



# EFFECTS OF CHRONIC ALCOHOL ON BEHAVIORAL FUNCTIONS AND ALPHA-2 ADRENOCEPTORS IN TWO RAT STRAINS

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## INTRODUCTION

Alpha-2 adrenoceptors (alpha-2 ARs) are involved in a variety of physiological and behavioral functions including depression and drug dependence. Studies suggest that increased alpha-2 AR density or sensitivity results in insufficient neuronal release of NE which may lead to depression. Moreover, a variety of antidepressant drugs and other treatments of depression are associated with decreases in the density and sensitivity of both central and peripheral alpha-2 ARs.

Alpha-2 ARs are also thought to be involved in alcohol's action. However, very little information on a direct interaction between alcohol and these receptors is available. The aims of this study were to: 1. determine whether inherent differences in alpha-2 AR densities exist between a putative animal model of depression, namely Wistar-Kyoto (WKY) rats and their control Wistar (WIS) rats, and 2. determine the effects of chronic alcohol administration on behavioral indices of depression and on the density of alpha-2 ARs in discrete brain areas of both rat strains. WKY rats, derived from WIS rats, are considered a suitable animal model of depression as they exhibit exaggerated immobility in the forced swim test (FST) compared to WIS rats. Our hypotheses were that depressive-like behavior in WKY rats is associated with higher alpha-2 AR density compared to WIS. Furthermore, alcohol administration would induce depressive-like behavior in WIS rats and exacerbates it in WKY rats and these behavioral effects are associated with increases in alpha-2 AR binding in both strains.

## METHODS

### Animals

Age matched adult female WKY and WIS rats (Harlan) were kept in a temperature-controlled room (24-26°C) on a 12:12 hour reversed light/dark cycle (lights on at 19:00). The animals had *ad libitum* access to food and water, except during experiments.

### Alcohol Vapor Exposure and Behavioral Testing

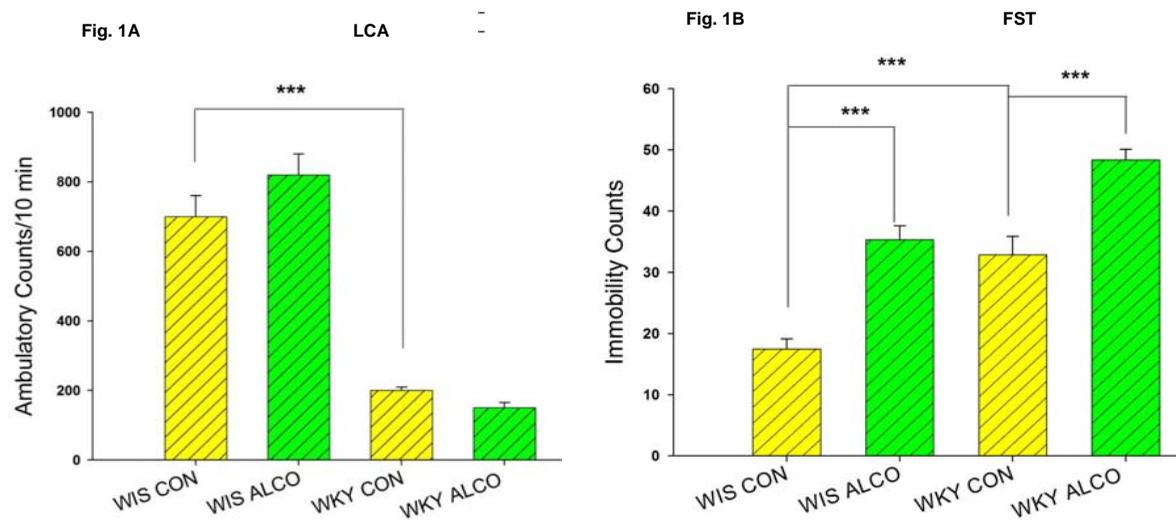
WKY and WIS rats were exposed 4 hrs daily to alcohol via inhalation chambers (La Jolla Alcohol Research Inc. San Diego, CA) for 10 days. The blood alcohol concentration in both strains was maintained at approximately 150 mg% during the exposure period. On day 11 automated analysis of locomotor activity (LCA) in an open field was performed for 10 min prior to the Forced Swim Test (FST).

FST, a modification of the method of Porsolt et al. (1977), measures immobility of animals in an inescapable cylinder of water. The total amount of time the animal demonstrates this behavior reflects the animal's state of behavioral despair. The animals were placed in the water cylinders for 5 minutes, videotaped and their swimming and immobility were scored at every 5 second interval according to Detke et al. (1995).

### Tissue Preparation and Receptor Binding

Two hours after the behavioral test, the animals were sacrificed for measurement of alpha-2 AR densities in discrete brain regions. Tissues were homogenized in ice-cold buffer (50 mM Tris-HCl, 3 mM MgCl<sub>2</sub>, and 1 mM EGTA, pH 7.4) and centrifuged at 48,000-x g at 4°C for 30 minutes. The pellet was re-suspended and store at -80°C till receptor binding. Alpha-2 AR levels were measured using 2.5 nM [<sup>3</sup>H]RX 821002 in the presence of unlabeled norepinephrine.

## RESULTS



Figures 1A and B. Effect of 10 day daily alcohol vapor exposure on locomotor activity and forced swim test immobility counts of WKY and Wistar rats. Values are mean ± SEM. N=7-8. \*\*\*P<0.001.

## SUMMARY OF RESULTS

- Chronic alcohol treatment resulted in a depressive-like behavior in WIS rats and exacerbated this characteristic in WKY rats.
- Alpha-2 ARs were higher in several brain regions (cortical areas and midbrain) of WKY rats compared to WIS.
- Alcohol treatment resulted in a down-regulation of these receptors in the cortical and midbrain areas of WKY rats, whereas WIS rats were not affected in any region.

## ACKNOWLEDGEMENTS

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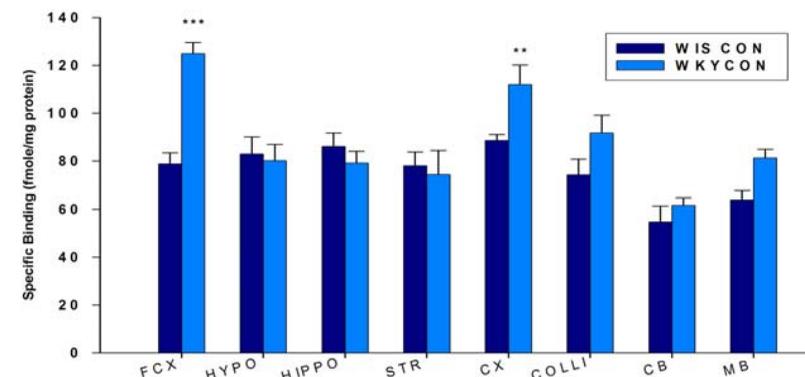


Figure 2. Baseline alpha-2 AR levels in different brain regions of WKY and Wistar rats. Values are mean ± SEM. \*\*\*P<0.001, \*\*P 0.01 compared to Wistar rats. N=7-8.

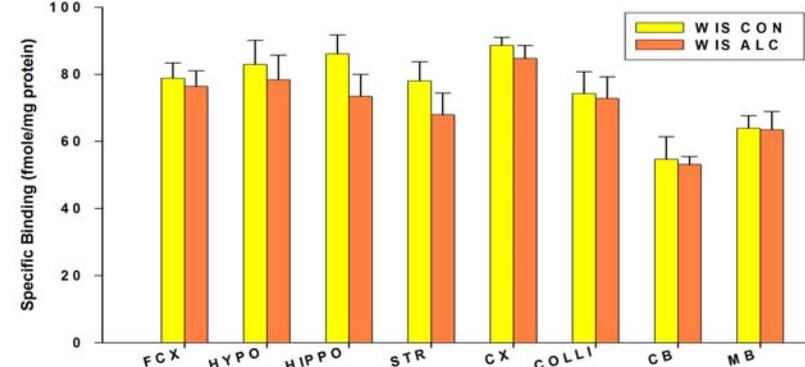


Figure 3. Effect of 10 day daily alcohol vapor exposure on alpha-2 AR levels in different brain regions of Wistar rats. Values are mean ± SEM. N=7-8.

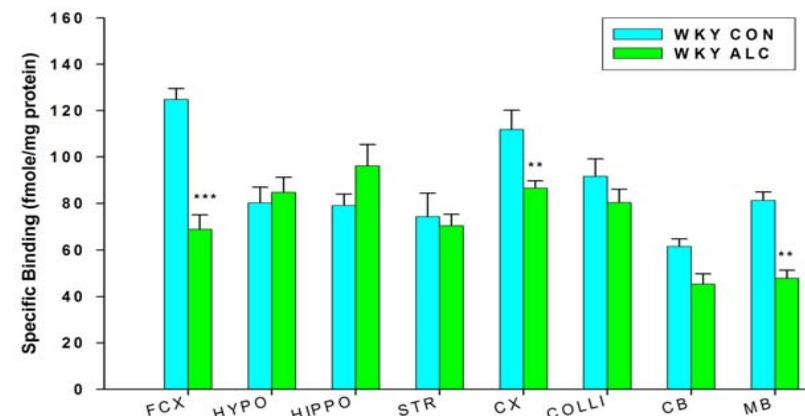


Figure 4. Effect of 10 day daily alcohol vapor exposure on alpha-2 AR levels in different brain regions of WKY rats. Values are mean ± SEM. N=7-8. \*\*\*P<0.001, \*\*P 0.01 compared to WKY control rats.

## CONCLUDING STATEMENT

These results do not support a direct role for central alpha-2 ARs in the inherent depressive-like characteristics of WKY rats or its exacerbation by alcohol. Similarly, no correlation between alcohol-induced depressive-like behavior and alpha-2 AR in WIS rats was noted. Thus, it may be suggested that basal alpha-2 AR densities and their response to alcohol are genetically determined and appear to be independent of the depressive-like behavior.