Caffeine exerts diverse actions in the body, including skeletal muscles, but a central stimulant effect may be the basis for its ergogenic effect (6). The study by Kalmar and Cafarelli (7) in this issue of the Journal of Applied Physiology investigates human neuromuscular fatigue and asks whether ingestion of caffeine alters voluntary activation, force, and the responses to femoral nerve and motor cortical stimulation. Here is some background.

Strong or sustained contractions can fatigue muscles and reduce their capacity to generate maximal voluntary force. This impairment may result not only from reduced force from the muscle but also from reduced output from the spinal motoneuron pool. This is known as “central fatigue” (for review see Refs. 2, 3). Demonstration of the suboptimal volitional output from the motoneuron pool is easily achieved using methods that interpolate an extra motor impulse via an external agency, such as a nerve stimulator. If a twitchlike increment in force is obtained with stimulation of the nerve innervating part of the contracting muscles, suboptimal motoneuron output is obvious. However, quantitation of the level of output to the muscle group is less easy. For example, whereas many motor nerves innervate the bulk of synergists in a particular task, they also innervate antagonists (e.g., stimulation of the common peroneal nerve contracts ankle dorsiflexors but also some plantar flexors, stimulation of the femoral nerve activates knee extensors but also two weak knee flexors), and hence the size of the superimposed twitch can be contaminated by unwanted force produced by antagonists, and voluntary activation is spuriously high.

Technical issues aside, the method is robust when a muscle is tested with single supramaximal stimuli (5). More recently, the term “supraspinal fatigue” has been defined (4, 10, for review see Ref. 3). It refers to that component of central fatigue that is due to failure to utilize available output from the motor cortex, and it can be demonstrated with transcranial motor cortical stimulation (TMS). Again, it is easy to produce a superimposed twitch during a maximal voluntary effort, but quantitation requires careful control of conditions, especially during fatigue (12).

As supraspinal fatigue develops with exercise, there are dramatic changes within the motor cortex (10, 11) and also in corticospinal “connectivity” with motoneurons (9). For example, the silent period in the electromyogram (EMG) after cortical stimulation lengthens (a reflection of intracortical inhibition) and the initial excitatory EMG response [motor evoked potential (MEP)] increases during fatiguing contractions, and there are depressions in MEPs and cervicomedullary evoked potentials (a test of corticomotoneuronal function) after exercise (1, 3, 9). A critical question in understanding central and supraspinal fatigue is: What are the causes of the loss of force and what are simply epiphenomena? Here, dissociation of force-related changes during fatigue and the excitability changes in the motor cortex has proven a crucial step. This is where the approach of Kalmar and Cafarelli (7) is helpful.

Kalmar and Cafarelli (7) have used caffeine ingestion to probe links between force and motor cortical output. They argue that, if a decrease in “central excitability” causes central fatigue with its associated failure in voluntary activation of the muscle, then caffeine, which increases central excitability (as represented by the size of the MEP), should reduce the fatiguing decline in voluntary force. Sets of repeated knee extensor contractions reduced force by ~35%, and performance was measured in two sessions: one with, and one without prior caffeine administration (6 mg/kg). TMS was delivered during weak contractions between exercise sets. Femoral nerve stimulation was applied during and after maximal voluntary contractions (MVCs) to assess changes in the M wave and in voluntary activation.

Before fatigue, caffeine increased voluntary activation in brief maximal efforts (by 2–3%) and increased the baseline MEP during very weak contractions (3% MVC). During fatiguing exercise, MEP size was elevated by caffeine compared with placebo, whereas maximal voluntary activation and force recovery were unaffected. That is, increased central excitability did not ameliorate the fatigue-related falls in voluntary activation and voluntary force. Furthermore, after caffeine, the MEP at the end of fatiguing exercise was not decreased compared with control values, so the impairment of voluntary activation seen at this moment is not due to impaired central excitability.

Previous observations, which dissociate central excitability and the development of supraspinal fatigue, have shown that voluntary activation can remain impaired after a fatiguing contraction, despite recovery of EMG responses to cortical stimulation (4). One possibility is that excitability of neurons in the pathway from the motor cortex to the muscle is normal, but drive to the motor cortical output neurons is suboptimal. The observations of Kalmar and Cafarelli (7) are more difficult to understand because they find the same maximal voluntary output from the motor pathway in two conditions, despite different outputs (the MEPs) in response to a fixed input (the cortical stimulus). This suggests that the measurement of central excitability represented by the MEP evoked in a very weak contraction might not be relevant to production of maximal voluntary force. Perhaps the caffeine-induced increase in motoneuron or motor cortical excitability observed at low forces does not hold with high forces. Indeed, there is evidence that such behavior can occur at the corticospinal connection at different levels of voluntary force (9). Alternatively, some of the cortical neurons that are stimulated by magnetic stimulation and that activate corticospinal neurons synaptically may not be involved in the generation of voluntary contractions. However, before fatigue, an increase in voluntary activation did occur when the MEP increased after ingestion of caffeine so that the dissociation of voluntary activation and central excitability may depend on fatigue. This might occur if the excitability of high-threshold motoneurons was differentially affected during the fatiguing protocol.

These observations highlight several aspects of current debate about the mechanisms of central fatigue. First, there are processes (some not covered here) that change the effective “excitability” of motor output pathways during voluntary activity. Not all of these changes act in the same direction, that is, to increase or decrease the central nervous system’s potential to generate muscle force. Second, many of them depend on the actual force being exerted and type of exercise being undertaken (e.g., intermittent or continuous): this contributes to
the task dependence of muscle fatigue (8). Hence, there is a dynamic relationship between the task commanded by the central nervous system, the descending and reflex drives to the motoneurons, and the outputs from them during fatiguing exercise. Drugs such as caffeine may allow some aspects of these relationships to be better understood.

REFERENCES


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