Experimental Malignant Hyperthermia

To the Editor:—There are three major flaws in the design and interpretations of the results of malignant hyperthermia experiments in susceptible pigs as reported by Gronert et al.1–4 First, the pigs used by Gronert et al. were obviously heterozygotic animals. Gronert et al. do not show any evidence of having concentrated the genetic defect via inbreeding of susceptible pigs. We have conducted a study of the genetic defect and find that inbred (homozygous) pigs are hypermetabolic (basal metabolic rates that are five times normal), hypertensive (blood pressures of 230/170 torr), and hyperthermic (muscle temperatures as high as 42.8°C) with the development of an intense peripheral vasoconstriction that makes the syndrome highly lethal.5–8

Second, Gronert et al. have not adequately controlled the starting temperatures of their experimental animals. Mean right atrial temperatures of experimental groups ranged from 36.5 to 38.7°C, indicating that some of the animals were hypermetabolic, and thus the heat-producing phase of the syndrome may already have been initiated. We have found that each animal must be cooled to 37°C prior to initiating an experiment in order to obtain consistent results. Buchs has shown that at any given ATP concentration, a two- or three-degree increase in temperature can cause a significant increase in actinomyosin interaction independent of changes in calcium concentration.9

Third, careful evaluation of the norepinephrine data published in Gronert's series of papers shows that norepinephrine in the blood was increasing at 10 to 20 min and reached statistically significant levels at 30 min. Thus, Gronert's data provide direct support for our hypothesis that an "excess activity of norepinephrine" may be the primary cause of the malignant hyperthermia syndrome. An "excess activity of norepinephrine" can occur without significant increase of norepinephrine in blood since the turnover of norepinephrine can be quite rapid without an appreciable increase of norepinephrine in blood. Released norepinephrine causes local vasoconstriction, and 90 per cent of the hormone is recycled by an active uptake mechanism, with only 10 per cent being released into the circulation.10

If we assume that Gronert's pigs have 50 to 75 per cent of the normal enzyme complement to degrade norepinephrine, then a substantial amount of hormone could be released and degraded before norepinephrine in the blood would increase. However, there would be an increase of the deaminated and orthomethylated metabolites. The overflow of norepinephrine must exceed the reuptake and catabolic capabilities before an increase in blood levels occurs—thus, the delay in the increase of norepinephrine in the blood of a heterozygous pig.

Our inbred strain of pigs may have only 1 to 25 per cent of the enzymatic capability to degrade norepinephrine, and thus would be much more sensitive to sympathetic overflow. We have developed a selective, precise, and highly specific liquid chromatographic procedure for quantitating norepinephrine and other biogenic amines in plasma of our susceptible pigs.11 We have observed higher-than-normal levels of norepinephrine, serotonin, dopamine, and other components in plasma of our pigs prior to induction of the malignant hyperthermia syndrome with halothane. After induction of the malignant hyperthermia syndrome the levels of these compounds increased severalfold, which is certainly indicative that there may be a deficiency of monoamine oxidase or catechol-o-methyltransferase.12 We have observed pathophysiologic symptoms of sympathetic hyperactivity in our pigs, and similar observations have been made by Wingard in a clan of malignant hyperthermia-susceptible people.13 Many of the malignant hyperthermia carriers and relatives are frankly hypertensive or have labile hypertension.14 Recently we have shown that total neuromuscular blockade with d-tubocurarine or metocurine iodide will prevent the subsequent development of the malignant hyperthermia syndrome in pigs.14 We have also shown that alpha receptor blockade with phentolamine will prevent the vasoconstriction and development of muscle rigor phases of the malignant hyperthermia syndrome.15 Thus, the key events in initiating the malignant hyperthermia syndrome appear to revolve around the function of the acetylcholine receptor as modified by norepinephrine, other biogenic amines, and thyroid hormones.16–20

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References


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In reply.—First, we purchase swine from several regional Poland China breeders who each have a minimum of 30 years' experience with their registered herds and who inbreed for greater muscle mass. Obviously, however, inbred homozygotic Poland China swine may not have inbred susceptibility to malignant hyperthermia. Susceptibility, as Williams et al. recommend,1 is best evaluated by a halothane challenge. They define susceptibility as the appearance of rigidity and fever within 20 min of exposure to halothane, and report an incidence of 55–57 per cent.1 At the time of purchase, we discard any animal in which these changes do not develop within 5 min, and find an incidence of about 50 per cent, suggesting that we have comparable inbreeding for malignant hyperthermia.

Their fivefold increased “basal” metabolic rates were determined by placing awake pigs into a calorimeter.2 But instead of reporting mean group values, they report values from individual animals, wherein

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