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Letter-to-the-Editor RE: Lai HH, Boone TB, Thompson TC, Smith CP, Somogyi GT: Using Caveolin-1 Knockout Mouse to Study Impaired Detrusor Contractility and Disrupted Muscarinic Activity in the Aging Bladder

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TO THE EDITOR,

In an important recent study, Lai *et al.*⁶ examined the impact of a *caveolin-1* gene deletion on the amplitude of muscle contractility mediated by nerve stimulation and carbachol in detrusor muscle strips obtained from 3 and 12 months old male mice. Detrusor underactivity (DU) which has been defined as a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span¹ is a remarkably common problem among frail older adults who suffer from incontinence or other voiding difficulties¹². The precise prevalence of DU among community-dwelling elderly remains unknown. Nevertheless, elevated post-void residuals are common in older individuals of both genders, while urodynamically documented DU in the absence of bladder outlet obstruction has been demonstrated in 59% of incontinent nursing home residents¹⁰. The clinical management of elderly individuals with DHIC (detrusor hyperactivity with impaired contractility) remains particularly unsatisfactory because antispasmodic anticholinergic medications may worsen retention, whereas bethanechol does not improve bladder emptying resulting from DU¹².

The "dense band" pattern with caveolar depletion has been described as being the ultrastructural pattern associated with normative bladder aging⁴, lack of estrogen¹⁵, diabetes¹¹ and injury³. Many key signaling molecules including muscarinic and purinergic receptors are known to cluster in caveolae¹⁴. Moreover, the authors have previously demonstrated a decreased ability of cholinergic agonists to mediate bladder muscle contraction in mice rendered null for the caveolin-1 gene⁷.

In view of the above considerations, we strongly agree with the decision Lai *et al.*⁶ to introduce age as a variable in examining the impact of caveolin-1 gene deletion on bladder muscle strip

contractility. At the same time, we feel that the findings of their careful studies need to be attributed to maturational rather than aging processes⁸. In particular, we are concerned with the authors' conclusion that since *caveolin-1* $-/-$ mice demonstrate a 50% decrease in their lifespan as compared to wild type *caveolin-1* $+/+$ controls, 1 year old *caveolin-1* $-/-$ mice should be considered as being "aged"⁶. Certainly, mutations in some genes can result in premature aging syndromes both in humans and in some animal models². Conditions such as progeria are felt to represent useful models for the study of aging since they are associated with an accelerated development of many of the phenotypic and biologic changes known to define normal aging². In contrast, the dramatically reduced lifespan observed in *caveolin-1* $-/-$ mice appears to arise from the development of specific diseases in these mice including pulmonary fibrosis, pulmonary hypertension and cardiac hypertrophy, which result in decreased viability and premature death⁹.

The presence of such early and ultimately lethal morbidity precludes the use of *caveolin-1* $-/-$ mice in traditional aging research. Nevertheless, *caveolin-1* $+/-$ mice could offer an extremely attractive and much-needed animal model of DU. As noted earlier, deletion of a single allele for the caveolin-1 gene appears to have no effect on the animals' survival or viability⁹. Thus, It would be very interesting to know whether Lai *et al.*⁶ have examined the impact of caveolin-1 haploinsufficiency on bladder muscle contractility. In rodent models, lack of estrogen^{15, 16} results in quantitatively similar declines in bladder muscle contractility, numbers of caveolae per length of bladder muscle sarcolemma, and caveolin-1 protein levels. Thus, it is plausible that haploinsufficiency involving a single allele for the *caveolin-1* allele in young (3 m. old)⁸ or mature (9–12 m. old)⁸ mice could result in detectable decreases in bladder muscle contractility. Furthermore, even if bladder muscle contractility proves to be similar in bladder muscle tissues obtained from younger *caveolin-1* $+/+$ and *caveolin-1* $+/-$ mice, functional differences may only become apparent and detectable once haploinsufficient mice reach old age (21–26 m. old)¹³.

Even if the impact of *caveolin-1* gene haploinsufficiency on muscle contractility proves to be quite modest, these types of studies could represent an important contribution to research addressing the pathophysiology of DU in the frail elderly. Unlike many conditions seen in younger populations, multiple risk factors can contribute to DU^{5, 12}. While the presence of any one single risk factor can only address a small portion of the overall risk of developing DU, the presence of multiple coexisting risk factors in any individual results in added risk, in many cases involving synergisms between different risk factors. Such considerations require the development of innovative investigative strategies for addressing the pathophysiology of complex multifactorial geriatric syndromes⁵.

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