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Doxasozin for Alcoholism

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Abstract

Recent preclinical and clinical evidence using prazosin indicates that a_1-blockade may represent a new approach to treat alcohol dependence (AD). While most of the alcohol research on a_1-blockade has been conducted testing prazosin, O'Neil and colleagues recently performed a set of preclinical experiments testing another a_1-blocker, i.e. doxazosin that has a longer half-life that may enhance clinical utility. Doxazosin and prazosin share the same chemical structure, in which the central element is a piperazine ring. O'Neil et al.'s main results are that doxazosin significantly reduced alcohol intake without affecting locomotor activity. As such, O'Neil and colleagues provide the first preclinical evidence of the possible role of doxazosin in AD. Additional translational research is needed to further test this hypothesis.

Keywords

alcoholism; craving; norepinephrine; prazosin; doxazosin

THOUGH early work suggested that the norepinephrine (NE) reuptake inhibitor desipramine prolonged the time to relapse in depressed alcoholics (Mason and Kocsis, 1991; Mason et al., 1996), research on alcohol pharmacotherapy has been slow to focus on the NE system. Recently, this interest has been renewed, due to the preclinical and clinical results reported for the a_1-blocker prazosin. The recent interest in prazosin for alcohol dependence (AD) was derived from the observation that prazosin-treated patients with co-occurring PTSD (for which prazosin has demonstrated efficacy) and AD often reported reduced and even complete cessation of alcohol drinking. Thus, it was hypothesized that prazosin reduces alcohol drinking, by suppressing hyperexcitability and stress-induced anxiety, which are both mediated, at least partially, by the alpha-NE system and which both may contribute to the development of AD (Rasmussen et al., 2009; Simpson et al., 2009). This hypothesis led

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to a set of experiments demonstrating that prazosin reduces ethanol self-administration and is more potent in ethanol-dependent rats than in non-dependent, thus suggesting that prazosin blocks dependence-induced increases in responding to alcohol (Walker et al., 2008). Subsequently, Rasmussen et al. (2009) demonstrated that both acute and chronic prazosin treatment decreases ethanol consumption in alcohol preferring rats. Both studies (Rasmussen et al., 2009; Walker et al., 2008) showed the lack of prazosin's effects on water intake. Therefore the decrease in alcohol intake was not due to a motor-impairing effect of prazosin on the ability of the rats to drink (Rasmussen et al., 2009). Based on this preclinical evidence, a 6-week double-blind controlled randomized clinical pilot study was performed (Simpson et al., 2009). After a 2-week titration, 24 alcohol-dependent subjects were treated with placebo or prazosin 16 mg three times a day (t.i.d.), the highest dose usually used in clinical practice (i.e. for hypertension). During the last 3 weeks, the prazosin group, compared to placebo, had a statistically significant reduction in drinking days per week, and a trend of reduction in drinks per week (Simpson et al., 2009). More recently, Fox and colleagues (2012) performed a human laboratory study that indicated that prazosin significantly reduces both cue- and stress-induced alcohol craving in treatment-seeking alcohol-dependent individuals. In summary, evidence using prazosin indicates that a_1-blockade may represent a new approach to treat AD, a feature consistent with the robust preclinical evidence that the NE system plays a key role in AD. Larger ongoing studies are now testing prazosin in patients with AD and in comorbid patients with PTSD and alcohol use disorder.

In the study by O'Neil and colleagues published in this issue of *Alcoholism: Clinical and Experimental Research*, the investigators replicated their previous preclinical work with prazosin, but now testing another a_1-blocker, i.e. doxazosin. Doxazosin and prazosin share the same chemical structure, in which the central element is a piperazine ring. O'Neil et al. (2013) performed three within-subject experiments with adult male P rats that were given 2 hour/day scheduled access to a 2-bottle choice, with food and water available ad libitum 24 hour/day. Rats were injected with doxazosin (0 – 10 mg/kg IP) 40 minutes prior to initiation of the alcohol access session in 3 trials (of 3, 5, and 5 consecutive days). The main result of this set of experiments was that doxazosin significantly reduced alcohol intake in all 3 trials. The 5 mg/kg dose consistently reduced alcohol intake, increased water drinking, did not affect locomotor activity, and resulted in a lower plasma alcohol concentration, suggesting that the doxazosin-induced reduction in alcohol drinking was not dependent on motor impairment or an alteration in alcohol clearance.

In the previous studies, prazosin was originally chosen, as it is the a_1-blocker prototype (the first selective blocker to be developed) and is likely to be the most lipophilic. While data with prazosin are quite interesting and promising, doxazosin also represents a potentially interesting novel pharmacotherapy. The set of experiments performed by O'Neil and colleagues (2013) provides the first preclinical evidence on the role of doxazosin in AD and represents an important gain in the scientific literature for several reasons. First of all, beyond prazosin, this study provides additional information on the importance of a_1-blockade to treat AD, thus suggesting that the effects previously reported for prazosin may be, in fact, a drug class effect related to the blockade of the a_1 receptor. Second, in clinical practice (e.g. hypertension, benign prostatic hyperplasia), a_1-blockers such as doxazosin

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with a long half-life are commonly preferred to short-acting ones, such as prazosin (Akduman and Crawford, 2001); therefore the study by O'Neil and colleagues (2013) represents an important platform for the potential development of doxazosin for AD. In fact, an important factor that has thus far limited the effectiveness of medications for AD patients is poor adherence to medication regimens (Garbutt et al., 1999; Weiss, 2004). Adherence to most medications is better with once-a-day dosing, rather than twice a day (b.i.d.) or three times a day (t.i.d.) dosing (Weiss, 2004). Prazosin must be given t.i.d., which may reduce patient adherence (Pool and Kirby, 2001; Tammela, 1997). In the prazosin clinical study for AD (Simpson et al., 2009), an Interactive Voice Response (IVR) system was used t.i.d. to remind subjects to take the study drug, an approach certainly laudable for a proof-of-concept clinical study, but not feasible for a future possible application of a medication in clinical practice. Doxazosin's prolonged $t_{1/2}$ (22 hrs) allows for once-a-day dosing, which facilitates patient compliance. Furthermore, unlike other a_1-blockers (i.e., prazosin), doxazosin can be taken at any time of day, with or without food – properties that further promote patient adherence (Kirby et al., 1998; Pool and Kirby, 2001). Yet, doxazosin has a more tolerable safety profile than prazosin. Hypotensive events often limit the administration of prazosin, especially when the goal is to titrate the medication up to the most effective dose, due to prazosin's rapid onset of action and short $t_{1/2}$ (Pool and Kirby, 2001). Although hypotensive side-effects may also occur with doxazosin, it has been highlighted that the slower onset of action of doxazosin and its relatively long $t_{1/2}$ decreases the likelihood of first-dose postural hypotension compared with prazosin (Fulton et al., 1995; Kaplan et al., 1995; Kirby et al., 1998). Moreover, though effective for lowering blood pressure in hypertensive patients, doxazosin has no significant effect on blood pressure in normotensive patients (Kaplan et al., 1995), thus further decreasing the risk of hypotension. In summary, like prazosin, doxazosin holds promise as a potentially interesting pharmacotherapy for AD, and it seems to have some additional pharmacological properties that might make doxazozin preferable to prazosin, should the role of doxazosin in AD be confirmed by other preclinical and human studies.

Research is certainly needed in order to further investigate the role of doxazosin in AD. One of most important questions is the ability of doxazosin to significantly cross the blood-brain barrier. Three a_1 subtypes have been identified, i.e. a_{1A}, a_{1B} and a_{1D} (Michel et al., 2000). While a_{1B} subtypes are highly expressed in the brain, a_{1A} and a_{1D} are highly expressed in the periphery (Gross et al, 1989; Michel et al., 2000). Like prazosin, doxazosin works on all a_1 subtypes, thus it is proposed to work both in the periphery and brain (Michel et al., 2000). Indeed, blockade of the a_{1B} subtypes (located in the brain) by doxazosin is thought to contribute to the central side-effects, such as dizziness and fatigue, thus indirectly demonstrating its CNS penetration (Gross et al., 1989; Hofner et al., 2002; Michael et al., 2000). Additionally, preclinical studies demonstrate CNS-actions of doxazosin, administered peripherally (McLeod and Cairncross, 1995). Likewise, a recent open-label pilot study with doxazosin (up to 8mg/day for 12 weeks) in 12 patients with PTSD showed a statistically significant improvement of the Clinician-Administered PTSD Scale during treatment (De Jong et al., 2010). Additional evidence of the central action of doxazosin is also its potential role in cocaine dependence. In fact, a recent human laboratory study with non-treatment seeking, cocaine-dependent volunteers reported that doxazosin 4mg/day significantly

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attenuated the effects of 20 mg IV cocaine on ratings of “stimulated”, “like cocaine”, and “likely to use cocaine if had access” (Newton et al., 2012). There were also trends for doxazosin to reduce ratings of “stimulated”, “desire cocaine”, and “likely to use cocaine if had access” (Newton et al., 2012). Another important issue that needs to be investigated more comprehensively surrounds what the most effective dose of doxazosin is while maintaining acceptable tolerance. For example, the cocaine study previously noted, used a dose of 4mg/day (Newton et al., 2012). On the other hand, before the study by O’Neil and colleagues (2013), we had independently hypothesized a role of doxazosin in AD, a hypothesis that we are currently testing in a proof-of-concept treatment trial (clinicaltrials.gov: NCT01437046), where we are using a dose of 16mg/day. However, future dose-ranging studies may help to identify possible dose-related effects. Finally, based on the literature with prazosin, it is important to determine if doxazosin is similarly or even more effective in alcoholic patients with PTSD comorbidity.

In summary, doxazosin may represent a new promising pharmacotherapy for AD, and additional translational research should be conducted to better delineate its role in effectively treating AD alone or with other co-morbid psychopathologies.

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