Alaina K. Guilbeau
L2
LSU Health Sciences Center, New Orleans, LA

Dr. Rinku Majumder, PhD,
Professor, Department of Interdisciplinary Oncology
LSUHSC

"Estrogen, obesity, and anticoagulant Protein S contribute to thrombosis in mice"

Protein S (PS) is an anticoagulant molecule present in humans and mice. Protein S binds and inhibits coagulation Factor IXa to control thrombin generation[1]. Protein S is imperative for normal hemostasis and the prevention of life-threatening thrombotic events, as demonstrated by numerous studies of patients with PS deficiency[2,3,4].

Pregnant women[5] and women who use estrogen-containing birth control pills [6] have lower levels of PS. Thus, it is postulated that estrogen downregulates PS expression in human. Because estrogen is synthesized by aromatase, which is highly expressed in adipose tissue[7], we expected that PS will be downregulated in obese mice and in mice treated with exogenous estrogen. Further, we suggest that the downregulation effects of obesity and estrogen on PS abundance will be synergistic. Neither of these relationships have been shown experimentally in a mouse model.

We used a thrombin generation assay to measure thrombin production in 24 mice weekly for six consecutive weeks. Half of the mice were obese, and the other half were lean. Of the 12 obese mice, 6 were treated with a 1.7 mg pellet of estradiol every 21 days, i.e., the obese+estrogen group (OE); the other 6 mice constituted the obese-only (O) group. Similarly, 6 lean mice were treated with estrogen (LE), and the other were untreated, i.e., a lean control (LC) group. Plasma was collected via venipuncture and centrifugation for each of the 5 weeks of treatment, along with week 0 before estrogen treatment began.

We found an increase in the average peak thrombin levels for both LE (70.4 nM, week 3) and O (44.46 nM, week 3) groups compared with LC (33.099 nM, week 3), and an even higher peak thrombin in the OE (95.34055 nM, week 3) group. Peak thrombin increased steadily in the OE group between weeks 1-3 of treatment (50.29 nM, 69.2 nM and 95.34 nM respectively), but decreased thereafter likely due to premature clotting before the thrombin assays. Likewise, peak thrombin increased in the LE group between weeks 1-4 (22.19 nM, 65.71nM, 70.44 nM and 74.35 nM), then there was a decrease in week 5 (17.65 nM). Currently, immunoblot and ELISA assays are being performed to measure PS levels in all the groups.

In conclusion, this study indicates that PS expression (or activity) may be downregulated by estrogen therapy, and this effect is exacerbated by obesity as seen in thrombin generation assays. This information draws attention to the increased risk of thrombosis in women who use hormonal contraceptives, who are pregnant, or especially women who are obese. The relationships between Protein S, obesity, and estrogen should be further investigated to establish preventative measures for this high-risk group.

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