the constructed curve at each of the observed spawner abundances. Finally, we performed the likelihood ratio test for depensation described above and repeated the procedure 100 times to estimate the statistical power.

Statistical power was greater than 0.95 for 26 stocks for $\delta = 2$ (Fig. 3). In each of these, large declines in abundance have occurred, providing data at reduced spawner abundances. If depensatory recruitment is a general phenomenon in fish populations through this observed range of decrease, we would have expected more than 3 of the 128 stocks examined to show significant depensation in the observed data. These results are robust to gamma- instead of log-normally distributed residuals, reasonable estimation error of spawners, and serial correlation in recruitment (*10*). It is possible that more complex behavior might be masked by shortcomings in our approach.

Theoretical analyses and previous nonstatistical descriptions of depensatory recruitment for fish stocks (*11*) are not substantiated by our comparative analysis of the available data. None of the extant stocks of cod, plaice, hakes, or other commercially valuable species, many of which have been very heavily exploited, displayed depensatory dynamics in reproduction. The great majority of the populations show evidence of increased survival at lower population levels (*12*). This analysis indicates that models with strongly reduced per capita reproductive success at the spawner abundance typical of currently surviving fish stocks are not generally applicable to fish population dynamics. The fish population collapses so far observed cannot be attributed to depensatory dynamics. The implication is that reductions in fishing mortality rates implemented by resource managers should enable currently remaining stocks to rebuild, unless environmental or ecosystem-level changes occur that alter the underlying dynamics of the stock. We conclude that the effects of overfishing are, at this point, still generally reversible.

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10. We repeated the analyses assuming gamma- instead of log-normally distributed residuals; the results were almost identical. Robustness to estimation error in spawners and serial correlation in recruitment were investigated by introduction of these effects into the procedure used to estimate power. Log-normal errors in the estimation of spawners ($\sigma = 0.2$) and first-order autocorrelation of 0.4 in recruitment did not increase type 1 errors if δ was held at 1. As expected, the power was reduced if depensation was present ($\delta = 2$); for the 26 high-power stocks, with errors in the estimation of spawners, the power was reduced by approximately 3% on average, whereas with autocorrelation, the power was reduced by approximately 1% on average. In addition, we tested the adequacy of the chi-square approximation to the distribution of the likelihood ratio statistic by calculating the type 1 error rate when $\delta = 1$ (approximately 3% on average for the 26 high-power stocks).
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13. We thank the many fish population biologists who generously provided their data and the Canadian Department of Fisheries and Oceans Northern Cod Science Program for financial assistance.

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Impaired Energy Homeostasis in C/EBPα Knockout Mice

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Mice homozygous for the targeted deletion of the *c/ebpα* gene, which expresses the CCAAT/enhancer-binding protein α (C/EBPα), did not store hepatic glycogen and died from hypoglycemia within 8 hours after birth. In these mutant mice, the amounts of glycogen synthase messenger RNA were 50 to 70 percent of normal and the transcriptional induction of the genes for two gluconeogenic enzymes, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, was delayed. The hepatocytes and adipocytes of the mutant mice failed to accumulate lipid and the expression of the gene for uncoupling protein, the defining marker of brown adipose tissue, was reduced. This study demonstrates that C/EBPα is critical for the establishment and maintenance of energy homeostasis in neonates.

C/EBPα, a basic leucine zipper (bZIP) transcription factor (*1*) detectable in the brain, lung, and gut, is most abundant in liver and adipose tissue (*2*). C/EBPα transactivates the promoters of energy-related genes such as lipid-binding protein (422/aP2) (*3*), insulin-responsive glucose transporter (GLUT4) (*4*), and phosphoenolpyruvate carboxykinase (PEPCK) (*5*) and has been proposed to be a regulator of genes involved in energy metabolism (*6*). C/EBPα is expressed late in gestation (*2*) coincidentally with increased glycogen synthase (GS) activity and the accumulation of hepatic glycogen (*7*). Mobilization of this glycogen provides glucose to the neonate during the first hours after birth, before suckling. Because prenatal gluconeogenesis is negligible (*8*), the fetus depends on maternal blood glucose as the source for energy and glycogen storage. At birth, expression of the genes for the gluconeogenic enzymes PEPCK and glucose-6-phosphatase (G6Pase) must occur for the newborn to establish energy homeostasis (*8*). Here, we report the development of a mouse strain with a deletion of the *c/ebpα* gene. Analysis of the homozygous *c/ebpα*-deleted mice demonstrates that the C/EBPα protein is critical to the production and maintenance

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of life-sustaining metabolic fuel levels in the neonate.

We used a gene targeting vector containing positive-negative selection markers (9) to generate murine 129Sv embryonic stem (ES) cells deficient for one copy of *c/ebpα* (Fig. 1). The *c/ebpα* deletion allele is termed *c/ebpα*^{m1}. Targeted recombinant clones constituted 22.1% of the geneticin (G418)- and 1,2-deoxyfluoro-β-D-arabinofuranosyl (FIAU)–resistant colonies. Two clones were used to produce chimeric males that transmitted *c/ebpα*^{m1} through the germ line. The loss of function of *c/ebpα* is recessive and heterozygous mice have no obvious abnormalities. Heterozygous mice were intercrossed and 440 offspring were genotyped at birth; of these, 106 (24.1%) were wild type (+/+), 90 (20.5%) were homozygous *c/ebpα*^{m1} (−/−), and 244 (55.4%) were heterozygous (+/−). The fraction of wild-type mice was within Mendelian expectations; the reduced proportion of −/− mice was significant (Pearson χ^2 test, $P < 0.05$), although most of the homozygous mutants survived to term.

At birth, the −/− mice were indistinguishable from their littermates; the gross morphology of major organs was normal, as were birth weights. However, the −/− neonates became lethargic several hours after birth and died by 8 hours postpartum. Blood glucose concentrations measured within 5 min postpartum were normal, but at 1 to 2 hours postpartum, the glucose concentration (mean ± SD) in the −/− mice (0.8 ± 1.6 mg/dl, $n = 7$) was significantly lower than that in the +/+ and +/− mice (32.4 ± 20.2 mg/dl, $n = 22$) (Student t test, $P < 0.0001$). By 5 to 8 hours postpartum, the glucose concentration was 37.9 ± 16.5 mg/dl ($n = 37$) in the +/+ and +/− mice; the −/− mice remained hypoglycemic, with glucose concentrations of 0.6 ± 1.3 mg/dl ($n = 10$). In contrast to their siblings, all of the mutant neonates had little or no milk in their stomachs, presumably from lack of energy to compete for nourishment. Hypoglycemic mice were rescued transiently for up to 40 hours with subcutaneous injections of 50 μl of 10% glucose at birth and every 7 hours thereafter. However, survival did not extend beyond this point despite appropriate suckling behavior and the presence of normal volumes of milk in the stomachs. Additionally, the −/− mice gained little weight (*10*).

Liver sections of the control mice stained for glycogen at 1 hour postpartum (Fig. 2A) contained abundant glycogen, whereas those of the −/− mice (Fig. 2B) had virtually none. Similarly, at 32 hours postpartum, the glucose-injected controls had glycogen and the glucose-injected mutants did not. On the 18th day of gestation, when glycogen storage has begun but before glycogenolysis has become substantial, the livers of the control fetuses also exhibited glycogen (Fig. 2C), whereas those of the C/EBPα-deficient fetuses had reduced quantities of glycogen (Fig. 2D). Thus, the absence of C/EBPα interferes with both prenatal and postnatal hepatic glycogen synthesis.

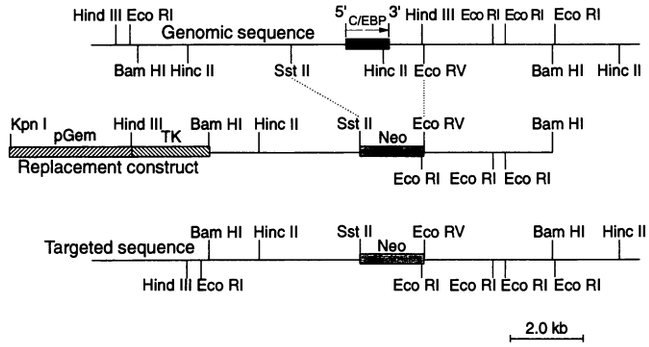

Fig. 1. Replacement of the *c/ebpα* gene by homologous recombination. A 14-kb sequence spanning *c/ebpα* was isolated from a murine 129Sv genomic library. A 10.5-kb Bam HI fragment was subcloned into pGemini. The *c/ebpα* gene and 2.4 kb of flanking sequences were excised with Sst II and Eco RV and replaced with PGK*neo*. MC1*tk* was placed at the 5′ end of the cloned sequence. Linearized plasmid (25 μg/ml) was electroporated into AB2.1 ES cells (1.8 × 10^6 cells per milliliter) (*27*). Recombination events were selected with the use of G418 (active ingredient, 0.18 mg/ml) and FIAU (0.2 μM). Of the first 113 colonies screened on Southern (DNA) blots, 25 yielded the expected homologous recombination event. Eight albino C57Bl blastocysts, all microinjected with 15 to 20 targeted ES cells, were implanted into each of seven female CBA/C57Bl surrogates. Sixteen chimeric males were obtained and tested by breeding with albino C57Bl females. Of the microinjected blastocysts, 12.5% produced founder males transmitting the Agouti phenotype at a frequency greater than 80%.

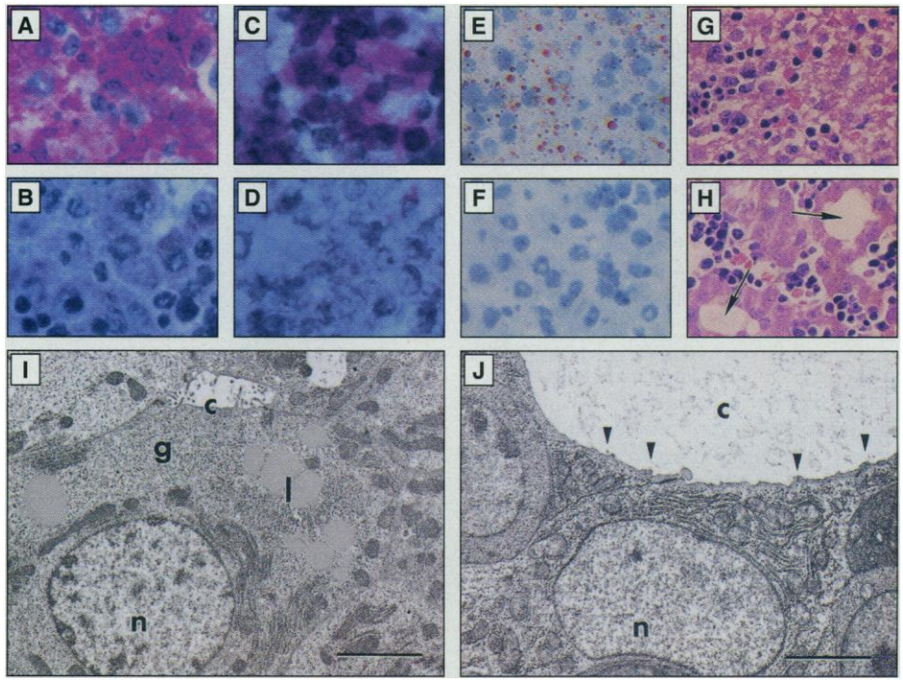

Fig. 2. Histology and TEM of the liver. (**A** through **D**) Periodic acid–Schiff (PAS) staining for glycogen (magenta) in livers from 1-hour-old control mice (A) and −/− mice (B) and livers from day 18.5 control fetuses (C) and −/− fetuses (D) (original magnification, ×400). (**E** and **F**) Oil red O staining for lipid droplets in livers from 32-hour-old control mice (E) and −/− mice (F) (original magnification, ×100). (**G** and **H**) Hematoxylin and eosin staining of livers from 5-hour-old control mice (G) and −/− mice (H) (original magnification, ×100). The hepatocytes of the −/− mice lack the clear, vacuolated cytoplasm of the control mice. Some enlarged intercellular spaces are indicated (arrows). (**I** and **J**) TEM of livers from 5-hour-old control mice (I) and −/− mice (J). TEM has confirmed the enlarged spaces to be dilated biliary canaliculi on the basis of several indications: The canaliculi are bordered by tight junctions and desmosomes; they possess protruding microvilli (arrowheads); and the absence of endothelial cells lining these regions precludes the possibility that they may be sinusoidal spaces. TEM also confirms the paucity of glycogen and lipid in the cells of mutant mice. Biliary canaliculi (c), glycogen granules (g), lipid droplets (l), and nuclei (n) are marked. Scale bar, 3.2 μm.

At 32 hours postpartum, all of the glucose-injected neonates had suckled and ingested milk. Hepatocytes from the +/+ and +/− mice contained the lipid droplets normally present in 1-day-old mice (Fig. 2E); livers from the −/− mice (Fig. 2F) failed to store the appropriate amounts of lipid. Histopathologic examination of control livers (Fig. 2G) versus −/− livers (Fig. 2H) revealed the formation of hepatocyte rosettes with reduced cellular volumes and dilated biliary canaliculi in the mutant mice. Transmission electron microscopy (TEM) showed the microvilli in the canaliculi of the −/− mice (Fig. 2J) to be shorter and fewer in number than those of the control mice (Fig. 2I). The reduced cytoplasmic volume of C/EBPα-deficient hepatocytes caused organelles such as mitochondria and the endoplasmic reticulum to appear more densely packed. Because bile thrombi and cholestasis were not found in these livers, increased intrahepatic pressure seems an improbable explanation for the dilated canaliculi. A more likely explanation of the liver dysmorphology is that the paucity of glycogen and fat stores results in smaller hepatocyte volumes, which create the correspondingly larger canalicular spaces (*11*).

To examine the possible molecular mechanisms responsible for the absence of hepatic glycogen in the −/− mice, we analyzed the expression of several genes on Northern (RNA) blots. Mean densitometer readings of total RNA collected from mice at 2, 7, and 32 hours postpartum are shown in Table 1. C/EBPα mRNA was absent in the −/− mice, and quantitation indicated that C/EBPα mRNA amounts in heterozygous neonates were approximately half of those in the wild-type neonates.

In accordance with the lack of glycogen in the livers of the C/EBPα-deficient mice, GS mRNA was reduced 50 to 70% in comparison with the control mice; this finding suggests that insufficient GS leads directly to low glycogen stores (*7*). Although the promoter elements of the GS gene have not been elucidated and altered transcription resulting indirectly from the loss of C/EBPα is possible, this study suggests that C/EBPα regulates the liver-specific expression of this gene.

At 2 hours postpartum, transcripts from the gene for cytosolic PEPCK were undetectable and the G6Pase gene was underexpressed by 70% in the livers of the mutant mice relative to the control mice. At 7 and 32 hours postpartum, PEPCK and G6Pase mRNA amounts matched those of the control mice, which suggests that C/EBPα regulates PEPCK and G6Pase transcription early in the perinatal period (*12*) and that additional factors control the subsequent gene activation observed by 7 hours postpartum. Other members of the C/EBP family of proteins such as C/EBPβ or the D-site binding protein (DBP), which also affect PEPCK gene transcription (*13*), may replace C/EBPα at the later time points to induce expression. Delayed transactivation of PEPCK and G6Pase likely contributes to the hypoglycemia in newborn −/− mice.

The mRNA for albumin, a serum protein involved in fatty acid transport, was reduced 50% in the mutant mice at 2 hours postpartum. However, unlike PEPCK and G6Pase, albumin mRNA amounts remained low at 7 and 32 hours postpartum, which suggests that C/EBPα is required for the transcriptional induction of the *albumin* gene. This observation agrees with work that showed activation of *albumin* by C/EBPα in cultured hepatocytes (*14*). The expression of *albumin* in the −/− mice may be a result of regula-

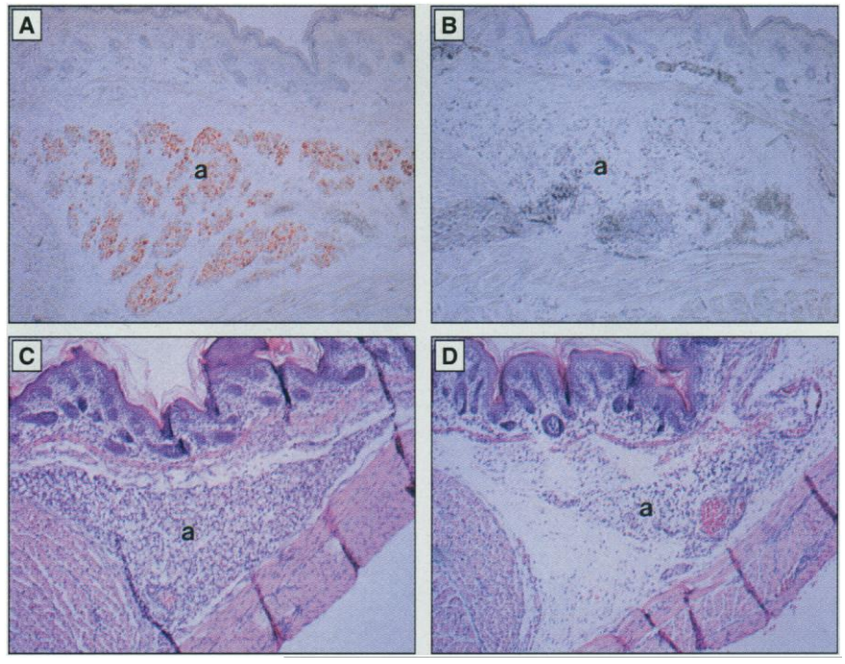

Fig. 3. Inguinal white adipose tissue. (**A** and **B**) Oil red O staining for lipid droplets in subcutaneous white adipose tissue from control mice (A) and −/− mice (B) at 15 min postpartum (original magnification, ×80). (**C** and **D**) Hematoxylin and eosin staining of white adipose tissue from 32-hour-old glucose-injected control mice (C) and −/− mice (D) (original magnification, ×80). White adipose tissue is marked (a). The lack of lipid accumulation in the mutant mice is evident.

Table 1. Densitometric values obtained from Northern blots. Liver tissues were collected at 2, 7, and 32 hours postpartum. Only the 32-hour-old mice had received glucose injections. Total RNA (25 μg) from wild-type (+/+), *c/ebpα*^{m1}/*c/ebpα*^{m1} (−/−), and heterozygous (+/−) neonates and from adult liver samples was examined for C/EBPα, GS, PEPCK, G6Pase, albumin, GLUT2, DBP, and C/EBPδ. Autoradiograms were quantified by densitometer and values were normalized to an internal β-actin control. Each data point represents the mean ± SD from three independent animals. ND, not determined.

RNA	2 Hours			7 Hours			32 Hours			Adult
	+/+	−/−	+/−	+/+	−/−	+/−	+/+	−/−	+/−	+/+
C/EBPα	2.4 ± 0.3	0	1.2 ± 0.2	1.5 ± 0.2	0	1.2 ± 0.5	1.6 ± 0.6	0	0.4 ± 0.1	3.5
GS	1.4 ± 0.3	0.6 ± 0.3	1.2 ± 0.4	1.1 ± 0.4	0.4 ± 0.2	1.1 ± 0.5	1.4 ± 0.5	0.2 ± 0.1	0.8 ± 0.2	0.5
PEPCK	0.7 ± 0.3	0	1.2 ± 1.1	2.4 ± 0.7	1.7 ± 0.6	3.1 ± 2.2	1.3 ± 0.1	1.1 ± 0.5	0.9 ± 0.2	9.1
G6Pase	0.7 ± 0.5	0.2 ± 0.1	0.8 ± 0.6	3.4 ± 1.0	3.1 ± 0.5	4.5 ± 2.0	0.7 ± 0.2	1.1 ± 0.5	0.6 ± 0.1	2.1
Albumin	2.6 ± 0.3	1.3 ± 0.4	4.3 ± 1.5	2.9 ± 0.1	1.9 ± 0.4	3.8 ± 0.6	3.6 ± 0.7	1.6 ± 0.1	2.9 ± 0.9	1.6
GLUT2	0.6 ± 0.2	0.5 ± 0.1	0.8 ± 0.2	0.5 ± 0.1	0.3 ± 0.1	0.7 ± 0.4	0.8 ± 0.3	0.3 ± 0.1	0.5 ± 0.1	1.4
DBP	1.7 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.8 ± 0.2	1.1 ± 0.2	2.5 ± 2.4	1.6 ± 1.1	1.9 ± 0.9	0.7 ± 0.1	1.3
C/EBPδ	0.2 ± 0.1	0.3 ± 0.1	0.5 ± 0.2	ND	ND	ND	ND	ND	ND	ND

tion by DBP, which has been shown to bind the *albumin* promoter (*15*). C/EBPα and DBP together may fully transactivate this gene. The amounts of mRNA for liver glucose transporter (GLUT2) and DBP were similar in the −/− and control mice at all time points. Neither C/EBPδ nor C/EBPβ mRNA amounts were elevated in compensation for the lack of C/EBPα.

The accumulation of lipids in both white and brown adipose tissue is dependent on C/EBPα. In subcutaneous inguinal white adipose tissue, the control mice (Fig. 3A) had lipid accumulation at 15 min postpartum, whereas lipid droplets could not be detected in the mutant mice (Fig. 3B). At 32 hours postpartum, lipid accumulation was more pronounced in the control mice (Fig. 3C) but was still absent in the −/− mice (Fig. 3D). This observation supports in vitro studies suggesting that maturation of white adipose tissue requires C/EBPα (*16*). The interscapular regions of the control mice (Fig. 4A) and the mutant mice (Fig. 4B) presented equal amounts of immature brown adipose tissue at 7 hours postpartum. By 32 hours postpartum, the volume of brown adipose tissue in the control mice had greatly enlarged (Fig. 4C), whereas the −/− mice showed no increase (Fig. 4D). Closer inspection of adipocytes revealed large lipid droplets, an indication of adipocyte maturation, in the control mice (Fig. 4E); the C/EBPα-deficient mice failed to accumulate these droplets (Fig. 4F).

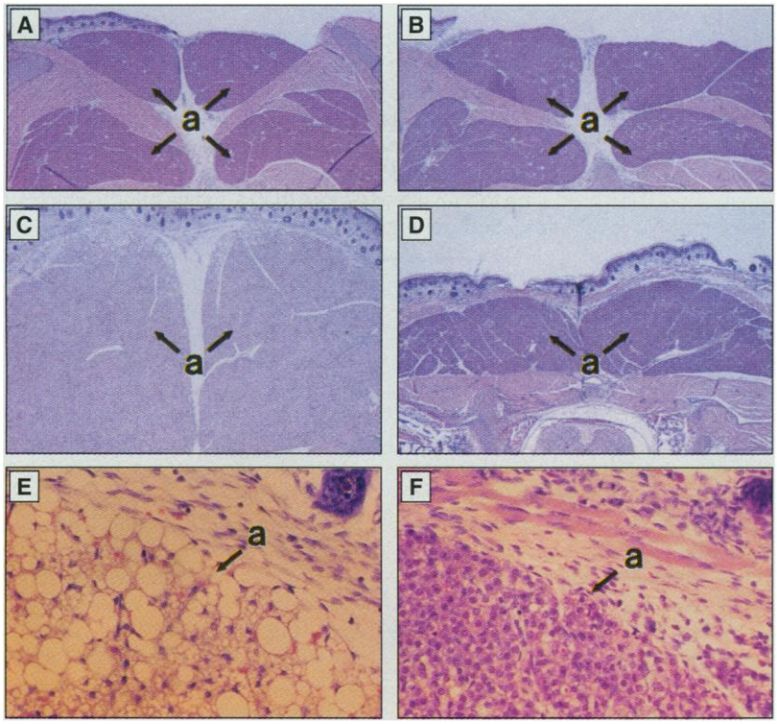

Fig. 4. Interscapular brown adipose tissue. (**A** and **B**) Hematoxylin and eosin staining of brown adipose tissue from 7-hour-old control mice (A) and −/− mice (B) (original magnification, ×20). (**C** and **D**) Brown adipose tissue from 32-hour-old glucose-injected control mice (C) and −/− mice (D) (original magnification, ×20). (**E** and **F**) Enlarged views of control (E) and C/EBPα-deficient (F) adipocytes at 32 hours postpartum (original magnification, ×200). Brown adipose tissue is marked (a).

Table 2. Densitometric values obtained from Northern blots. Brown adipose tissue was collected from the interscapular region of mice at 2 and 32 hours postpartum. The 32-hour-old mice had received glucose injections. Wild-type (+/+), *c/ebpα*^{m1}/*c/ebpα*^{m1} (−/−), and heterozygous (+/−) samples are indicated. Tissue from pairs of neonates of like genotype were combined to yield sufficient quantities of total RNA (25 μg per lane) for analysis of UCP, FAS, GLUT4, and 422/aP2. Densitometer values were normalized to β-actin. Each data point represents the mean ± SD from three independent pairs of animals. ND, not determined.

RNA	2 Hours			32 Hours		
	+/+	−/−	+/−	+/+	−/−	+/−
UCP	3.6 ± 1.0	0.1 ± 0.1	2.5 ± 1.1	2.8 ± 0.8	1.4 ± 1.0	2.1 ± 0.5
FAS	ND	ND	ND	2.0 ± 0.1	1.8 ± 0.4	1.0 ± 0.3
GLUT4	1.2 ± 0.2	1.0 ± 0.2	1.0 ± 0.1	0.4 ± 0.1	0.5 ± 0.2	0.4 ± 0.1
422/aP2	1.5 ± 0.1	1.3 ± 0.2	1.3 ± 0.2	1.2 ± 0.1	1.3 ± 0.1	1.0 ± 0.2

Northern analysis of brown adipose tissue collected 2 hours postpartum showed that the gene for uncoupling protein (UCP) was minimally expressed in mutant mice (Table 2). UCP is the defining functional marker of differentiated brown adipose tissue and is responsible for heat generation through uncoupled mitochondrial respiration (*17*); C/EBP family members have been shown to transactivate the promoter sequences of UCP (*18*). However, the small amount of UCP mRNA was transient; at 32 hours postpartum, the −/− mice had amounts of mRNA that were nearly 60% of normal. Thus the expression of UCP is delayed or reduced, or both, in the absence of C/EBPα.

Messenger RNAs for fatty acid synthase (FAS), GLUT4, and 422/aP2 were unaltered in the C/EBPα-deficient mice. FAS is a key enzyme in the pathway of fatty acid synthesis; GLUT4 and 422/aP2 are adipocyte markers that C/EBPα transactivates in 3T3-L1 cells (*3*, *4*). The loss of C/EBPα apparently does not affect the perinatal expression of these genes in brown adipose tissue. Because fatty acid synthesis is low from birth until weaning (*19*) and because lipid catabolism appears to be normal in the −/− mice (*20*), the absence of triacylglycerol accumulation in the mutants is likely the result of aberrant lipid processing or storage. Genes involved in lipid storage that are critical to survival are candidates for C/EBPα regulation.

Previous studies had correlated low expression of C/EBPα and hypoglycemia in mice with the radiation-induced deletion at the albino locus (*21*). Mice deficient in fumaryl acetoacetate hydrolase (FAH) mirror the phenotype of the albino mice and were found to have reduced liver glycogen (*22*). FAH mutant mice have elevated amounts of C/EBP-homologous protein (CHOP-10) (*22*), a dominant-negative inhibitor of C/EBP family members (*23*). Sequestration of C/EBPα by CHOP-10 may be the molecular basis for the hypoglycemic state in the albino and FAH-deficient mice.

At present, the absence of C/EBPα in humans has not been identified clinically and the complete array of phenotypic abnormalities in the −/− mice has not been associated with a specific human syndrome. However, a rare human disorder mimicked by C/EBPα-deficient mice is GS deficiency. This disease causes low glycogen storage and can cause severe bouts of hypoglycemia (*24*). A more common human condition that resembles the phenotype of the mutant mouse is that found in premature infants. C/EBPα is normally expressed late in gestation (*2*), corresponding to the last trimester of human

fetal life. In this study, mice without C/EBPα were retarded in their development; their lungs appeared immature on histologic analysis (25), they had an inadequate supply of body fat, they had insufficient liver glycogen, and they suffered from hypoglycemia. These are all symptoms consistent with those of the preterm infant (26). The incomplete developmental activation of *c/ebpα* and its target genes may affect the metabolic state of the premature neonate. We have shown in vivo that C/EBPα is required for the normal energy-related functions of the liver and of brown and white adipose tissue. C/EBPα-deficient mice will be useful for studying the complex metabolic requirements of preterm infants.

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10. At 32 hours postpartum with glucose, the weights of the +/+ and +/− mice increased from their birth weights by 32.4 ± 9.9% (mean ± SD; n = 53) whereas the weights of the −/− mice increased by 9.6 ± 9.8% (n = 10) (Student t test, $P < 0.0001$).
11. Alanine transaminase and alkaline phosphatase activities in serum collected at 32 hours postpartum indicated no overt hepatic injury in the C/EBPα-deficient mice. Histology confirmed that there was no hepatocellular necrosis in the −/− mice. However, measurements of serum amino acids indicated large amounts of tyrosine in mutants (435.0 ± 226.9 μmol/liter, n = 4) relative to controls (115.6 ± 35.2 μmol/liter, n = 7) (Student t test, $P < 0.05$), which suggested potential alterations in tyrosine metabolism.
12. Additional Northern blots (not shown) indicated some variation in the time of expression of PEPCK and G6Pase in the control mice, although the C/EBPα-deficient neonates were consistently delayed. Within 2 hours after birth, 3 of 10 control mice and 5 of 5 −/− mice had reduced amounts of mRNA for both enzymes.
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Impact of Food and Predation on the Snowshoe Hare Cycle

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Snowshoe hare populations in the boreal forests of North America go through 10-year cycles. Supplemental food and mammalian predator abundance were manipulated in a factorial design on 1-square-kilometer areas for 8 years in the Yukon. Two blocks of forest were fertilized to test for nutrient effects. Predator exclosure doubled and food addition tripled hare density during the cyclic peak and decline. Predator exclosure combined with food addition increased density 11-fold. Added nutrients increased plant growth but not hare density. Food and predation together had a more than additive effect, which suggests that a three-trophic-level interaction generates hare cycles.

The 10-year cycle of snowshoe hare populations and those of their predators is one of the dominant perturbations of the boreal forests of North America. Predation and food shortage have been postulated as the major factors causing these fluctuations (*1*). Because in all cyclic populations many factors will change in a manner correlated with population density, necessary conditions can be recognized only by experimental manipulations (*2*). From 1976 to 1984, we manipulated food supplies of snowshoe hares (*Lepus americanus*) in the southern Yukon and showed that the cyclic decline could not be prevented by either artificial or natural food addition (*3*). Single-factor manipulations have been criticized in field ecology because they may miss important interactions between factors (*4*). For the past 8 years, we have carried out large-scale experiments on nutrients, supplemental food, and predation in the Yukon to untangle the causes of the hare cycle and the consequences the hare cycle has for the vertebrate community. By crossing a predator reduction manipulation with food addition we estimated interaction effects caused by the failure of factors to combine additively.

We chose 1-km^2 blocks of undisturbed boreal forest near Kluane Lake, Yukon, as our experimental units (*5*). The boreal forest in this region is dominated by white spruce (*Picea glauca*) and was not disturbed by logging, fire, or extensive fur trapping during our studies. We used a factorial design to untangle the effects of food and predation on hares. Three areas were used as controls (*6*). Two experimental areas were provided with ad lib supplemental food year-round. We excluded mammalian predators by building one electric fence in the summer of 1987. In the summer of 1988, we built a second electric fence to use for the combined predator reduction–food addition treatment (*7*). Since January 1989, the electric fences have worked effectively to prevent mammalian predators from entering the two areas. The fences are permeable to snowshoe hares. Beginning in 1987, we added nitrogen-potassium-phosphorus (NPK) fertilizer to two blocks of forest to increase plant growth (*8*). We chose to manipulate a few large areas rather than many small areas because of the failure of most field experiments to address large-scale issues (*9*). We captured, marked, and released snowshoe hares every March and October and estimated densities with the robust design (*10*).

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