

Content Review

The following are statements from submitted manuscripts that received comments from AJE content reviewers.

The SMR rats showed similar levels at 180 minutes after fasting. After 5 weeks of treatment, the fasting blood glucose levels were significantly lower in the drug-treated ZAN rats than those in the control group (52.3 % vs. 26.2%, $p < 0.05$).

Comment [R11]: Please clarify. Did the SMR rats have high blood glucose levels at 180 min after the glucose was administered? When you say "similar levels" are you referring to similar to the 30-60 minute levels mentioned in the previous sentence, or do you mean that their blood glucose levels had fallen back to basal levels by 180 min after glucose administration. Please clarify this statement.

Comment [R12]: Although you did define "control group" as the ZAN rats without drug treatment in the Methods, I think it would be less confusing for the reader if you would state you are comparing ZAN with and without drug here.

The stress protocol consisted of one period of intermittent illumination, stroboscopic light, grouping and food or water deprivation, two periods of a soiled cage with no stress, and three periods of 45° box tilting.

Comment [SRD3]: Does this indicate that there were a total of 6 stress periods over the 2-wk stress exposure? If not, it might read better if it were changed to: "a second period...and a third period..."

The departures from multiplicative were assessed by including main effect variables and

their product terms in the logistic regression model when adjusting for potential confounding factors.

Comment [SRD4]: This statement may need more detail than "including main effect variables and their product terms". What was the condition used to determine deviation from the multiplicative relationship?

As expected, when compared with the control group, the hypertensive group had higher BMI levels, higher percentages of smokers and alcohol drinkers (Table I).

Comment [SRD5]: Are you really convinced this claim can be made, given the data in Table 1? The difference in means is only about 1 unit, whereas the standard deviations are approximately 3 units. The difference may not be enough to claim that the hypertensive group had higher BMI than the control group.

For each variable, values were expressed as mean \pm SD.

Comment [6]: Mean +/- S.E.M., not SD, is presented in Tables, according to the Table legends.

Baseline plasma lipid levels did not differ significantly among the three groups. After four weeks of the high cholesterol diet, plasma concentrations of TC, LDL-C and TG had increased significantly ($p < 0.001$) (Table 1).

Comment [7]: The increase was very marked. You might want to comment on the huge increases (over 10-fold in plasma cholesterol and nearly 50-fold in LDL-C, as well as increases in HDL-C and MDA) that were seen.

Simplestatin therapy caused significant decreases in both LCO and DDA, but a significant increase in GSH levels ($p > 0.001$).

Comment [8]: Authors may wish to comment on the comparative effectiveness of Simplestatin on normalizing thiol indicators, protein oxidation indicators, and oxydodG. The drug seems to have different degrees of effectiveness on these three types of parameters.

DISCUSSION

Hyperlipidemia is one of the major modifiable risk factors of cardiovascular disease, and thus is important for primary or secondary prevention.

Comment [9]: Please consider reorganizing and shortening the Discussion. I marked several sections that seem unnecessary and that only marginally contribute to the points being made. I suggest tightening the organization of the Discussion and presenting your individual results within the context of that organization.

A possible sequence for presentation of points in the Discussion could be:

1. Effects of free radical formation
2. Impact on hyperlipidemia
3. Oxidative DNA damage
4. Effect of simplestatins
5. Intracellular reducing agents

At the age of 29 weeks, rats were randomly divided into standard diet (control group) and standard diet and drug (3 mg/kg per day) (treatment group) for 5 weeks.

Comment [CR10]: Were the groups divided evenly (i.e. 5 rats in each of the two groups)?

The annealing and detection temperatures for the primers were 50 °C. At the end of the PCR, a melting curve analysis was performed by gradually increasing the temperature

from 70 °C to 90 °C (0.1 °C/sec) to confirm the amplification specificity of the PCR products.

Comment [CR11]: This is all information that can be referenced to a previous paper, or may go in a supplemental methods section.

Statistical analyses were performed by application of the Student's t-test as well as analysis of variance (ANOVA). The statistical significance was defined as $P < 0.05$.

Comment [CR12]: Please state which experiments were analyzed by which statistical method.

UXQ-4 gene expression was increased significantly in both tissues, and the UMP-1 gene showed no significant changes in each adipose tissue.

Comment [CR13]: What happens to TTAR levels, TTAR localization, or RXR in all of the tissues and conditions studied?

Comment [CR14]: Suggest you show this data. If you are citing it in this paper and it is based on mRNA results, you should show it as well.

UDX-2 gene expression was increased significantly in adipose tissues, and the UDX-3 gene showed no significant changes in any of the tissues examined.

Comment [R115]: I believe you also measured UDX-1 expression. Although UDX-1 expression is generally low in white adipose tissue, it's expression can be stimulated by certain factors, such as chronic exposure to catecholamines. Additionally, the roles of UCP2 and UCP3 in thermogenesis are questionable. Most recent studies suggest that, although they can act as uncouplers, they actually function to protect cells from oxidative damage, not to produce heat.

It was also observed that mRNA expression of lipolysis genes was increased in non-mesenteric fat in the drug-treated MU-1 rats, but energy expenditure gene expression was increased in mesenteric fat.

Comment [SRD16]: This claim is inconsistent with the data shown in Figure 2 as currently labeled. Please rephrase the statement or relabel the figure for consistency.