hippocampus, as a region responsible for memory storage (particularly short-term memory),

learning, emotional responses, and spatial mapping of the environment (37).

These observations indicate the importance of further investigating the role of lipoprotein lipase in the nervous system, with particular emphasis on the hippocampus. ■

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