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PART 1:

Journal Name:	International Journal of Biochemistry Research & Review
Manuscript Number:	MS: 2012 IJBcRR 2833
Title of the Manuscript:	Hormonal Sensitivity of Adenylyl Cyclase in the Myocardium, Brain and Testes of 18-month-old Non-Diabetic and Diabetic Rats

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PART 2: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	1. Metabolic syndrome (MS) including diabetes is common in elderly patients with strongly related to cardiovascular disease and cerebrovascular events. Thus research on the pathogenesis in the elderly is of great significance. Present study showed that changes of the hormonal regulation of AC system in the brain, myocardium and testes of control and diabetic rats with aging. However, the tissues belong respectively to different system. As we all know, other tissues, such as gastrointestinal, renal and even pulmonary tissue are also involved with the disease, so why are these tissues not studied? Thus, the potential interaction between the systems observed in the study should be explained reasonably in the manuscript.	1. In order to explain the choice of the rat tissues we have added the following text to the Introduction (after the purpose of the study, see below). “The choice of the tissues, such as the brain, myocardium, and testes, for the study was dictated by the following reasons. Functional abnormalities of the hormonal signaling in the diabetic brain lead to neurodegenerative diseases and cognitive deficit [Scheen, 2010; Shpakov et al., 2011], and also induce a lot of dysfunctions in the peripheral organs and tissues, including the heart and testes [Bruning et al., 2000; Baccetti et al., 2002; Mah, Wittert, 2010; Mandavia et al., 2012]. It should be noted that the decline of reproductive function in diabetes is a result of impairment of different components of the hypothalamo-pituitary-gonadal axis, as the central (hypothalamus) and peripheral (gonads) [Bruning et al., 2000; Baccetti et al., 2002; Pitteloud et al., 2005; Dandona et al., 2008]. The alterations in the cardiovascular and reproductive systems are the most frequent complications of T2DM, especially in the case of long-term T2DM and its inadequate therapy. Clinical studies show that diabetic cardiomyopathy is a leading cause of death of diabetic patients, and also demonstrate the relationship between male infertility and T2DM-



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	2. It is well known that gender influence on reproductive dysfunctions is different in male and female with diabetes. Therefore, the authors not only need to claim an effect of age on the changes of hormonal sensitivity of adenylyl cyclase, but also should discuss the influence of gender in the manuscript.	induced hypogonadotrophic hypogonadism and spermatogenic failure [Mah, Wittert, 2010; Chiha et al., 2012; Magge, 2012].” (the references were added to the List of References) An additional argument in favor of the choice of the brain, heart and testes is the fact that in these tissues we previously described in details the hormone-sensitive AC system, in rats with short-term models of diabetes of the types 1 and 2 in particular. This allowed us to systematically approach to studying the functional state of AC system in these tissues in the present work. Of course, the study of AC system in the kidney and gastrointestinal tract is of great interest. However, it is a matter of great independent study. 2. Indeed, there is a lot of data on gender influence on reproductive dysfunctions in T2DM. However, we studied only male rats and DM-induced impairment in their reproductive system, and do not have sufficient grounds to discuss the complications of the female reproductive systems. In this respect, earlier we investigated hormone-sensitive AC system in the uterus and ovaries of female rats with streptozotocin model of type 1 DM, and detected a wide spectrum of alterations of hormonal signalling in these tissues (Shpakov A.O., Bondareva V.M., Chistyakova O.V. Functional state of adenylyl cyclase signaling system in reproductive tissues of rats with experimental type-1 diabetes // Cell Tissue Biol. 2010. V. 4. №.
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	3. Hormone-sensitive AC system plays an important role in the insulin secretion and regulation of glucose. As indices of the glucose metabolic abnormalities, glucose, glucose tolerance test and plasma insulin of different month of age of the models should be presented and analyzed with statistically. 4. Recent researches showed that insulin in central nervous system play an important role on fertility of male mice rather than that in the testes. Thus, in present experiment alteration of the AC system in testes of rats with age and diabetes contributes to the reproductive dysfunction should not be speculated conclusively.	2. P. 208–214). To focus on the male reproductive system, we made the next changes in the text. In the Results section (page 7, line 271) the phrase “of attenuation of reproductive functions in T2DM.” replaced by “of the weakening of the male reproductive system in T2DM”. In the Discussion section (page 12, line 446) the phrase “the reproductive dysfunctions” replaced by “the dysfunctions of the male reproductive system”. 3. We have presented the table (Table 1) with the body weight, plasma glucose and insulin levels in three-, eight-, and 18-months-old diabetic and control rats and modify the text. We also presented the figure (Fig. 1) with glucose tolerance test. Additionally, we have presented Excel files with the data for Table 1 and Fig. 1 (the data are presented as the $M \pm SD$). 4. We agree with the remark that abnormalities in the central mechanisms (in the brain insulin signalling system, in particular) in the diabetic brain are also responsible for the development of complications of reproductive system. In this regard, we changed the last sentence in the Discussion and added the phrase with the corresponding references (see below). “In our view the changes of the testicular AC system we identified in very long neonatal DM, which increase significantly with the disease duration, are one of the factors that cause the dysfunction of the male reproductive system in T2DM. It should be noted that the brain
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		hormonal signaling also plays an important role in control of the male reproductive functions [Bruning et al., 2000; Ghasemi et al., 2013]. Thus, the alterations of hormone-sensitive AC system identified by us in the brain of rats with long-term neonatal T2DM can also be regarded as causal factors leading to deterioration in the functioning of the male reproductive system in diabetes.” We also discussed the relationship between the central nervous system and the reproductive system in the Introduction (see above, the answer to the first comment).
<u>Minor</u> REVISION comments		
<u>Optional/General</u> comments		