

Sex-related differences in the efficacy of Baclofen enantiomers on alcohol drinking and dopamine release in the core of the nucleus accumbens

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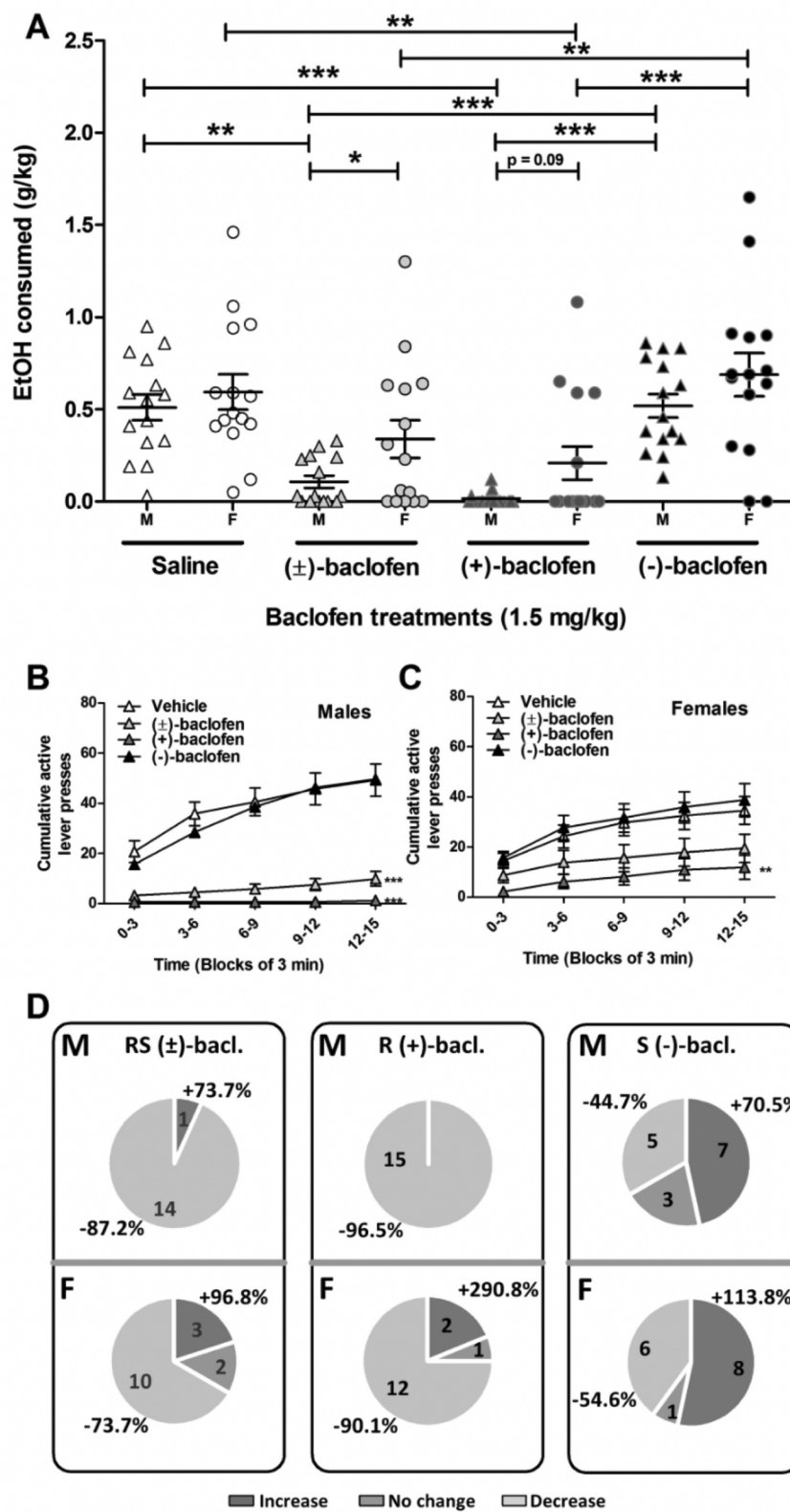
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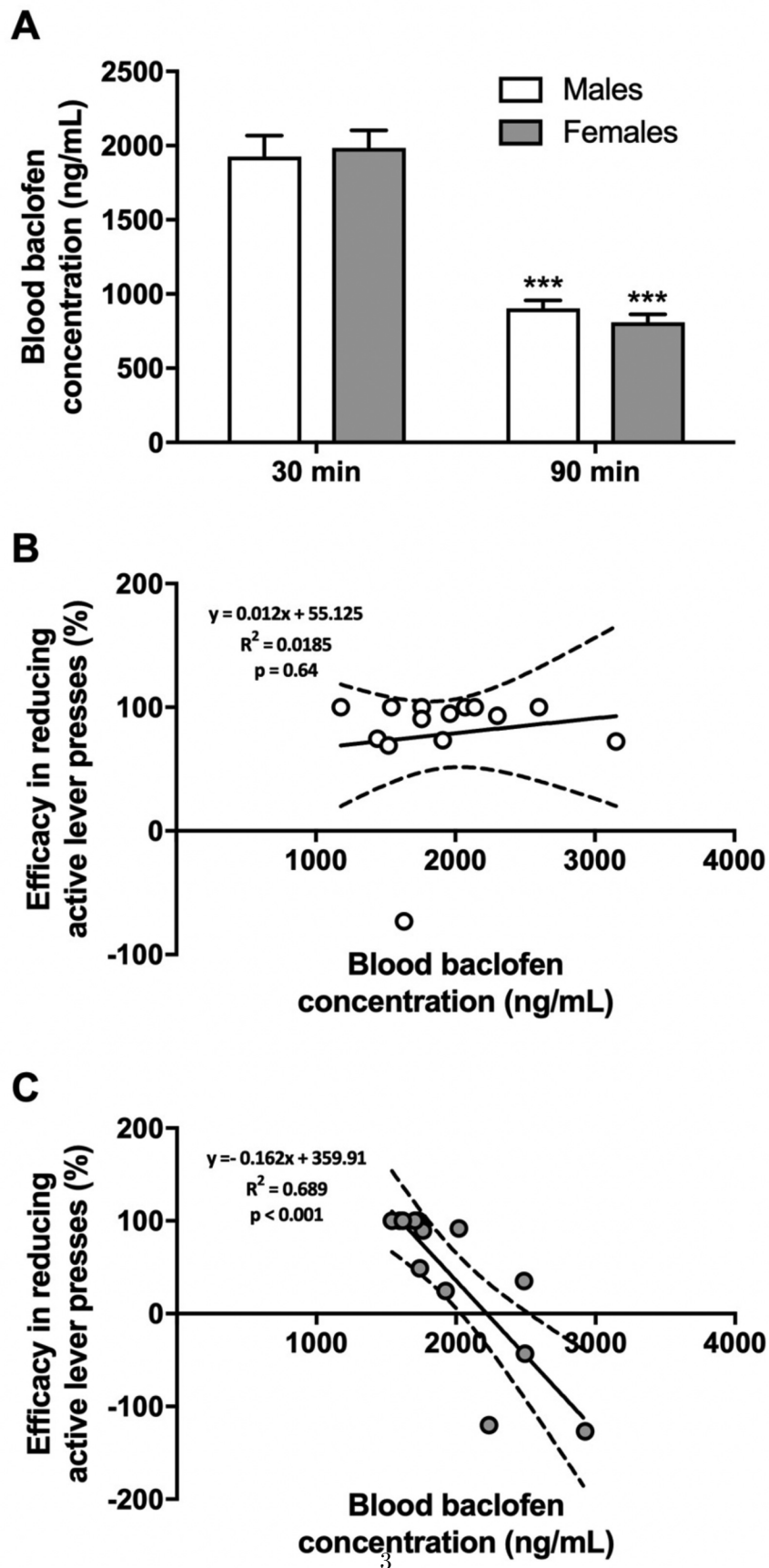
Abstract

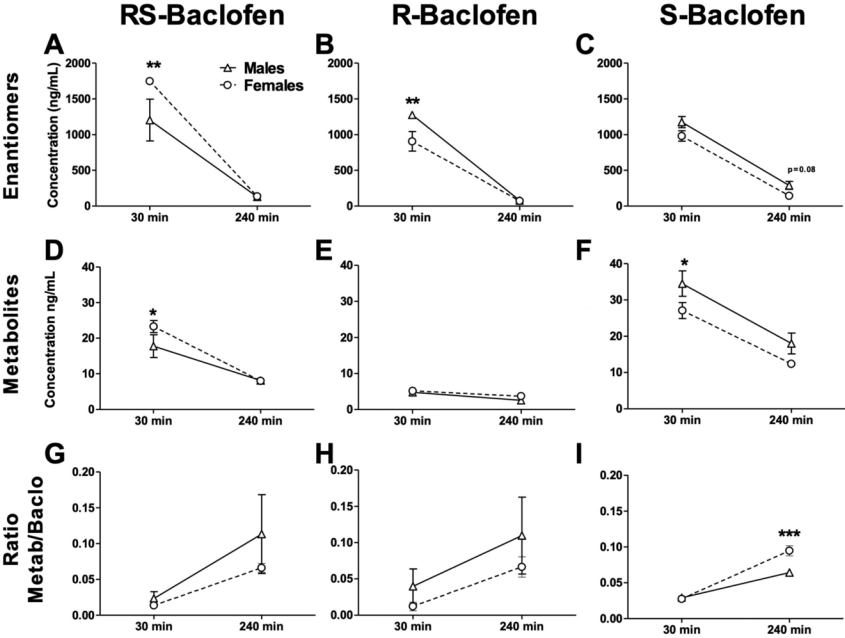
Background and Purpose. Clinical studies on the effectiveness of Baclofen in alcohol use disorder (AUD) yielded mixed results possibly because of differential effects of the enantiomers and sex-related differences. Here we examined the effect of the different enantiomers on ethanol intake and on evoked dopamine release in the nucleus accumbens (NAcc), in both male and female Long Evans rats. **Experimental Approach.** Fifteen rats from each sex were trained to chronically self-administer 20% ethanol solution in daily 15min sessions and were treated with the different enantiomers (RS(\pm), R(+) and S(-)). **Key Results.** RS(\pm)-Baclofen and R(+)-Baclofen reduced ethanol intake in both males and females but more females were non-responders or less sensitive to the treatment. S(-)-Baclofen did not have any effect on average but in some individuals, especially in the females, increased ethanol intake by at least 100%. There were no sex-differences in Baclofen pharmacokinetic but a strong negative correlation was found in females with a paradoxical effect of increased ethanol intake with higher blood Baclofen concentration. The R(+) and RS(\pm) enantiomers decreased dopamine release in both sexes and this effect was attenuated after chronic ethanol intake. Dopamine release was increased by S(-)-Baclofen specifically in females after chronic ethanol intake. **Conclusion and implications.** Our results demonstrate a sex-dependent effect of the different enantiomers of Baclofen and the increase of ethanol intake in females may be related to an increasing effect on dopamine release. Our results should warrant future clinical studies on AUD pharmacotherapy that will deeply analyze sex difference.

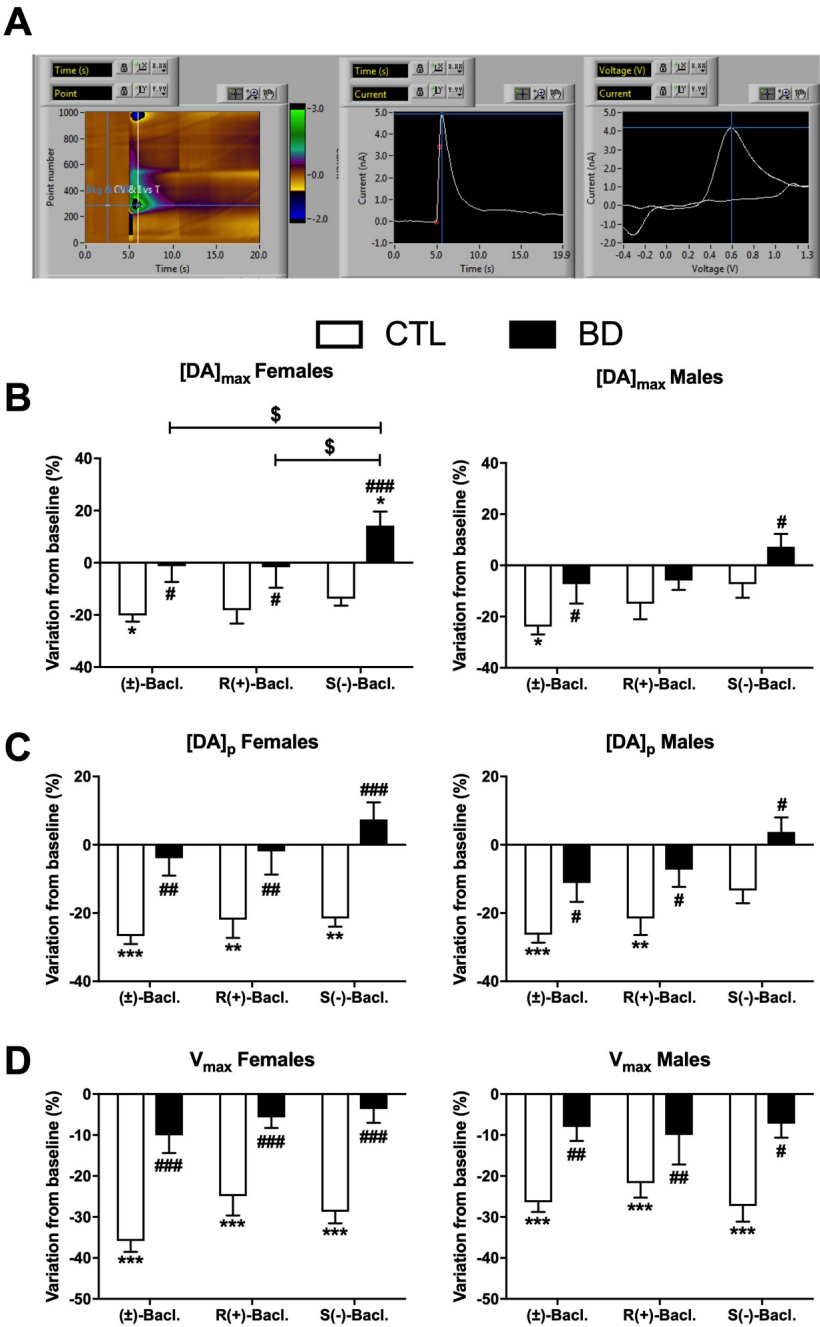
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