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Perspective

Individual Variations in the Mechanisms of Nicotine Seeking: A Key for Research on Nicotine Dependence

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Tobacco users are estimated to be at least 1.1 billion worldwide. Although tobacco dependence is not associated with obvious behavioral disruptions, alleviating it is a major public health concern and a main societal challenge, as it produces severe long-lasting health-related problems, leading to 6 million deaths every year. Available therapies for smoking cessation have limited efficacy, warranting the need for developing better therapeutic strategies, which depend on understanding the mechanisms that underlie tobacco dependence, in which nicotine is considered to have a central role.

The relevance of preclinical animal models to nicotine dependence is questioned because their predictive validity is considered poor (Hong *et al*, 2010). In spite of this, preclinical animal models of nicotine seeking have been proved useful, as they have helped in understanding the mechanisms underlying nicotine seeking. These models, in line with clinical studies, have consistently demonstrated that both pharmacological factors (PF) and non-pharmacological factors (NPF) promote nicotine seeking and have helped identify underlying neurobiological mechanisms (Stoker and Markou, 2015).

Increasing psychological, genetic, and neurobiological data support the notion that the contribution of PF and NPF to nicotine seeking differ from smoker to smoker, thus possibly contributing to the observed heterogeneity in the population of smokers (Hiroi and Scott, 2009). It could also contribute to the incongruence between the multiple diagnosis tools, the inconsistent relationship between craving and smoking cessation outcome, and the limited predictive validity of animal models. This might also eventually reduce our ability to identify relevant therapeutic targets for smoking cessation (Potvin *et al*, 2015).

For instance, a single-nucleotide polymorphism of the *CHRNA5* gene has been associated with heavy smoking, which appears to be caused by a lowered sensitivity to the aversive effects of nicotine (Fowler and Kenny, 2014). In smokers who carry this CHRNA5 risk allele, compared with noncarriers, nicotine seeking through PF is increased, namely through withdrawal avoidance, whereas susceptibility to NPF, in particular cue-induced craving (Janes *et al*, 2012), is decreased. This supports the notion that the two types of factors (PF/NPF) can vary independently. Fast nicotine metabolism is another risk factor for heavy smoking and low cessation rates (Mamoun *et al*, 2015). Fast nicotine metabolizers are more sensitive to withdrawal than their slow metabolizer counterparts, but differently from the CHRNA5 case, they are also more responsive to drug cues (Falcone *et al*, 2016); a difference possibly due to their specific nicotine pharmacodynamics that might favor cue conditioning. Altogether, specific combinations of risk and protective factors, like these and many others, will determine the individual mechanisms underlying nicotine seeking.

We propose that the predictive validity of animal models might increase by taking into account these individual variations. This implies determining, within the same individuals, the influence of both PF and NPF in the control of nicotine seeking, and evaluating how individual psychobiological factors and length of nicotine exposure (early *vs* late nicotine use) affect this balance (Figure 1).

The exploration of individual differences in nicotine self-administration is at a very early stage. A recent exhaustive review by Falco and Bevins (2015) on individual differences in the behavioral effects of nicotine refers to only four self-administration studies that investigated the relationships between impulsivity-related psychobehavioral traits and nicotine self-administration. However, even this very limited body of research has produced inconsistent results and has yet to identify underlying mechanisms of nicotine seeking.

Now important conditions are met for investigating individual variations in nicotine seeking. Over the last 15 years, tremendous progress has been made in modeling nicotine taking in rodents using intravenous self-administration. Newer developments include the exploration of alternative routes of administration (Cohen and George, 2013) or even self-administration (www.simply-lab.com) (ie, vapor inhalation), as well as the influence of social factors on nicotine taking (Wang *et al*, 2014). Thanks to these models,

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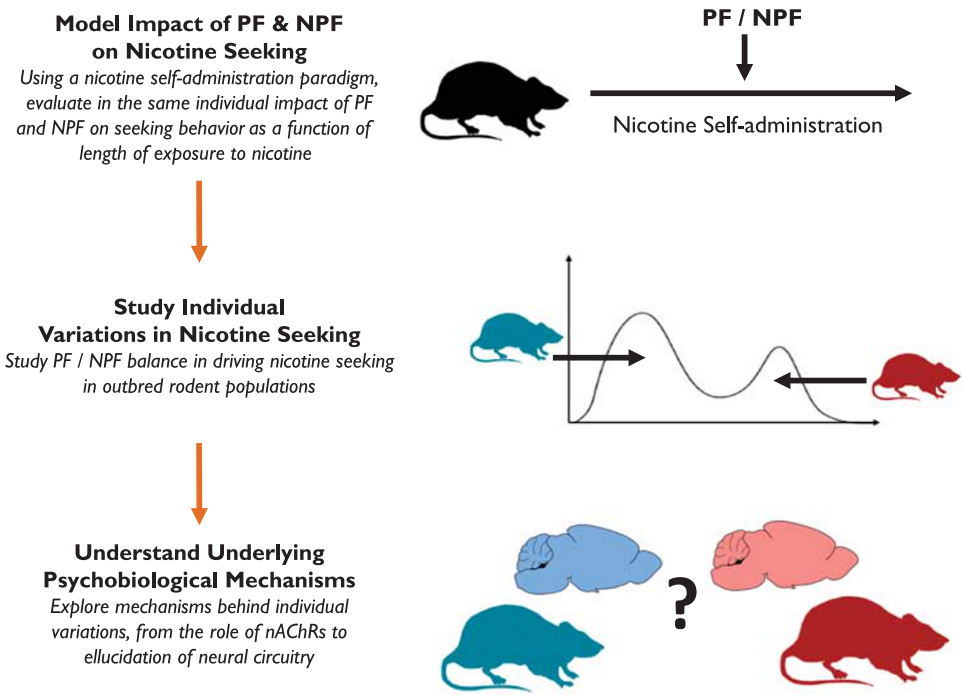

Figure 1 Individual-based approach for the mechanisms of nicotine seeking. We propose a three-level strategy for an individual-based animal model of nicotine seeking: (1) modeling, in the same individuals, and as a function of duration of nicotine self-administration, the impact of pharmacological factors (PF) and non-pharmacological factors (NPF) on nicotine seeking; (2) exploring individual variations in the balance between PF and NPF in the control of nicotine seeking, based on such a model, and (3) exploring the underlying psychobiological mechanisms of these individual differences, from a circuitry down to a molecular level, using complementary tools and approaches, such as outbred rodents characterized for personality traits associated with risk for nicotine dependence (impulsivity, novelty seeking and so on), genetically-manipulated rodents with altered expression of specific nAChR subtypes, or reproducing human allelic variations in nAChR subtypes associated with increased risk for nicotine dependence, and tools such as opto- and chemogenetics, viral tracing techniques, and brain calcium imaging in freely behaving rodents that allow for precise investigations of neural circuit function, including those relevant to nicotine seeking.

key information has been collected on the control of nicotine seeking by PF and notably NPF, thanks to the seminal work of Anthony Caggiula and Eric Donny (Pittsburgh University, USA) on the complex control of nicotine seeking by conditioned factors. Also significant, investigating the mechanisms by which nicotine alters contextual learning, Thomas J Gould and colleagues (Temple University, Philadelphia, USA) have contributed to the current view on how nicotine withdrawal might promote seeking through cognitive impairments and negative affective state.

Over the same time period, new mouse genetic models have been developed to reproduce human allelic variations in nAChR subtypes associated with increased risk for nicotine dependence (Morel *et al*, 2014). Furthermore, newer experimental tools, such as opto- and chemogenetics, viral tracing techniques, and brain calcium imaging in freely behaving rodents allow for precise investigations of neural circuit function, including those relevant to nicotine seeking. Personality traits, like reactivity to novelty, anxiety, and impulsivity, associated with increased risk for nicotine dependence in humans, are now also well characterized in rodents, providing the opportunity to study their role in nicotine seeking.

More recently, two promising studies support the notion that consistent individual differences in the reinforcing and incentive effects of nicotine can be observed. In an outbred strain of rats, Grebenstein *et al* (2015) reported individual variations in nicotine self-administration. Superficially, the nicotine reinforcement threshold and degree of compensation when decreasing nicotine dose were predicted by nicotine clearance, suggesting that nicotine seeking might be controlled by PF in some individuals, and less so in others, through biochemical differences affecting pharmacokinetics. Echoing the fast/slow metabolizer phenotypes in humans, the observations of Grebenstein *et al* (2015) offer interesting perspectives for studying the PF *vs* NPF balance in controlling nicotine seeking by identifying individual differences in nicotine metabolism.

In search for the mechanisms of individual vulnerability to cocaine or opioid addiction, sophisticated procedures have been developed to investigate psychobehavioral factors such as attribution of incentive salience to drug cues that might influence drug seeking. In the so-called sign trackers rats (STs), food- or drug- (cocaine, opioid) associated discrete cues are both more attractive (elicit approach) and more wanted (are conditioned reinforcers) than in goal trackers rats (GTs), in which presentation of reward-associated cues elicits approach to the location of reward delivery. For nicotine, Yager and Robinson (2015) showed that if STs rats want more a nicotine-associated cue, they approach a nicotine cue similarly to GTs, demonstrating nicotine-specific mechanisms of salience attribution. This model not only opens perspectives for the study of the mechanisms of salience attribution in general, but offers the opportunity to

study the control of nicotine seeking by NPF and PF as a function of individual differences in salience attribution to nicotine cues.

CONCLUSION

Tobacco use is the net balance between factors promoting smoking maintenance ('seeking mechanisms') and factors promoting smoking cessation ('motivation to stop'). Even if capturing motivation to stop is a challenge in animal models, they allow exploring mechanisms promoting nicotine seeking and taking.

Data support that individual variations in the mechanisms of nicotine seeking contribute to the heterogeneity of the population of tobacco smokers and may explain in part the limited efficacy of current therapeutic strategies for smoking cessation. Conditions are met to study these individual variations and identify their underlying neurobiological mechanisms using preclinical models in rodents. This strategy could increase our ability to develop individual-based therapeutic strategies for tobacco dependence.

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The authors declare no conflict of interest.

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