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Commentary

Kappa Antagonist JDTic in Phase I Clinical Trial

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The biological bases for depression are unknown, but it is clear that depressive episodes can be precipitated by stressful experience and individuals at risk for depression are particularly vulnerable to the adverse effects of stress. Similarly, stress exposure enhances the risk of drug addiction, and addicted individuals will often increase their consumption of addictive drugs or relapse when stressed (Brady and Sinha, 2005). These insights suggest that pharmacological treatments that enhance stress resilience might be useful complements to other modes of behavioral interventions, and a proresilience medication may benefit individuals at risk for depression or addiction.

Recent preclinical studies have focused on the central role of the dynorphin peptides as key mediators of the dysphoric and proaddictive responses to stress (Bruchas *et al*, 2010). The dynorphins are endogenous opioid peptides that are released by stressful stimuli and activate the kappa opioid receptors (KORs), which are broadly distributed in mammalian brain. The putative role of the dynorphins in mediating the stress response in humans is supported by both preclinical and human studies. In human subjects, KOR agonists produce strong feelings of dysphoria, and selective KOR agonists, developed as non-addictive opioid analgesics, failed clinical trials because of their adverse effects on mood. In rodents, KOR antagonists block stress-induced depression-like behaviors, anxiety-like, and drug-seeking behaviors without affecting behaviors in the absence of stress (Carroll and Carlezon, 2013).

The validity of these animal models has been sufficiently established to justify human studies of the therapeutic potential of kappa opioid antagonists, but selective kappa antagonists appropriate for human use are still in the early stages of drug development. Clinical studies using non-selective drugs that block kappa receptors are encouraging, however. High doses of naltrexone reduce ethanol consumption in alcoholics, and the mixed opioid buprenorphine, which is a potent kappa antagonist, has been found to reduce cocaine craving and increase mood in treatment-resistant depression (Carroll and Carlezon, 2013; Ehrich *et al*, 2014). Because these drugs are not selective, interpretation of the receptor mechanisms behind these treatments is not clear; nevertheless further evaluation using selective KOR antagonists in a double-blind design seems warranted.

Dr F Ivy Carroll and colleagues at Research Triangle Institute (North Carolina) have developed extensive preclinical data on JDTic, a 4-phenylpiperidine derivative ((3*R*)-7-hydroxy-N-[(2*S*)-1-[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]-3-methylbutan-2-yl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide), which acts as a highly selective and long-lasting kappa antagonist. In the current issue of *Neuropsychopharmacology*, Buda *et al* (2014) report on the first phase I clinical trial results for JDTic, assessing its safety, tolerability, and pharmacokinetics in a double-blind, placebo controlled, randomized trial evaluating single oral doses in healthy adult males.

Subjects were carefully screened to rule out medical disorders (including ECG, physical exam, extensive laboratory tests) and were admitted to the research clinic for 6 days with a follow-up visit (14 days after the dose date) to repeat the assessments. Telemetry, among other safety tests, was performed from admission until 24 h following the dose. Half of the subjects received placebo ($n=6$) and half were dosed with JDTic (1 mg; $n=6$). Overall, the adverse events attributed to JDtic were similar to those reported with placebo, except for cardiac events, such as bradycardia and ventricular tachycardia (VT), which were seen only in the JDTic group. The episodes of VT occurred in two subjects, were not sustained (NSVT), and were asymptomatic. Preclinical experiments in monkeys showed that JDTic administration resulted in a short run of NSVT. Other safety measurements, including clinical laboratory studies, 12-lead ECG, psychomotor function, and measures of mood, did not differ between groups during admission or at follow-up.

Overall, these results indicate that JDTic administration is associated with short lived, but detectable ventricular tachycardia in 2/6 subjects receiving the active dose. The episodes of NSVT were asymptomatic, were not seen in the majority of subjects, and sporadic. NSVT is known to occur in the general population, although at a low rate. Nonetheless, the likelihood that these cardiac events were induced by JDTic is high, given that both events occurred at a similar time following dosing, the low incidence of sporadic VT expected in healthy subjects, and the presence of kappa receptors and dynorphin in cardiac tissue. Given the potentially serious clinical consequences of VT and concerns

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that individuals with cardiovascular disease may have heightened vulnerability, the decision was made by the safety board of this study that further human trials of this drug would not be ethically justified.

The unresolved question though is whether this adverse response is an off-target effect of JDTic, an anomaly of this study, or a general property of KOR antagonists. The authors thoughtfully address this question and cite evidence that dynorphin and KOR are expressed in heart tissue, although their physiological roles are not yet defined. However, the mechanism of this adverse effect is not at all clear. The plasma concentrations of JDTic in this trial were extremely low, and extensive clinical experiences with nonselective KOR antagonists (ie naltrexone and buprenorphine) have rarely observed this adverse effect. As cited in by Buda *et al* (2014), JDTic is not a simple competitive KOR antagonist, but rather activates cJun N terminal kinase (JNK), which is a stress kinase having broad effects on cell physiology. It is not known if JDTic activates JNK in cardiac tissue, but if the adverse events are a consequence of JNK activation, alternative KOR antagonists that do not activate JNK may be safer alternatives. The LY2456302 compound developed by Eli Lilly is an example of a KOR antagonist that does not strongly activate JNK. In a recent phase 1 trial of LY2456302, the authors concluded that the drug was well-tolerated with no clinically significant findings (Lowe *et al*, 2014). Moving forward with KOR antagonists seems justified by their therapeutic potential; however, a better understanding of how JDTic produced its adverse cardiac responses and how to avoid them in future drug development remains a significant challenge.

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