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16. In other experiments, *un*inhibited phosphodiesterase activity, measured by the method of C. R. Filburn and J. Karn [*J. Anal. Biochem.* **52**, 505 (1973)] was decreased about 10 percent by octopamine.
17. Although equipotent at $10^{-5}M$, at $10^{-3}M$ norepinephrine was somewhat more effective than tyramine, consistent with data on light production. Dopamine was slightly less active biochemically than reported in physiological studies (*11*).
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31. A supermaximal concentration of octopamine was used in the additivity experiments in order to avoid a partial antagonism of octopamine by norepinephrine, which can occur when [norepinephrine] >> [octopamine] (*9*).

32. I thank Edward Hunnicutt for technical assistance. This research was supported in part by a grant from the National Reye's Syndrome Foundation.

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Cholecystokinin in the Brains of Obese and Nonobese Mice

Abstract. *Extracts of the cerebral cortex of genetically obese* (ob/ob) *mice with hyperphagia contain 0.05 ± 0.02 microgram (mean ± standard error) of cholecystokinin octapeptide equivalent per gram of wet weight compared to 0.15 ± 0.01 microgram per gram for their nonobese littermates and 0.20 ± 0.01 microgram per gram for normal LAF_1 mice. These findings are suggestive of a causal relation between the diminished brain immunoreactive cholecystokinin content and the unrestrained appetite of the obese mice.*

Over the years work from a number of laboratories has suggested a role for cholecystokinin (CCK) as a satiety factor, perhaps through some type of negative signal from the gastrointestinal tract (*1*). A more direct role for CCK as a neuroregulator has been suggested by the observation that CCK peptides are not restricted to the gut but are found in the brain and appear to be localized in cortical neurons (*2*). Mice that are genetically obese (*ob/ob*) are known to have voracious appetites and seem likely candidates to manifest abnormalities in brain CCK. We now report a comparison of the concentrations of immunoreactive CCK in extracts of the cerebral cortex of *ob/ob* mice, their nonobese littermates, and normal mice of another genetic strain.

A heterozygote breeding pair of the C57BL/6J strain was obtained from Jackson Laboratory, Bar Harbor, Maine. The mice were bred for two successive generations in our laboratory, and the *ob/ob* mice and their nonobese littermates were killed when they were between 6 and 9 months of age. Normal LAF_1 mice had been bred in our laboratory for several years. The mice were killed with lethal doses of sodium pentobarbital. The entire brains were removed, hemisected in the sagittal plane, and immediately frozen on Dry Ice and stored at −70°C until extracted. While still frozen the right half of each brain was added to 0.1*N* HCl to produce a concentration of 0.1 g of tissue (wet weight) per milliliter. The extraction solution was boiled for 3 minutes. The tissue was then homogenized in the extraction solution with a Teflon tissue grinder. The immunoreactive CCK content of the extracts was determined by a radioimmunoassay system described previously (*2*) in which the cross-reactivities of CCK and its COOH-terminal octapeptide (CCK-8) are virtually identical on a molar basis.

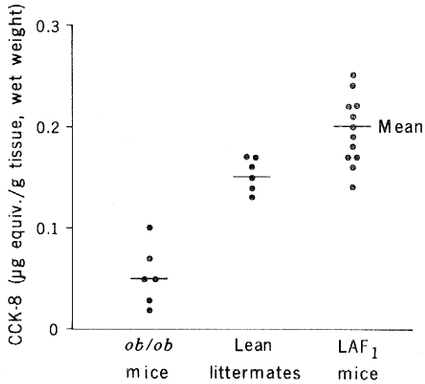

Fig. 1. Scattergram of the concentrations of immunoreactive CCK in extracts of the cerebral cortex of *ob/ob* mice, their nonobese littermates, and normal mice.

The mean body weights (± standard error) of the *ob/ob* mice, their lean littermates, and the LAF_1 mice were 69 ± 2, 30 ± 1, and 28 ± 4 g, respectively. The distribution of the concentrations of immunoreactive CCK in brain extracts of these three groups of animals is shown in Fig. 1. The mean concentrations (± standard error) were 0.05 ± 0.02, 0.15 ± 0.01, and 0.20 ± 0.01 μg of CCK-8, respectively, per gram of tissue (wet weight). There was no difference in brain weight among the three groups. Therefore, the immunoreactive CCK content of the brains of the *ob/ob* mice averaged only about one-third that of their nonobese littermates and one-fourth that of other normal mice.

More than a decade ago Schally and associates (*1*) demonstrated that intravenous and subcutaneous injection of "enterogastrone," a preparation now known to be rich in CCK, caused reduced food intake in mice, whereas glu-

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cagon, secretin, glucose, and bovine serum albumin, similarly administered, did not. Subsequently several groups have shown that intravenous or intraperitoneal administration of purified CCK or CCK-8, or both, can elicit satiety-like behavior in several animal species (*1*). However, the doses administered were so large that they resulted in circulating levels likely to be in excess of those occurring postprandially.

It has long been appreciated that damage to the ventromedial hypothalamus results in hyperphagia and obesity. Thus if CCK were to be involved in control of appetite by the ventromedial hypothalamus one would expect that it would be more effective from intracranial than from peripheral sources. The observations in rats of Stern *et al.* (*3*), that intraventricular caerulein (a sulfated decapeptide with seven amino acids in common with CCK-8) was more effective in limiting eating than was systemic caerulein, and of Maddison (*4*), that the operant response to food was modulated with intracranial doses tenfold smaller than intraperitoneal doses, are consistent with this expectation.

The current study unequivocally demonstrates that *ob/ob* mice who manifest hyperphagia have a strikingly lower cerebral cortical content of CCK than their lean littermates and other normal mice. It suggests, further, that the lower amount of CCK in the brain may be causally related to the unrestrained appetite of these mice. Whether the deficiency of CCK is restricted to the brain or occurs also in the gut of the *ob/ob* mice has yet to be determined.

EUGENE STRAUS
ROSALYN S. YALOW
Solomon A. Berson Research Laboratory, Veterans Administration Hospital, Bronx, New York 10468,
and *Mount Sinai School of Medicine, City University of New York, New York 10021*

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Target Range–Sensitive Neurons in the Auditory Cortex of the Mustache Bat

Abstract. *Echolocating bats determine distance to targets by the time delay between their emitted biosonar pulses and the returning echoes. By varying the delay between synthetic pulses and echoes in stimulus pairs at various repetition rates and durations, neurons have been found in the auditory cortex of the mustache bat* (Pteronotus parnellii rubiginosus) *which are sensitive to target range during the search, approach, and terminal phases of prey capture or landing. Two classes of range-sensitive neurons were found: (i) tracking neurons, whose best delay for response to an echo following the emitted pulse becomes shorter and narrower as the bat closes in on the target, and (ii) range-tuned neurons, whose best delay is constant, and which respond to the target only when it is within a certain narrow fixed range. Range-tuned neurons are specialized for processing echoes only during a particular period of the search, approach, or terminal phases of echolocation, and they provide support for a theory of ranging in bats that incorporates groups of neurons with a spectrum of preferred echo delays to detect target distance.*

Using echolocation, insectivorous bats are able to hunt flying insects in total darkness by producing a series of stereotyped biosonar signals and listening to echoes (*1*). In the cochlea of the bat's inner ear, echoes are converted into the activity of spiral ganglion cells (cochlear nerve fibers), whose discharge rates depend on signal amplitude and frequency and whose short recovery cycles enable them to follow acoustic events occurring at a rate of up to 3000 to 4000 per second in stimulus-locked (or phase-locked) fashion (*2*). All the information available for echolocation is contained, therefore, in the activity of these peripheral neurons. Higher auditory nuclei in the brain then process the echo information, sorting out for analysis such parameters as relative target velocity (*3*), size (*4*), and location (*5*).

For target ranging, bats analyze the delay between the emitted pulse and returning echo (*6*), so the responses of neurons to paired stimuli of differing delays (that is, recovery cycles) have been studied to explore neural mechanisms for processing information about target range. Spiral ganglion cells respond to both the emitted pulse and the echo even from a target at a very short range (*2*). In the lateral lemniscus and inferior colliculus, this stimulus-locked response is preserved not only by a group of tonic neurons, but also by a group of phasic neurons, which act essentially as reliable event markers for target ranging (*2, 7–10*). In contrast, many other inferior collicular neurons have significantly different recovery cycles (*2, 7, 8*) and have been categorized into six types: undelayed short and medium suppression, undelayed long inhibition, delayed inhibition, temporary recovery, and facilitation. Any of the first five types were also included in the sixth category when they showed facilitation (*11*). There is thus a broad spectrum of recovery cycles in the population as a whole. On the basis of these neurophysiological data, Suga and Schlegel (*7*) proposed a model for target ranging that consisted of three levels containing (i) tonic on-responding neurons with short recovery cycles, (ii) phasic on-responding neurons with a broad spectrum of recovery cycles, and (iii) neurons tuned to echoes with specific delays. Neurons somewhat comparable to those in the third group, but much more fascinating, have recently been found in the intercollicular nucleus (*12*) and the auditory cortex (*13*). In this report we present some of the extensive data from the mustache bat, *Pteronotus parnellii rubiginosus* (*14*), demonstrating neural mechanisms for encoding or processing range information.

The mustache bat produces biosonar signals (called pulses), each consisting of a long constant-frequency (CF) component followed by a short frequency-modulated (FM) component (Fig. 1A). Each component often contains four harmonics (H_{1-4}). Therefore, in total there are eight definable components in each pulse (CF_{1-4}; FM_{1-4}). When the bat is not compensating for a Doppler shift, the CF_1 of the first harmonic (H_1) is 30 to 31 kHz, and its FM_1 sweeps down from the CF frequency by 5 to 6 kHz. The second harmonic (H_2) is always predominant in the orientation sound (*3, 15–18*) and is used for an acoustic behavior called Doppler shift compensation (*18*). The duration and repetition rate of sound emission systematically vary in a target-oriented flight. When the mustache bat is hunting but has not detected a target (search phase), pulses are about 20 to 30 msec in duration and are repeated roughly five to ten times per second. When the bat detects a target and approaches it,

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