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Review

# Tribute to: Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area [William Corrigall, Kathleen Coen and Laurel Adamson, Brain Res. 653 (1994) 278–284]

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ABSTRACT

In this paper, Dr. Corrigall and collaborators described elegant experiments designed to elucidate the neurobiology of nicotine reinforcement. The nicotinic receptor antagonist dihydro-β-erythroidine (DHβE) was infused in the ventral tegmental area (VTA) or nucleus accumbens (NAC) of rats trained to self-administer nicotine intravenously. Additionally, DHβE was infused in the VTA of rats trained to self-administer food or cocaine, and nicotine self-administration was assessed in rats with lesions to the peduculopontine tegmental nucleus (PPT).

A number of key themes emerged from this fundamental study that remain relevant today. The primary finding was that infusions of DHβE in the VTA, but not in the NAC, lowered nicotine self-administration, suggesting that nicotinic receptors in VTA are involved in the reinforcing action of nicotine. This conclusion has been confirmed by subsequent findings, and the nature of the nicotinic receptors has also been elucidated. The authors also reported that DHβE in the VTA had no effect on food or cocaine self-administration, and that lesions to the PPT did not alter nicotine self-administration. Since this initial investigation, the question of whether nicotinic receptors in the VTA are necessary for the reinforcing action of other stimuli, and by which mechanisms, has been extensively explored. Similarly, many groups have further investigated the role of mesopontine cholinergic nuclei in reinforcement.

This paper not only contributed in important ways to our understanding of the neurochemical basis of nicotine reinforcement, but was also a key catalyst that gave rise to several research themes central to the neuropharmacology of substance abuse.

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**Contents**



*Microinfusions of the nicotinic antagonist dihydro-ß-erythroidine (DHßE) were used to examine the role of the mesolimbic dopamine system in nicotine reinforcement in rats. Infusions of DHßE into the ventral tegmental area (VTA) prior to the start of i.v. nicotine self-administration sessions resulted in a significant decrease in the number of nicotine infusions voluntarily obtained. In contrast, the same doses of DHßE infused into the nucleus accumbens were without effect on nicotine self-administration. The reductions caused by DHßE were specific to nicotine reinforcement; neither operant responding maintained by food, cocaine self-administration, or spontaneous locomotor activity were altered by local applications of DHßE within the VTA. The reduction in nicotine self-administration following treatment in the VTA was also specific to the nicotinic antagonist, and was not duplicated by infusions of the muscarinic antagonist atropine. Partial lesions of the pedunculopontine tegmental nucleus, the likely origin of cholinergic fibers to the VTA, were without*

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*effect on nicotine self-administration, suggesting that the effects of DHßE were not due to disruption of a tonically active cholinergic input to the VTA from this source. These data show that nicotine acts within the VTA region to initiate processes which are critical to the reinforcing properties of the drug. © 1994. William Corrigall, Kathleen Coen and Laurel Adamson. Brain Research (1994), 653: 278-284*

This paper describes the results of elegant experiments designed to elucidate the neurobiology of nicotine reinforcement and involvement of the mesolimbic dopamine system in the reinforcing action of drugs of abuse. In many ways, this paper was a key catalyst that gave rise to several research themes central to the neuropharmacology of substance abuse. It is probably because of this wide scientific impact that the paper has been cited a total of 469 times since its publication in 1994.

Dr. Corrigall and collaborators investigated the hypothesis that the reinforcing effect of nicotine is mediated by its action on the mesolimbic dopamine system. This hypothesis was formulated on the basis of four main lines of pre-existing evidence. First, it was known that dopamine antagonists (Corrigall and Coen, 1991) and lesions to ascending mesolimbic projections (Corrigall et al., 1992) could reduce nicotine self-administration. Second, nicotinic receptors were localized in both the ventral tegmental area (VTA) and in the nucleus accumbens (NAC) (Clarke and Pert, 1985; Swanson et al., 1987), and the was electrophysiological (Calabresi et al., 1989; Lichtensteiger et al., 1982) and neurochemical (Imperato et al., 1986; Izenwasser et al., 1991; Mifsud et al., 1989) evidence of nicotine-induced activation of the mesolimbic dopamine system. Finally, it was known that nicotine could stimulate locomotion activity when administered directly in the VTA (Museo and Wise, 1990; Reavill and Stolerman, 1990).

In this context, Dr. Corrigall and collaborators explored whether the reinforcing effect of nicotine is mediated by actions on VTA cell bodies, on NAC terminal fields, or both. Thus, the nicotinic receptor antagonist dihydro-β-erythroidine (DHβE) was infused in the VTA and NAC of rats trained to self-administer nicotine intravenously. Additionally, in order to interpret the findings, the authors infused DHβE in the VTA of rats trained to self-administer food or cocaine, and tested nicotine self-administration in rats with ibotenic lesions to the peduculopontine tegmental nucleus (PPT). This region was selected because of its established role in the reinforcing and stimulatory actions of stimulants and opiates (Bechara and van der Kooy, 1992, 1989), and because it provides cholinergic innervations to the VTA (Clarke et al., 1987; Rye et al., 1987; Sugimoto and Hattori, 1984).

A number of key themes emerged from this fundamental study that remain relevant today. The 20 years following this study saw the emergence of intense research on the behavioral neuropharmacology of nicotine reinforcement and the role of mesopontine cholinergic systems in reinforcement. Below are themes spawned by the ideas presented by the authors.

The primary finding was that infusions of DHβE in the VTA, but not in the NAC, lowered nicotine self-administration. However, with many drugs of abuse self-administered on fixed-ratio schedules, decreasing the reinforcing value of each infusion (by decreasing the unit dose, for example), typically results in an increase in infusions obtained. Therefore, acknowledging the possible ambiguity of the DHβE effect in the VTA, the authors noted that for nicotine, there is an inverted-U function relating nicotine dose to self-administration, with maximal rates of responding occurring at a narrow range of intermediate doses (Rose and Corrigall, 1997). Importantly, if the dose within this range is changed, there is not much change in responding (Corrigall, 2001), and when the dose is decreased, compensatory increases in responding do not seem to occur (Corrigall and Coen, 1991; Corrigall et al., 1992). Hence, the authors concluded that the effect of DHβE in the VTA likely reflected an interference with the local action of nicotine leading to reduced reinforcing efficacy.

This conclusion has been supported by a number of subsequent findings. For example, it has been demonstrated that rats will self-administer the cholinergic agonist carbachol directly in the posterior portion of the ventral tegmental area, and that this behavior is attenuated by local infusions of DHβE (Ikemoto and Wise, 2002). Similarly, mice can learn to self-administer nicotine directly in the VTA, and this is disrupted by intra-VTA administration of DhβE (David et al., 2006).

As well, the nature of the nicotinic receptors in the VTA has been elucidated. Hence, in mice lacking the β2 subunit of the nicotine receptor, nicotine self-administration is attenuated, and nicotine fails to stimulates dopamine release in the ventral striatum (Picciotto et al., 1998). In these animals, lentiviral re-expression of the β2 subunit in the VTA normalizes nicotine self-administration (Orejarena et al., 2012). In addition, it has been determined that α4β2- and α6β2-subunit containing nicotinic receptors in cell bodies/axons of the VTA are necessary and sufficient for systemic (Pons et al., 2008) and intra-VTA nicotine (Exley et al., 2011) self-administration, as well as nicotine-induced motor stimulation (Gotti et al., 2010).

This said, the peculiarities of intravenous nicotine self-administration in animals are still not fully understood. More specifically, it has been shown that when a progressive ratio schedule is employed, an increase in break-point with increases in nicotine dose can be observed (Donny et al., 1999). However, there are several examples of divergent findings when comparing nicotine self-administration on fixed and progressive ratio schedules (Coen et al., 2009). For example, bupropion decreases the reinforcing properties of nicotine measured by a fixed-ratio schedule, but it has no apparent effect on breaking points for nicotine self-administration on a progressive ratio (Bruijnzeel and Markou, 2003).

Another important issue addressed by Dr. Corrigall and collaborators was whether DHβE in the VTA antagonized the direct action of nicotine on local cells, or an action of acetylcholine released in the same region as a result of an effect of nicotine in other regions of the brain. The authors presented two lines of evidence in support of the former mechanism: first, DHβE in the VTA had no effect on food or cocaine self-administration; and second, ibotenic lesions to the PPT did not alter nicotine self-administration. Since this initial investigation, the question of whether nicotinic receptors in the VTA are necessary for the reinforcing action of other stimuli, and by which mechanisms, has been extensively explored. Similarly, many groups have investigated the role of PPT in drug-induced reinforcement using a variety of methods and procedures.

Thus, it is now recognized that mid-brain DA neurons exhibit two distinguishable rhythms of firing – a tonic mode and a phasic mode characterized by a bursting activity (Grace and Bunney, 1984a, 1984b) – and that the diversity in properties and location of nicotinic receptor subtypes plays a critical role in these rhythms (Faure et al., 2014). For example, the bursting pattern is dependent on cholinergic, glutamatergic and gamma-aminobutyric-acid-releasing projections coming from the PPT and the laterodorsal tegmental nucleus (LDTg; Grace et al., 2007). It is believed that these mesopontine nuclei act as a form of gait control that allows DA neurons to burst in response to excitatory glutamatergic inputs. Importantly, nicotinic receptors modulate DA cell activity and DA release according to their location on glutamatergic, cholinergic and GABAergic afferents of the VTA DA neurons (Dani and Bertrand, 2007; Grady et al., 2007; Klink et al., 2001).

This has important implications for the results of Dr. Corrigal and collaborators because nicotine-induced activation of DA neurons can be due to direct excitation of the DA cells, modifications of presynaptic terminals onto the soma of DA neurons, and/or disinhibition of the DA cells (Changeux et al., 1998; Dani and