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# Role of the σRs for Development of Medications

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I found that several N-substituted benztropine (BZT) analogs (JHW 007 and AHN 2-005) can dose-dependently decrease self-administration (SA) of stimulants cocaine (Coc) or d- methamphetamine (MA) despite their high affinity and high selectivity for the dopamine transporter (DAT) [1,2]. In addition, the sigma receptor (σR) antagonist rimcazole and its analogs (SH 3-24 and SH 3-28) dose-dependently decrease Coc SA [3]. The antagonist actions of the BZT and rimcazole analogs were quite distinct from the effects of the standard DA uptake inhibitors and other σR antagonists. For example, standard DA uptake inhibitors (WIN 35,428, methylphenidate and nomifensine) dose-dependently shifted the dose-effect curve of Coc SA to the left, suggesting a potentiation of the reinforcing effects of Coc whereas standard σR antagonists (BD 1008, BD 1047, BD 1063, AC 927 and NE 100) were without effects on Coc SA [2-4]. Importantly, the BZT and rimcazole analogs both are more potent in decreasing Coc SA than in decreasing food-maintained behavior [2,3], suggesting selectivity of their effects on Coc SA. Further, a wide range of doses of the BZT and rimcazole analogs failed to maintain responding above vehicle levels when substituted for Coc [2,3,5,6], suggesting little if any abuse liability of their own. The lack of the reinforcing effects of the BZT analogs was also quite distinct from a substantial capacity of the typical DA uptake inhibitors to maintain responding when substituted for Coc [2-4] indicating that these compounds have abuse liability of their own. Finally, studies with *in vitro* radioligand binding assays demonstrated relatively high affinities of the BZT and rimcazole analogs for the DAT as well as to σRs [3,7]. A Subsequent study demonstrated that combinations with typical DA uptake inhibitors and the selective σR antagonists can decrease Coc SA, suggesting dual inhibition at the DAT and σRs as a potential combined target approach for medical treatments for Coc abuse [3]. The published study [3] was chosen as the March 2012 Featured Article on the NIDA-IRP website (http://irp.drugabuse.gov/hotpaperArchive. php), indicative of a substantial interest in this field of research. Thus one of my current research interest is to further explore this "dual inhibition" hypothesis as a target for Coc abuse medications.

The second research interest of mine is an unexpected by-product of the study on "dual σR/DAT inhibitions." In the middle of a previous study, I found a capacity of the σR agonists (DTG and PRE-084) to 1) dose-dependently shift to the left a dose-effect curve for Coc SA and 2) substitute for Coc or d-MA in rats trained to self-administer Coc or d-MA, respectively [1,4]. The discovery of the reinforcing effects of the σR agonists was unexpected because a number of the previous studies generally failed to observe substantial behavioral effects of the σR agonists [8]. Further, a subsequent study demonstrated a sensitivity of reinforcing effects of the σR agonists to pretreatments with the σR antagonists (BD 1008, BD 1047 and BD 1063) [4], suggesting that the reinforcing effects of these drugs were mediated by σRs. In addition, the reinforcing effects of the σR agonists did not occur in naïve subjects and were distinct from those of Coc. For example, Coc SA was dose-dependently antagonized by the selective DA receptor antagonists (SCH 39166 and L-741,626) as expected [9]. In contrast, neither SCH 39166 nor L-741,626 alone or in combinations affected the SA of the σR agonists (DTG and PRE-084, [9], unpublished data). These results suggest a unique reinforcement mechanism that is DA-independent. The lack of the reinforcing effects of the selective σ1R agonists in naïve

subjects were reproduced with (+)-pentazocine. However, the selective σ1R agonists PRE-084 and (+)-pentazocine were reinforcing after acquisition of SA of Coc or d-MA. Finally, an additional study indicated the lack of a Coc-like discriminative-stimulus effects of the σR agonists DTG and PRE-084 in rats [10]. Thus these studies on the σR agonists suggest that stimulants can induce a DA-independent reinforcing mechanism that is mediated by DA independent pathway(s). The published study [4] was chosen as the July 2010 "Hot" paper on the NIDA-IRP website (http://irp.drugabuse.gov/hotpaperArchive.php), indicative of substantial interest in this research. Thus this second research interest is to investigate the DA-independent reinforcing mechanism induced by experience with Coc SA. I believe that these studies will shed light on understanding the mechanisms underlying the intractability of stimulant abuse to pharmacotherapy, and may lead to better medical treatments for stimulant abuse.

The third research interest of mine is to determine the role of specific receptors in food reinforcement mechanisms with behavioral economic mathematical models in genetically engineered animals. I have previously focused on DA receptor subtypes in collaboration with Drs. Katz and Soto (Johns Hopkins University). Some of these results were previously published [11]. Future studies will focus on cannabinoid systems and CB1 receptors using genetically engineered knockout and wildtype littermates. The cannabinoid CB1 receptors are one of the most abundant receptors in the brain. In addition, the cannabinoid CB1 receptors are implicated in a number of psychiatric diseases including a substance abuse. If these studies indicate a substantial role of CB1 receptors in the reinforcing effects of food, subsequent studies will confirm that role using conditional knockouts and RNA silencing (post-transcriptional gene silencing). On the other hand, a previous study that the σR antagonists generally are more potent in decreasing responding maintained by food presentation than in decreasing responding maintained by Coc injections [4]. However, effects of the σR ligands on operant behavior have not been well characterized.

σ1Rs are intracellular chaperone proteins that translocate from their primary endoplasmic reticulum localization to different subcellular compartments upon agonist actions, and regulate ion channels and G-protein-coupled-receptor signaling [12-14]. In fact, reports have implicated σ1Rs in various biological functions, and drugs acting at these receptors have been studied for therapeutic effects in psychiatric disorders including substance abuse, depression and dementia [8,15].

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Thus investigating role of the σRs should be an avenue for development of medications for a wide range of diseases.

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