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Response to "Malignant Hyperthermia — human stress triggering" in reference to original article "Mechanistic models for muscle diseases and disorders originating in the sarcoplasmic reticulum" http://dx.doi.org/10.1016/j.bbamcr.2010.11.009

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We are grateful to Drs. Gronert, Tobin and Muldoon for pointing out the fact that MH-type reactions have been induced in humans by stress. We were aware of the work cited, but, in an effort to stress the point that there is duality to the cause of MH reactions (a point which is fully developed in other parts of the review), we stated "… triggering of an MH reaction, … requires the presence of both a causal mutation and either a triggering anesthetic, or, in the case of pigs, stressful conditions." Nevertheless, their commentary illuminates an area to which we had not given appropriate attention or clarity.

In our further comments, we will attempt to clarify the issue raised. Multiple ryanodine receptor isoforms are encoded by multiple genes, *RYR1*, *RYR2* and *RYR3*; and this is also the case for RyR1-interrelated and -interacting muscle Ca^{2+} regulatory proteins, including, dihydropyridine receptors, calsequestrin and Ca^{2+} pumps and exchangers. Structure/function differences among RyR1, RyR2 and RyR3 proteins within any species are much greater than the differences among RyR1s expressed in different species, such as humans and pigs, and this is also the case for the interacting Ca^{2+} regulatory proteins. The potential for expression of different mixes of a whole variety of Ca^{2+} regulatory proteins (Michael Berridge [1] has aptly described them as a "Ca^{2+} signaling toolkit") is what gives each muscle its special properties. Over time, evolution, separating humans and pigs as unique species, has altered the muscle milieu in which Ca^{2+} regulatory proteins function, inevitably altering the precise manner in which their signaling functions are regulated. Accordingly, it is always a great relief to scientists to find that knockout or knockin mouse lines, or lines over-expressing transgenes, display the characteristics of the human disease, since this is often not the case.

In comparing RyR1-related diseases in pigs and humans, there are apparent differences. For example the halothane challenge test failed to identify heterozygous MH pigs, making it impossible to eliminate the gene from breeding stock until the precise mutation was identified [2]. By contrast, the vast majority of heterozygous MH humans are identified by their own or a relative's reaction to anesthetics. On the other hand, the reason to rid swine stocks of the MH mutant (*HAL*/*RYR1*) allele has nothing to do with their halothane-sensitivity, but much to do with the fact that homozygous MH pigs are highly susceptible to stress and often die before they reach the market — hence the name for the disorder is not porcine MH but porcine stress syndrome (PSS).

The analog of the porcine MH mutation in the *HAL*/*RYR1* gene (R615C in pigs: R614C in humans) has been reported in about 82 unrelated human cases and/or families and has been found to be homozygous in 5 cases [3–5]. There is also a report of a C35R homozygote [6] and there are several reports of compound heterozygotes for causative *RYR1* mutations. Since presentation was unremarkable in any of these reports, it can be inferred that these patients were clinically normal. In one report [5], a homozygous R614C woman was the mother of two children, suggesting robust health. R163C is one of the most frequent MH mutations worldwide and it has been studied in generations of patients, but case 2 described by Drs. Gronert, Tobin and Muldoon is the only report of a possible stress-induced death linked to this mutation. Even the presence of the R163C mutation in their case study does not, in itself, prove association of sudden death with an MH reaction.

Since it seems clear that the vast majority of heterozygous MH humans are not particularly susceptible to stress-induced MH, the cases cited by Drs. Gronert, Tobin and Muldoon tend to be the exception rather than the rule for human MH. Indeed, in a recent publication [7], one of the authors of the commentary described a 30-year debate in which the central issue "– is the idea that some MH susceptible patients may develop awake nonanesthesia-related manifestations similar to that seen in porcine stress syndrome." She further wrote, "Although a link has never been established by controlled clinical studies, individual case reports and a small number of clinical series support an association between unexpected exertional rhabdomyolysis and MH susceptibility, two syndromes characterized by abnormal intracellular skeletal muscle calcium regulation."

The genetic basis of exertional rhabdomyolysis is an important issue for the uniformed services and Dr. Muldoon, as well as Drs Gronert, Tobin and others must be lauded for taking on the worthy cause of developing "stress-induced MH" into a viable research area within the MH field [8]. However, any statement concerning an

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association between human stress and MH episodes must be made with the utmost caution since it could cause unnecessary and unjustified alarm among MH patients.

Addendum:

Drs. Gerald Gronert, Joseph Tobin and Sheila Muldoon, are prominent academic clinicians in the MH field. As a component of our response to their Letter to the Editor, they have here drawn up guidelines for advice to MH patients, which we fully support, that attempt to reconcile the fact that most MH patients will not experience a stress-related episode, but a subset of rare MHS patients is at higher risk.

Most MHS patients have no awake symptoms during adverse conditions and need not limit environmental/stress situations. As with the normal population, they'll sensibly adapt to adverse conditions. Rare MHS patients, with a personal or family history of intolerance to heat or other stress, should not over-exert. If early symptoms begin, they should reduce stressful activity to minimize the likelihood of a stress-induced MH episode. They should begin symptomatic treatment, particularly cooling. Each patient must determine her/his own limits, and have dantrolene capsules available.

But rhabdomyolysis looms; it may occur during MH and in other conditions of skeletal muscle. Associated with anesthesia, it can be explosive in release of potassium and myoglobin, with immediate hyperkalemic cardiac arrest, and gradual evidence of renal failure. One example suffices: an 11 y/o girl arrested after receiving succinylcholine, with potassium >10 mEq/L, and creatine kinase 671,744 IU/L. She required cardiac bypass perfusion with saline to restore potassium to normal, hemodialysis, and she recovered fully. Contracture studies at UC Davis 20 months later ruled out MH [9].

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