



TITLE

Exogenous administration of a cocktail mimicking *Candida albicans* autoregulatory alcohols affects the progression of hematogenously disseminated candidiasis in mice

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ABSTRACT

Candida albicans is a polymorphic fungus that causes opportunistic infections in humans. The ability of *C. albicans* to switch between different morphologies is thought to underlie its success as a pathogen. Recently our group demonstrated that culture supernatants of *C. albicans* contain a mixture of autoregulatory alcohol molecules capable of inhibiting *in vitro* filamentous growth of planktonic *C. albicans* cells. Additionally, a cocktail solution containing isoamyl alcohol, 2-phenylethanol, *E*-nerolidol and *E,E*-farnesol (simulating a 96-h culture supernatant) was shown to regulate *C. albicans* morphological transition in a similar fashion.

OBJECTIVES

The aim of this study was to investigate whether the identified autoregulatory alcohols, through the exogenous administration of the cocktail solution, could affect the progression of infection in a murine model of hematogenously disseminated candidiasis.

METHODS



For the disseminated candidiasis model, immunocompetent BALB/c female mice (age 6 to 8 weeks old) were infected by lateral vein injections with suspensions containing $3 \times$

10^5 *C. albicans* CAF-2 cells (four to eight animals per group). Afterwards, animals were divided into two groups for alcohol administration (1 ml, intraperitoneally): one control group received vehicle solution alone (5% ethanol), and the other group received the cocktail solution of autoregulatory alcohol molecules simulating a *C. albicans* 96-h supernatant (94 μ M isoamyl alcohol, 70 μ M 2-phenylethanol, 3.2 nM *E*-nerolidol and 18 nM *E,E*-farnesol). The effect on infection was monitored by survival curves and by determining fungal organ burden at scheduled times (days 1, 2 and 3) postinfection. For all animals, upon death or sacrifice, brain, spleen, and kidneys were removed for the determination of fungal burden (total CFU per gram of tissue). All experiments were performed in accordance with institutional regulations at the University of Texas at San Antonio. Survival data and organ fungal burdens were analyzed using the Mantel-Cox log rank test and Mann-Whitney test, respectively.

RESULTS

The median survival of control mice receiving the vehicle alone was 6 days. The administration of the cocktail solution significantly delayed the time of death to 9 days ($p= 0.005$). At days 1 and 2 post-infection fungal burden in organs retrieved from mice treated with the cocktail solution was similar to control mice. However, on day 3 animals that received the cocktail solution displayed lower renal and brain fungal burden compared to control mice receiving the vehicle solution alone ($p= 0.03$).

CONCLUSIONS

The cocktail solution containing autoregulatory alcohol molecules simulating a 96-h culture supernatant shows an *in vivo* protective effect against disseminated candidiasis. These findings indicate that the autoregulatory molecules isoamyl alcohol, 2-phenylethanol, *E*-nerolidol and *E,E*-farnesol may play a role during *C. albicans* pathogenesis.