A New Science in Muscular Performance

RESEARCH SUMMARIES ON β-ALANINE/ HISTIDINE SUPPLEMENTATION AND THEIR ROLE IN HYDROGEN-BINDING, pH-CONTROLLING, AND CARNOSINE STORAGE IN SKELETAL MUSCLE

An Exclusive Interview with Mark Tallon, Ph.D

THE RESEARCH IN BRIEF

It is well known that increased muscle mass, strength, and extended muscular performance occur most effectively when exercise routines are performed to complete exhaustion. A reaction in our bodies known as "metabolic acidosis." That is, the point a muscle reaches extreme fatigue, so you can no longer perform an exercise or even push out another repetition. This biochemical reaction is brought about during the breakdown (hydrolysis) of ATP, the primary source of energy production in all cells, including muscle. In short, **acidosis is the generation of protons (H+, hydrogen ions),** which causes a fall in blood and, more crucially, muscle pH[20].

During intense exercise, however, the decrease in pH (increased acidity) is hugely accelerated and directly linked to muscle fatigue[8]. The increased acidity inhibits enzymes vital for energy production as well as the force-producing capacity of your muscles[4]. New research on β-alanine/histidine and its ability to synthesize carnosine in skeletal muscle has indicated blocking hydrogen ions and stabilizing the inevitable decline in pH levels can have a positive, marked effect on muscular contraction, power, and output. A concept that will be known as H^+Blocker: A New Science in Muscular Performance.

THE RESEARCH AT WORK

We all know how effective, as well as wildly popular, creatine has become. But has the *next* generation of performance supplementation finally arrived? New research from the UK, Russia, and Korea may be laying the path for a performance aid, called β-alanine/histidine (a carnosine synthesizer), which is expected to eclipse the success of creatine monohydrate.

Skeptical? We don't blame you, especially considering the mounting release of bogus supplements on the market. That's why we tracked down the world's leading carnosine researcher—nutritional biochemist Mark Tallon, Ph.D., to provide us with answers to our probing questions about the potential of β-alanine/histidine, its effects on carnosine, and its role in muscle metabolism. Questions like: **What is carnosine? How does it work? Why is it important to muscular performance? What does the science say? Is it safe? And, should I be using it?**

We knew Dr. Tallon wouldn't rest on marketing hyperbole but would instead use only the latest scientific evidence to substantiate his findings and theories about β-alanine/histidine and carnosine synthesis—and would reveal why he believes this is an exciting *new* science in muscular performance.

THE SEARCH FOR THE NEXT CREATINE...

Carnosine, a chemical structure composed of a combination of two amino acids—histidine and β-alanine—was discovered in 1900. Over the past 100 years or so, the research focus has developed around assigning carnosine a biological role, or biological function, you might say. The search has spanned the disciplines of human physiology, biochemistry, and even neurochemistry. But it wasn't until the early 1990's that the first of two human papers was released on the role of carnosine in muscle metabolism, indicating its true nature with respect to exercise performance. Dr. Tallon now believes that due to the recent onslaught of current research underway, this new performance aid, β-alanine/histidine, will eventually surpass the popularity of creatine.

iSatori Technologies: When did you first become interested in carnosine?

Dr. Mark Tallon: Back in 1999, after securing a doctorate under the guidance of Professor Roger Harris, is when I first started to review the research on carnosine metabolism. During this time, the issues of carnosine and muscle performance and other areas of a more pathological nature, such as age-induced muscle loss, were only in their infancy. Basically, it was just beginning to reveal that it could potentially play a functional role in skeletal muscle function. Previously, its primary role had pretty much been believed to be as an antioxidant; although there were two studies, namely those from Parkhouse, et al. (1995)[23], and Harris and Greenhaff (1998)[14] that had started to lay the foundations for my doctoral work in human physiology and nutrition surrounding carnosine.

IT: What is carnosine?

MT: In simple terms, carnosine is a *di*-peptide composed of the amino acids β-alanine and histidine[4].

IT: What role does carnosine play in muscle metabolism?

MT: Before we discuss carnosine any further, I believe it's important that we take a step back and talk about the muscle itself and what it undergoes during intense exercise. From this understanding, we can better comprehend the importance and role of carnosine.

It is well known that increased muscle mass, strength, and extended muscular performance occur in the most effective manner when exercise routines are done to complete exhaustion. However, it is during intense exercise that we commonly experience a reaction in our bodies known as "metabolic acidosis." This is the point at which our muscles reach extreme fatigue and can no longer perform an exercise or even push out another repetition. This is commonly referred to in the gym as "muscle failure."

If we were to take a peek inside the muscle fibers and plasma, during this period of intense exercise, what we would see is a specific chain of biochemical reactions. First, the breakdown (hydrolysis) of ATP would occur, which is the primary source of energy production in all cells, including muscle. Next, acidosis occurs. **In short, this reaction, which is brought on by the breakdown of ATP, instigates the generation of protons or hydrogen ions (H^+) in the muscle cells. Consequently, this rise in H^+ ions causes a fall in blood and, more detrimental, a decline in muscle pH levels**[20]. Thereby, raising the overall level of acidity in the muscle.

With prolonged muscular activity, the decrease in pH (increased acidity) is hugely accelerated, and thus, it is directly linked to muscle fatigue and ultimate failure[8]. In other words, the acidity inhibits enzymes vital for the maintenance of ATP, energy production, as well as the force-producing capacity of your muscles[13].

The good news is that after reviewing the past research, as well as carefully examining the data I am currently working on in my own lab regarding β-alanine/histidine supplementation and its ability to synthesize carnosine in skeletal muscle, I've found clear evidence that by binding hydrogen ions and blocking the inevitable decline in pH levels, one can expect to experience a positive, marked effect on their muscular performance.

IT: Okay, we get it. Now, could you expand on the idea behind blocking the increase in hydrogen ions and stabilizing pH levels in muscles?

MT: Sure. In muscle, the first line of defense is a series of compounds that can chemically associate themselves with the H+ ions which cause fatigue. These compounds are more commonly known as "**buffers**." Think of buffers essentially as compounds that attach to free H+ ions. And because it is the free concentration of these H+ ions in fluid (plasma or intracellular fluid in the muscle) that causes the decrease in pH, any way of removing or combining H+ ions with another compound will help maintain pH levels. **In essence, this buffering effect causes a slowdown in declining muscle pH**[22]**. The result is a substantially extended period of muscular effort, particularly during high-intensity exercise**[24]**.**

BY BINDING HYDROGEN IONS AND BLOCKING THE INEVITABLE DECLINE IN PH LEVELS, ONE CAN EXPECT TO EXPERIENCE A POSITIVE, MARKED EFFECT ON THEIR MUSCULAR PERFORMANCE.

As evidenced by clinical data, and what's most promising for us, is that in the case of skeletal muscle, the most effective buffer is the *di*-peptide carnosine (β-alanine/histidine)[3,4].

IT: Mark, does this explain then how we would achieve a maintenance, or "buffering" effect, of pH? And how exactly does this happen?

MT: The factor that primarily influences the buffering capacity of carnosine is something known as p*K*a. Don't hide just yet. What I am about to explain is not overly complex, yet it's very important to further appreciate the role of carnosine in muscle metabolism. This [p*K*a] value is linked to how much of a compound is bound to H+ ions at different pH levels. Our bodies' normal pH is around 7.0. Because of this, a buffer must have a p*K*a close to pH 7.0 to be beneficial. For instance, a nutrient with a p*K*a of 7.0 would have 50% of its total hydrogen ion binding capacity bound to protons.

This leaves the remaining 50% of the nutrient free to attach to other circulating H+ ions—such as the excessive amount produced during intense exercise.

Another way of looking at this is to imagine carnosine as a four-seated car with two people sitting in the front (hydrogen ions), leaving two seats empty in the back to pick up two more people (additional hydrogen ions). Therefore, the more carnosine in the muscle, the more H+ ions we can pick up. As a result, this helps prevent the associated decline in pH. It just so happens that carnosine has a p*K*a of 6.83. Strikingly close to the 7.0 pH found in our bodies, *isn't it*? It's for this reason, as I stated earlier, carnosine (β-alanine/histidine) is one of the, if not *the*, most effective buffers, or pH stabilizers, in human skeletal muscle.

IT: So, how could increased muscle stores of carnosine increase performance?

MT: How might carnosine affect performance...? I was beginning to wonder when you would get to this question. Well, we know from research, it's definitely the case that *carnosine is preferentially concentrated in the Type II muscle fibers*[14]. This is even more apparent in the Type IIx fibers[23,26], which provide us with the fast-twitch muscle characteristics needed to propel the Maurice Greene's of the world to sprinting excellence. Or, better stated to those who lift weights, Type II muscle fibers are what most of the top professional bodybuilders have more of, versus Type I fibers. This, in theory, might be why it could be easier for them to build more muscular bodies, faster and larger, than the rest of us.

We also know carnosine is high in the muscles of those exposed to prolonged and low muscle pH (such as diving mammals). This decrease in pH is not due to lactate per se, as you may have been told in the past, but rather the production of hydrogen ions (H+) as part of the process of energy generation. Like these mammals, our own systems can be placed under conditions of prolonged and low pH when we work at higher intensities. During the period of high-intensity exercise, we need a huge increase in our rate of energy production, and this can cause some problems, biochemically speaking. For instance, in events such as an 800-meter run or intense weight training, energy turnover is high, and as such, hydrogen ion formation is multiplied accordingly. As hydrogen ions are released, muscle pH begins to fall, leading to muscle force loss and ultimately fatigue[8,20]—unless we can prevent the inevitable decrease in pH, that is!

Thus, creating a physiological environment to increase our ability to work harder for longer is our goal. The extent to which carnosine can delay acidosis (pH decline) is relative to its concentration in our muscles, and this is where supplementation may play an important role.

IT: As a follow-up from that last question then, would carnosine be beneficial to any specific athletic event or training?

MT: Without question, it is most beneficial to those who participate in sprinting type activities or other highly intense exercises, such as resistance weight training. In a study recently published from my lab on bodybuilders in the *Journal of Strength and Conditioning Research,* we measured the greatest muscle carnosine contents to date, a level so high it may account for more than half of skeletal muscles' total buffering capacity[27]. (See Figure 4.) The values measured were in the range of 40 to 50 mmol/kg-1 dw, which is a value nearly three times that found in untrained subjects[27]. This indicates exercise, which requires high levels of ATP production, elevated carnosine levels in the muscles, which is highly beneficial to performance.

In another landmark study, by Parkhouse, et al., muscle samples were analyzed from a series of athletes, and carnosine was found to be higher in the power-/sprint-based athletes rather than the longer distance endurance athletes. Research carried out in 2002 by Suzuki and colleagues in Japan demonstrated that carnosine concentrations in Type IIx (fast-twitch) muscle fibers was directly related to mean power output during 30-second sprint cycling. Based on these studies and the fact that carnosine is approximately double the concentration in Type II muscle fibers compared to Type I's (slow-twitch endurance fibers), **carnosine is definitely a compound ideally suited to bodybuilders, sprinters, or any athletes involved in high-intensity resistance exercise.**

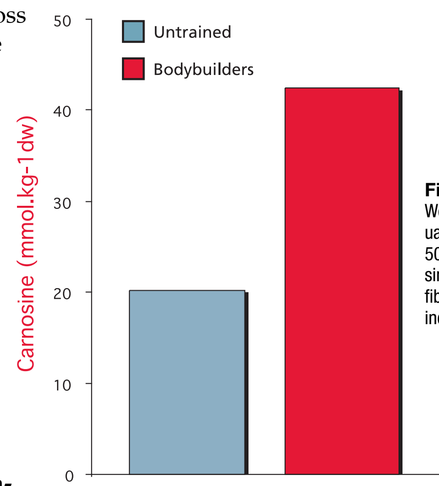


Figure 2.0
Well-trained individuals experience over 50% greater carnosine stores in muscle fibers than untrained individuals.

IT: So what variation have you measured or observed in human subjects or athletes?

MT: Well, as many of my studies are in review at present, I have to be careful how much I give away until they are published in their respective scientific journals and are made for distribution; however, what I can say is that we have biopsies from some extremely well-trained bodybuilders, over untrained individuals, and we have seen around a 50% increase in whole muscle carnosine[27], which could be much higher in Type II fibers due to the preferential distribution. This would have a huge impact on performance and resistance to high-intensity fatigue if we could achieve this through supplementation.

There was also a study by Suzuki last year presented at the 2004 ACSM, which I mentioned earlier, that showed significantly higher mean power during repeated sprints in subjects with higher muscle carnosine concentrations. Beyond this, I have taken it myself, and for any high-intensity type of workout, it appears to work fantastically.

IT: Have you taken any performance measures to date?

MT: To date, we have looked at different measures of contractility using involuntary electrical stimulation of the muscle and some performance tests.

For β-alanine supplementation, we have valid performance data just presented at the 2005 ACSM [American College of Sports Medicine] scientific conference in Nashville, Tennessee. It was presented that increased muscle carnosine contents with β-alanine supplementation increased the ability to perform maximal exercise at intensities experienced in the gym[18]. In this study, subjects were tested using a maximal bike test, and 110% of the final power output was calculated. Subjects were then tested at this 110% of exercise capacity, and time to fatigue was measured. These subjects were then given either β-alanine or a placebo and tested again, using the same test at four weeks and 10 weeks. (See figure 3.) If you look at the data, this study proves unequivocally that "β-alanine supplementation enhances muscle and exercise performance."

IT: You suggested earlier that with increased muscle stores of carnosine might come enhanced muscle function. How could this be achieved? And have you carried out dosing studies?

MT: What's interesting is that supplemental carnosine is already sold in a few health-food stores over here in Europa, but it's promoted as either an antioxidant or an "anti-aging" agent. Yes, we have shown that carnosine can be elevated within skeletal muscle and have carried out a series of studies on different dosing regimens of between three and 30 grams a day. The problem at the moment is the cost of carnosine. The production costs are by no means cheapest, or really even cost-effective for that matter, so we have begun to do most our work on the use of β-alanine and histidine. Aside from the histidine component, β-alanine's potential for synthesizing carnosine was first described in cell-culture studies back in 1994[4]. The work by the same authors that identified many of the vital functions of carnosine has shown β-*L*-aspartyl-L-histidine to be the natural biological precursor for carnosine, and as such, is metabolized in a similar way as carnosine[2].

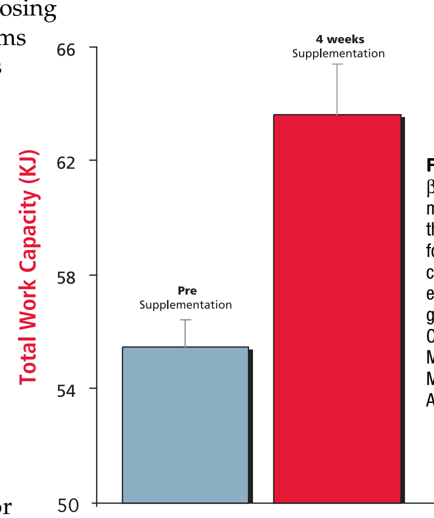


Figure 3.0
β-alanine supplementation increased the ability to perform maximal exercise at intensities experienced in the gym. American College of Sports Medicine Annual Meeting, Tennessee. Abstract 1833.

When considering dosage, we would have to start by looking at the research from Dr. Mark Dunnett, who, incidentally, studied under Professor Roger Harris for his doctorate in carnosine metabolism in equine physiology. Dr. Dunnett demonstrated that the use of 100 mg/kg-1 of bodyweight of β-alanine for 30 days in conjunction with histidine at 12.5 mg/kg enhanced muscle carnosine by 18% in Type IIb fibers[10]. The only downside was this dosing study was performed on horses and not on humans. But it did lend us more relevant insight into proper dosages. Then in 2003, research presented at the *American College of Sports Medicine* on β-alanine in humans **demonstrated that by consuming 800 mg four times a day for five weeks, a significant load or increase in muscle carnosine levels was achieved**[15].

IT: That explains quite a bit, but just to step back for a second, what's actually happening biochemically to achieve "carnosine loading"?

MT: To answer that, we have to briefly hit on a bit of carnosine science 101 …

When we eat a food containing carnosine, it gets broken down into its constituent amino acids; namely, histidine and β-alanine, by the enzyme carnosinase, which is highly active in blood. These amino acids are then taken up into the muscles, where they are reassembled or resynthesized to carnosine by carnosine synthetase. We know little of the transport system and are some years away from the knowledge we have on creatine transports, but we believe it may travel through muscle plasma using similar transporters as creatine.

IT: Could you give us a breakdown of the research that verifies these concepts of carnosine synthesis in humans and maybe focus a little on the supplementation trials you hinted at earlier?

MT: Sure, no problem. Let me give you a little history on carnosine feeding and then bring you up to speed on where we are with the human work.

Although dietary studies have been rare until recently, you can find some information within the literature. Many initial clues regarding the pathways of carnosine synthesis have emerged from restrictive diets and specifically the removal of one of carnosine's constituent amino acids. In a study looking at the removal of histidine from the diet for a period as short as 24 days and up to 12 weeks, we found it to significantly reduce muscle carnosine levels. Although this indicates that, in restrictive states, histidine is important, what about non-deficient states where meat and other carnosine/histidine foods are consumed?

Thus far, there have been four human supplementation studies which concentrated on enhancing muscle carnosine stores. Three of these are on β-alanine and only one on carnosine. These studies have ranged from a period of four to 10 weeks, and all show increased levels of muscle carnosine, whether supplemental carnosine or β-alanine was used. From these studies, we have learned that there is a definite influence of feeding histidine, and it seems this combination of β-alanine and histidine is the main nutrient for enhancing muscle carnosine stores. We have also found out that supplementation with carnosine or β-alanine enhances carnosine contents in both Type I and Type II fiber types to similar degrees. This may have implications for enhancing not only anaerobic exercise performance but also high-intensity aerobic exercise.

Again, what we still do not know is what the "optimal" supplementation dose is and for how long before we reach maximal muscle concentrations, like we know for creatine. Research indicates that right around 3.2 grams of β-alanine supplementation, daily, can likely impart the desired benefits[15]. However, this is only achieved after at least three to four weeks of continuous usage.

IT: Are you able to ingest carnosine from simply eating meat?

MT: Yeah, sure. But keep in mind, one gram of β-alanine delivers the same amount of L-carnosine as is potentially available from the ingestion of 80 grams of turkey. That means, in U.S. conversions of weight and mass, you would have to eat nearly one pound of turkey to achieve the required minimal supplemental dose of carnosine. *Would you want to do that three or four times a day?*

IT: Well, Dr. Tallon, your findings on carnosine and the use of the β-alanine/histidine compound is certainly exciting. What is your research looking into now?

MT: At present, we are broadening our understanding of the biochemical pathways for the synthesis of carnosine, as well as looking into some novel delivery systems that may further enhance previous levels of uptake. We are also investigating the specifics of training-induced changes in muscle carnosine.

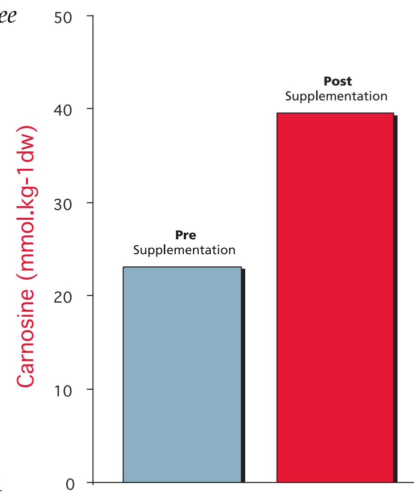


Figure 4.0
A 71% increase in muscle carnosine stores following five weeks of supplementation of β-alanine as contained in H+Blocker.

IT: To that point, are there any other nutrients, in your opinion, that might enhance the uptake or usefulness of β-alanine and histidine?

MT: Interesting that you should ask that question, because only recently have we begun to explore this topic. Understanding basic physiology, you would know that for a muscle to contract, calcium must be able to leave the muscle. One way of doing this is through a receptor. Think of a receptor as a transport system. The receptor I'm referring to is called a Ryanodine Receptor (RR)[21]. **During intense exercise, the release of calcium ions may be prevented, causing a decline in the ability of your muscles to contract and produce force**[21]. What's interesting is that carnosine has been shown to stimulate RR-mediated calcium release from the muscle[5]. So wouldn't it be great if we could enhance it? In theory, this would mean more force production in the muscle. And not surprisingly, evidence has shown carnosine is not only able to do this, but in a recent scientific paper, it was found that **these effects of carnosine can be further enhanced with the addition of caffeine**[11]. This study demonstrated that the combination of these two compounds significantly enhanced the ability of human muscle fibers to prolong the generation of force via increased efficiency in the release of calcium by the RR system. Technical, I know. But it provides clear evidence that caffeine works to enhance carnosine.

As an adjunct to caffeine, the addition of carbohydrates, in the form of simple sugars, seems to show promise as well for carbohydrate oxidation and improved delivery of nutrients. Carbohydrate oxidation is the amount of carbohydrate your body burns to produce energy. In a study by Yeo and colleagues (2005)[28], a mix of carbohydrates in conjunction with caffeine was compared with carbohydrates alone. The study assessed the increase in plasma glucose between the two supplement forms, and there was a 26% increase in carbohydrate use when used in combination with caffeine. This substantial increase in oxidation of carbohydrates could help maintain muscle and liver glycogen stores, enhance time to fatigue, and increase insulin levels at a much faster rate than carbohydrates given alone.

Thus, if one were to combine carbohydrates and caffeine, it would make sense that it would increase the uptake of β-alanine and histidine into muscle at an enhanced rate, allowing a faster rise in carnosine levels within skeletal muscle.

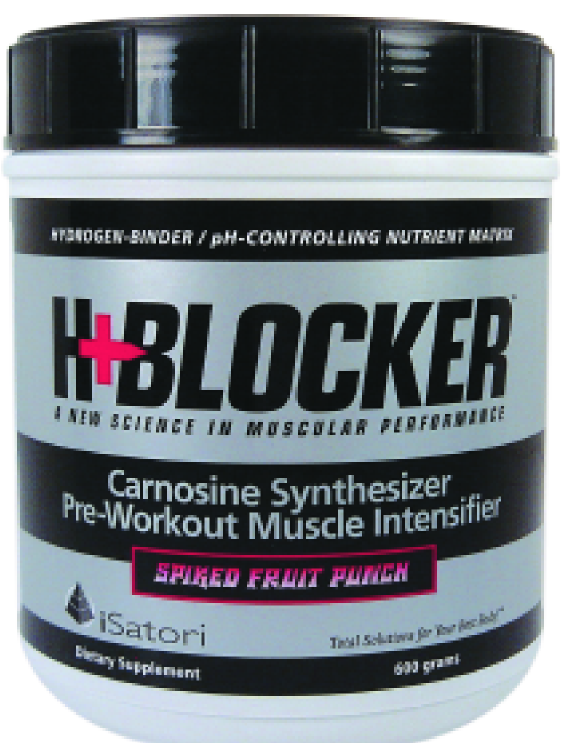
IT: Admittedly, this is truly exciting and quite a breakthrough. Where do you think your research will be going in the future?

MT: For our laboratory here in the UK, our interests are in human metabolism and the biochemistry of high-intensity muscle fatigue. So additional research on carnosine and its related metabolites will continue, as will its distribution in different athletic populations and, more specifically, the localization and distribution of carnosine in individual muscle fibers.

Of equal interest, we will be conducting a trial on a new supplement I have helped formulate, in collaboration with iSatori Technologies, which was based on my latest research with β-alanine and histidine. It's called H+Blocker. In the case of H+Blocker, its formulation is, in my humble opinion, the only one on the market today where every ingredient has been verified clinically effective in its suggested role and at the correct dosages shown by science to work. Based on the data we know so far, biochemical changes with the nutrients included in H+Blocker will be noticed after three to four weeks of continuous use and, even more promising, will keep increasing for at least up to 10 weeks[17] and probably for as long as you take it. Therefore, unlike many supplements, the benefits of H+Blocker will keep increasing as time goes on, allowing users to experience a significant increase in their ability to enhance maximal exercise performance at intensities normally experienced in the gym[17].

IT: I know this exciting new research about carnosine, and H+Blocker, will help a lot of athletes and fitness enthusiasts reach their goals. Thank you for sharing your knowledge and insights with us.

MT: It's been a pleasure, and I appreciate you allowing me to share my recent findings. I'm truly excited by the role β-alanine, histidine, and carnosine synthesis may be able to play in helping fitness enthusiasts, bodybuilders, and serious weight trainers increase their muscular performance.



••• BENEFITS OF H+BLOCKER WILL KEEP INCREASING AS TIME GOES ON, ALLOWING USERS TO EXPERIENCE A SIGNIFICANT INCREASE IN THEIR ABILITY TO ENHANCE MAXIMAL EXERCISE PERFORMANCE AT INTENSITIES NORMALLY EXPERIENCED IN THE GYM. •••

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