



The Brain Connection

In the quest to improve human performance, brain chemicals called neurotransmitters may represent the next frontier

BY AMBY BURFOOT

As the days ticked down to the 1988 Olympic Marathon Trials, Paul Gompers faced a tantalizing problem—one no other runner had ever encountered. A brilliant Harvard grad and Rhodes scholar, Gompers had spent the previous year studying biochemistry at Oxford University, where he had worked with a professor engaged in revolutionary research. The findings suggested that endurance performance could be improved by manipulating certain brain chemicals called neurotransmitters.

In fact, an experimental drink concocted in the biochem lab promised to increase mental concentration while decreasing fatigue. If Gompers drank it during the Marathon Trials, he might expect to improve by several percent. He was already a 2:11 marathoner. A 2 percent improvement would bring him down to 2:09, a time certain to qualify him for the U.S. Olympic Team.

In the end, Gompers decided against trying the drink. "I felt I had a 50-50 chance of making the team anyway," he recalls. "I didn't think I should risk anything by messing with those odds."

Gompers's estimate proved accurate. After running with the leaders for 19 miles and holding third until the 23-mile mark, he faded and finished fourth. He'll never know if the brain



Last opportunity? Paul Gompers (7) had a chance to take a "brain drink" before and during the 1988 U.S. Olympic Marathon Trials but decided against it. He finished fourth.

drink might have lifted him onto the Olympic Team.

By the next Marathon Trials in 1996, however, runners may be able to use such a beverage with confidence, the same way they drink replacement fluids today. Neurotransmitter research has exploded in recent years. New studies have yielded a few answers, launched ever-more-intriguing theories and caused a scramble among pharmaceutical and sports drink companies eager to catch the rising tide.

At least one world-famous marathoner, Alberto Salazar, believes he has already experienced the power of neurotransmitter manipulation. Yes, *that* Alberto Salazar. The one whose famed tenacity gained him three New York City wins and a Boston '82 victory, to name just the most famous of his many successes.

In 1983 and '84, his luck ran out. By his own admission, Salazar's physical problems since 1983 would fill a medical textbook. Suffice it to say that while training for the 1984 Olympic Marathon, he caught 12 colds in 12 months. Several of them deteriorated into bronchitis. "My immune system was totally shot," he recalls. "I caught everything. I felt like I should have been living in a bubble."

After Salazar's Olympic disappointment—he finished 15th—things got



worse. Even when he stopped running for periods of time, he never felt good. As recently as a couple of years ago, he remembers, he found it "agonizing" to jog an easy 5 miles at lunch with some Nike coworkers.

Then last summer, on a tip from a friend, Salazar began taking Prozac, an antidepressant drug that boosts levels of the neurotransmitter serotonin. At the time, he had been training for several months for the Hood to Coast

Look to the brain: Oxford University biochemist Eric Newsholme first proposed the central nervous system hypothesis of fatigue in 1987.

Relay. He felt quite pleased that he could manage three repeat miles in 5 minutes each.

Two days after beginning to take Prozac, Salazar ran six repeat miles in 4:42. He was stunned. "I thought my watch was broken," he says now. In the

days and weeks that followed, he continued to feel an energy he hadn't known for almost a decade.

By spring he was running 130 miles a week and decided to enter South Africa's famed 53.8-mile Comrades Marathon. In possibly the most amazing comeback in the history of marathoning, Salazar won Comrades, his first major race victory since the 1982 New York City Marathon (see page 76 for more on Salazar's Comrades win).

Salazar was elated over his performance but even happier that he has regained his health. "I didn't really care how fast I ran at Comrades," he said. "The only thing that's important to me is that Prozac has helped me lead a normal life again."

THE CENTRAL NERVOUS SYSTEM HYPOTHESIS

In 1987, Gompers's advisor at Oxford, Eric Newsholme, Ph.D., first proposed a theory that came to be known as the "central nervous system hypothesis" of fatigue. Basically, Newsholme proposed this: If you're interested in endurance, look beyond carbohydrate-loading. Look beyond maximum heart rate. Look beyond caffeine, sports drinks and anaerobic threshold.

If you want to understand and control fatigue, Newsholme suggested, look to the brain. Always look to the brain.

In his fatigue studies, Newsholme focused on serotonin, a neurotransmitter that appears to modulate drowsiness. Newsholme figured it wouldn't do a marathoner much good to feel sleepy at the 20-mile mark, so he decided to test ways of limiting serotonin in the brain. Less serotonin, less drowsiness.

Earlier research had shown that prolonged exercise increases blood levels of tryptophan, an essential amino acid that the brain converts to serotonin. To limit serotonin, Newsholme would have to prevent tryptophan from reaching the brain. One way to do this: dump more branch chain amino acids (BCAAs) into the blood. The BCAAs compete with tryptophan for access to the brain. The more BCAAs in the blood, the less chance that tryptophan will reach the brain and be converted to serotonin.

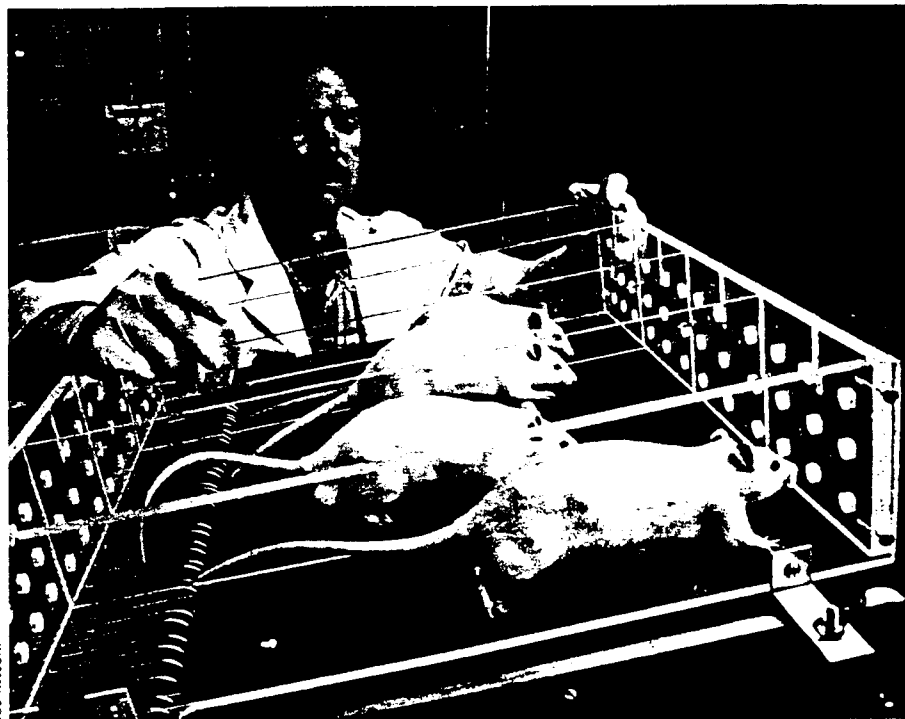
To test his theory, Newsholme devised a sports drink full of BCAAs and administered it to athletes in several experiments. One showed that soccer players who received the BCAA drink during a match scored higher on a test of mental functioning after the match than before. That is, they got sharper when they should have gotten wearier.

In a second test, Newsholme and colleague Eva Blomstrand conducted a BCAA experiment with 193 experienced runners in the Stockholm Marathon, timing the runners at both the 10-K mark and the finish. With this data, the researchers computed a ratio showing how much the runners slowed down during the marathon. They hypothesized that the runners who drank the BCAA mixture would slow down less than those who drank a placebo.

This didn't prove true for runners

who finished in under 3:05. However, among those runners finishing between 3:05 and 3:35, the BCAA group slowed 5 to 6 minutes less than the placebo group. "We think this happened because less-fit runners produce more free fatty acids, which liberate tryptophan," says Newsholme. "So these runners would have more to gain from the BCAAs' ability to limit tryptophan's access to the brain."

Newsholme continues to work with a Swedish company, Pripps, to develop a sports drink based on his research. He believes it could prove useful for anyone from marathoners to students taking tests, to businessmen



attending key meetings, to truck drivers and airline pilots—anyone who needs to fight fatigue and maintain mental alertness. "The drink would be an interesting development of a good theoretical idea that we followed up with good experimental results," he says. Pripps plans to market the drink in some European countries this fall.

When Mark Davis first heard about Newsholme's central nervous system hypothesis, he was conducting studies on the causes of fatigue during prolonged exercise, with a particular focus on possible brain influences. The Newsholme theory immediately captivated him.

Davis, now a professor of exercise science at the University of South Carolina, has conducted a series of studies on both rats and humans. In one endurance experiment on bicyclists who pedaled for up to 4 hours and 15 minutes, he showed that sports drinks

don't succeed by glucose replacement alone. They also seem to limit the increase of blood tryptophan during exercise, and hence to limit the increase of brain serotonin. "In addition to the expected findings that carbohydrate feedings can delay muscle fatigue," Davis says of this study, partially funded by Gatorade, "we found that they can decrease central nervous system fatigue."

This result helped convince Davis that serotonin plays an important role in endurance performance. It also raised a key question: Could he manipulate performance by manipulating brain serotonin? That is, could he decrease per-

The rat race: In experiments with treadmill-running rats, Mark Davis found that their endurance decreased as their brain serotonin increased, and vice versa.

formance by increasing serotonin and increase performance by decreasing serotonin? To show that he could would greatly strengthen the central nervous system hypothesis.

A human study proved impossible because Davis and colleague Stephen B. Bailey couldn't find a readily available drug that would decrease brain serotonin levels. They could, however, find drugs that would work with rats. And when they injected these drugs into rats before a treadmill-running test, the results perfectly mirrored the hypothesis: a drug that increased serotonin drastically decreased performance, and vice versa. "We don't want to jump on the bandwagon

too early," says Davis, "but this suggests that serotonin could be something really important."

CAN PROZAC HELP YOU RUN FASTER?

While Newsholme and Davis have been pursuing controlled scientific studies, Paul Raether, M.D., has been engaged in an experiment of one: himself. Raether, the man who first told Salazar about Prozac, ran a 2:16:13 marathon in 1981. Just 28 at the time, he dreamed of running faster.

The next year, however, Raether fell into a tailspin that he couldn't pull out of. At first he thought he had simply overtrained, but he didn't get better

By October, Raether was fit enough to win the masters division of the Harvard Health Downtown 5-K in 15:20. Later, he dipped under 15 minutes for 5-K, clocking a 14:58. A subsequent Achilles' tendon injury forced a layoff until late spring.

As a physician, Raether has spent months trying to analyze and understand his Prozac experience. The simplest theory makes the most sense to him. The lists of symptoms for clinical depression and for overtraining are nearly identical, including fatigue, inability to concentrate, lack of motivation, muscle soreness, sleep problems and appetite disturbance. Are the two therefore linked?

between the placebo and Paxil trials, but there was a significant difference in performance. After taking Paxil, the cyclists' endurance slipped by an average of 23 minutes. Concluded the researchers: "This result supports the suggestion that there is a central component to fatigue, which is mediated by the activity of serotonin."

Wilson and Maughan are now about halfway through a follow-up study in which they are giving subjects Paxil for four days before the laboratory cycling test. "We haven't collected all our data," says Maughan, "but so far it looks like the results are similar to the first experiment. We're reasonably confident that something's happening here."

In his South Carolina lab, Davis conducted a nearly identical bicycling endurance study (except that he gave his subjects Prozac instead of Paxil) with nearly identical results. Whether on a placebo or on Prozac, subjects showed no differences in blood glucose, blood lactate or stress hormones. But the Prozac caused endurance performance to decline, on average, by 11 minutes. "These data suggest that serotonin likely plays a role in central nervous system fatigue during prolonged exercise in men," says Davis.



When in Boston . . . study Boston Marathoners: MIT professor Richard Wurtman did, and found that their performances could be improved with a sports drink containing choline, a compound that regulates the neurotransmitter acetylcholine.

when he rested. Over the next 11 years, Raether kept running whenever he had the energy, visited and spoke with dozens of medical specialists, read everything he could about overtraining and still felt lousy.

Finally, last year, he decided to consult with a psychiatrist friend, who encouraged him to try Prozac. He did, starting in May. "Within a week, I felt great again," says Raether, who practices medicine in Portland, Oregon. "I was turning 40 in August, so I trained and raced myself into shape."

Raether speculates that perhaps a medication that improves one condition can improve the other. Just as Prozac often lifts the fog of depression, perhaps it can also lift the yoke of overtraining.

This intuitive reasoning, while appealing, has drawbacks. The biggest the only two human studies on Prozac and endurance performance have shown a negative effect. In the first, Wendy Wilson of England's Loughborough University and Scottish exercise physiologist Ron Maughan gave seven trained bicyclists either a placebo or a Prozac-like drug called Paxil. They next asked their subjects to cycle to exhaustion in the laboratory, where all their physiological variables could be measured.

The results showed no differences in heart rate, carbohydrates burned, oxygen consumption or blood lactate

LOOKING DOWN ANOTHER ROAD

Given that he's widely regarded as the world's leading expert in the field of serotonin studies, you might have expected MIT's Richard Wurtman, Ph.D., to end up conducting research similar to Newsholme's and Davis's. But he hasn't. Instead, Wurtman has been investigating the endurance effects of another neurotransmitter, acetylcholine, and he followed a particularly elegant path to get there.

In 1985 and 1986, Wurtman and colleagues collected blood samples, before and after the Boston Marathon, from a group of runners who raced the marathon. They then analyzed the samples for differences. The biggest change they found was in choline, a compound that regulates production of the neurotransmitter acetylcholine. The marathoners' choline levels had dropped about 40 percent over the course of the 26.2 miles.

"Since acetylcholine helps signal the muscles to contract," says Wurtman, "you didn't have to be a rocket scientist to think that this choline-acetylcholine connection could have a major effect on exercisers."

The next question: If the runners were given a choline-laced drink, would this improve their endurance performance? To find out, Wurtman asked