

# Cell adhesion signaling pathways

## First responders to cocaine exposure?

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**Abbreviations:** Abl, abelson; Arg, abelson-related gene; Arp2/3, actin-related proteins 2/3; BDNF, brain-derived neurotrophic factor; Cdk5, cyclin-dependent kinase 5; D1, dopamine receptor type 1; D2, dopamine receptor type 2; DARPP32, dopamine and cAMP-regulated phosphoprotein 32; F-actin, filamentous actin; PSD95, post-synaptic density 95; ROCK, Rho kinase; Rho, RhoA GTPase; trkB, tyrosine receptor kinase B

The 100 billion neurons comprising the human brain are wired together using structural extensions termed axons, dendrites and dendritic spines. Addictive drugs remodel dendritic spine structure in certain brain regions and with repeated exposure, induce psychomotor sensitization and impair behavioral flexibility. We recently reported that low-dose cocaine exposure, in combination with knockout of Arg—an adhesion-regulated nonreceptor tyrosine kinase that stabilizes neuronal shape starting in adolescence—recapitulates both features of chronic drug exposure in rodents. In light of these and other recent findings in the field, we suggest that cell adhesion receptors and their downstream cytoskeletal effectors act as “first responders” to psychostimulant exposure. In this model, cell adhesion factors act to stabilize existing dendritic spines in response to cocaine, and reduced expression/function is expected to increase vulnerability. Moreover, this model anticipates that increased sensitivity to psychostimulants in adolescence relates to neuronal pruning processes that occur during this developmental period.

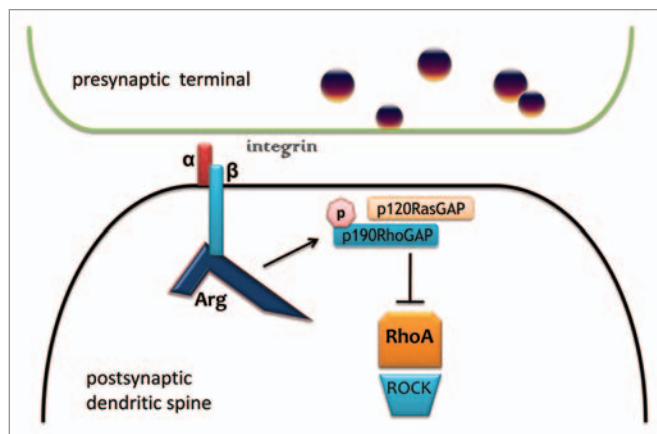
Growth factor and adhesion receptors direct changes in cell shape and movement by acting on downstream intracellular signaling cascades that coordinate cytoskeletal dynamics. For example, integrin-mediated adhesion activates Abl family kinases to regulate cell shape and motility in several physiological contexts: fibroblast migration, breast cancer invasiveness, neuronal outgrowth and branching, and synapse and dendrite stability in the adult brain.<sup>1</sup> In primary pyramidal neurons and other cell types, Abelson-related gene (Arg) phosphorylates p190RhoGAP in a signaling cascade that ultimately results in the inhibition of the RhoA (Rho) GTPase, a master regulator of cytoskeletal rearrangement (Fig. 1).<sup>2-5</sup> Rho activation induces neurite retraction, a process required for pruning and refining neuronal connections during development,<sup>6</sup> but inappropriate Rho activation

in mature neurons leads to synapse loss and dendritic regression. Thus, integrin:Arg interactions stabilize existing synapses and the dendritic spines that house them.

Spine morphology is regulated by intrinsic biological processes, as in the case of dendritic spine pruning during post-natal development,<sup>7</sup> and external environmental stimuli such as exposure to addictive psychostimulants.<sup>8,9</sup> In the ventral striatum, acute cocaine robustly increases spine density, corresponding with increased expression of PSD95, a postsynaptic marker, and the Arp3 subunit of the Arp2/3 complex, which promotes nucleation of new F-actin branches.<sup>10</sup> This early immediate spinogenic response to cocaine appears to constitute an acute burst in spines, while chronic cocaine exposure accelerates spine clearance and turnover, increasing cofilin expression, which promotes F-actin disassembly.<sup>10,11</sup> Infusion of latrunculin A, a neurotoxin that results in F-actin depolymerization and spine collapse, potentiates cue-induced reinstatement, an animal model of relapse,<sup>12</sup> and blocking cocaine-induced spinogenesis using more subtle manipulations potentiates psychomotor sensitization to cocaine,<sup>13,14</sup> suggesting initial cocaine-elicited striatal spine growth, as occurs early in drug exposure, protects against vulnerability to repeated drug exposure (review in ref. 15).

We recently reported exaggerated psychomotor and other sensitivities to cocaine in *arg* knockout mice, which have pre-existing spine density and stability deficits.<sup>5,16</sup> Our findings in these Arg-deficient mice—particularly exaggerated psychomotor sensitivity to cocaine, recapitulated in Figure 2A—can be interpreted as indicating that pre-existing spine deficiency results in mice that are “pre-sensitized,” and thus more vulnerable to repeated cocaine exposure and to developing reward-seeking behavior.<sup>17-20</sup> An additional possibility is that cocaine sensitivity is enhanced in *arg*<sup>-/-</sup> mice because these animals lack a major player—Arg kinase—in the signaling cascades that would otherwise act to stabilize existing spines (via integrin-mediated adhesion) in response to cocaine. In support of this possibility, acute cocaine increases  $\beta$ 1-integrin expression (a likely upstream Arg regulator) and decreases Rho activity (a downstream Arg effector) in the ventral striatum<sup>21,22</sup>—both responses would be expected to stabilize existing dendritic spines in response to cocaine and may

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**Figure 1.** Arg interacts with  $\beta$ -integrin tails and p190RhoGAP to stabilize synapses, spines and dendrites. Arg is activated through a physical interaction with intracellular  $\beta$ -integrin tails, which allows for p190RhoGAP phosphorylation and recruitment to the membrane by p120RasGAP. This complex inhibits RhoA GTPase activity. In the absence of RhoA inhibition, RhoA acts on ROCK to destabilize the actin cytoskeleton, leading to spine and dendrite collapse and synapse loss. Conversely, ROCK inhibition elongates dendritic branches.<sup>47</sup>

in fact act in the same pathway, with Arg:p190RhoGAP interactions functioning as the intermediary between the two (see Fig. 1). In the absence of Arg and related cytoskeletal regulatory factors, the cellular response to repeated cocaine would be biased towards spine clearance and, as we have shown, exaggerated behavioral sensitivity on multiple measures. Thus, emerging evidence, including ours, suggests spine stability may have protective properties in the face of repeated drug exposure.

The serine/threonine kinase Cdk5 has been widely regarded as a regulator of cocaine sensitivity since its original identification as a DARPP32 binding partner.<sup>23</sup> As with Arg deficiency, Cdk5 inhibition or forebrain deficiency promotes psychomotor sensitization to cocaine<sup>23–25</sup> and also blunts acute cocaine-induced striatal spinogenesis.<sup>26</sup> Recent evidence indicates that, like Arg, Cdk5 acts via a p190RhoGAP-Rho-ROCK cascade, in this case mediated by Src, such that Cdk5 inhibition promotes cytoskeletal reorganization.<sup>27</sup> Thus, as we hypothesize with Arg, cocaine-mediated activation of Cdk5<sup>23</sup> may brake psychomotor sensitization by stabilizing existing spines against repeated cocaine exposure.

The majority of studies regarding mechanisms of psychostimulant-induced spine reorganization have been conducted using ventral striatal tissue extracts or microinfusion, but psychostimulant-induced spine reorganization is documented in several brain regions, including orbital subregions of the prefrontal cortex.<sup>28</sup> Human neuroimaging studies document prefrontal hypofunction,<sup>29–32</sup> poor impulse control and behavioral inflexibility<sup>33</sup> in cocaine addicts. In monkeys, diminished glucose utilization in the orbital cortex is associated with both early and late phases of cocaine self-administration,<sup>34,35</sup> as well as noncontingent drug administration.<sup>36</sup> These and other findings support the view that atrophy of so-called “inhibitory control” processes mediated by the prefrontal cortex and associated limbic-striatal circuits

are both characteristic of addiction and promote further drug use.<sup>37,38</sup> Inability of animals to mount an immediate cell adhesive/cytoskeletal response to cocaine to either maintain existing spines or generate new spines in specific regions may exacerbate this cyclical decline.

Using an instrumental “reversal learning” task in which mice must shift responding from a previously reinforced aperture to a newly reinforced aperture within an operant conditioning chamber, we tested this hypothesis and found that drug-naïve *arg*<sup>-/-</sup> mice showed modest deficits in reversal (recapitulated in Fig. 2A, left), consistent with the effects of orbitofrontal lesions in mice performing the same task.<sup>39</sup> *arg*<sup>-/-</sup> mice could, however, acquire the reversed contingency over time, such that the number of errors was indistinguishable from wild type (wt) levels for a given reversal (Fig. 2B, middle). High-dose psychostimulant exposure impairs performance on similar reversal tasks,<sup>40–42</sup> but we administered subthreshold concentrations of cocaine to wt and *arg*<sup>-/-</sup> mice, such that wt mice were unaffected. *arg*<sup>-/-</sup> mice were, by contrast, vulnerable, executing >4-fold more errors a full week after the last cocaine exposure.<sup>16</sup> These findings, recapitulated here in Figure 2B at right, provide some of the first evidence that spine instability and cocaine exposure have synergistic consequences for inhibitory control processes.

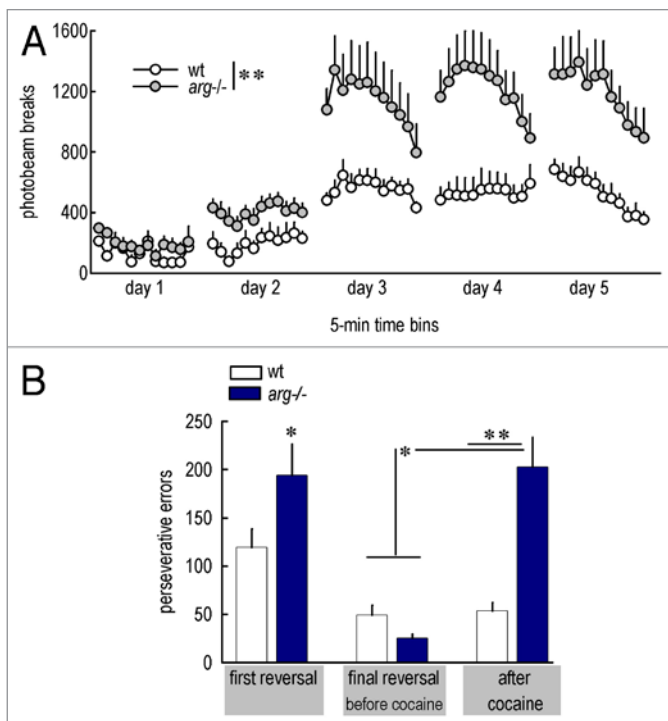
As discussed above, previous studies indicate that Arg acts as part of a Rho inhibitory pathway in the brain to mitigate synapse and spine pruning processes during post-natal development, allowing for the maintenance of dendritic arbors throughout the adult life of the animal. Disruption of this pathway via the loss of Arg increases Rho activity, leading to a loss of synapses and branch points in the cortex<sup>3</sup> and hippocampus<sup>5</sup> first detectable in early adolescence. Also during early adolescence, the neurotrophin Brain-derived Neurotrophic Factor (BDNF) stimulates growth of cortical neurons by enhancing the rate of dynamic branch motility,<sup>43,44</sup> and the loss of BDNF signaling through its high-affinity trkB receptor results in cortical dendrite arbor shrinkage after postnatal day 3.<sup>45,46</sup> Like Arg, BDNF is thus critical for the outgrowth and maintenance of neurons in the transition from prenatal development to adulthood, and like *arg*<sup>-/-</sup> mice, *bdnf*<sup>-/-</sup> mice show heightened sensitivity to food reward as adults, which can be rescued by replacing BDNF in the orbitofrontal cortex (Gourley and Taylor, unpublished). Obviously, BDNF and Arg differ in certain ways—for example, acute activity-dependent BDNF release stimulates dendritic growth but destabilizes spines,<sup>43,44</sup> presumably allowing for the growth of new spines, whereas Arg appears to primarily act as a stabilizing factor for both dendrites and spines. Nonetheless, these and other findings point to the orbital cortex in particular as a site at which disruptions in adolescent cortical development via multiple molecular targets may manifest in adulthood as hypersensitivity to reward.

These findings imply that pharmacological agents that promote cell adhesion or growth factor signaling may be effective pharmacological adjuncts to cognitive-behavioral therapies for addiction and other diseases in which cytoskeletal abnormalities are thought to play causal or contributing roles. Towards this goal, the ROCK inhibitor, fasudil, was recently shown to

increase dendritic length during the prodromal period in a mouse model of Alzheimer's Disease (see again Fig. 1).<sup>47</sup> This compound is clinically approved in Japan to treat cerebral vasospasm,<sup>48</sup> suggesting it could be safely adopted as a treatment adjunct in addiction. One caveat, however, is that manipulation of putative targets may be expected to have site- or cell type-selective effects that could complicate the development of novel pharmacotherapies. For example, while orbitofrontal BDNF deficiency appears to confer hyper-sensitivity to appetitive reward in the context of instrumental responding for food (as described above) or in terms of passive consumption of palatable foods,<sup>49</sup> selective gene knockdown in dorsomedial prefrontal subregions has the opposite effects.<sup>50</sup> These subregions supply the striatum with BDNF via anterograde transport,<sup>51</sup> and recent studies indicate that BDNF plays unique and specific roles in the postnatal growth, development and maturation of striatal neurons.<sup>52</sup> Moreover, BDNF-mediated cocaine sensitivity appears to be differentially affected by the activation of dopamine D1- relative to D2-containing cells, which are largely segregated in striatal systems.<sup>53</sup> This profile may account for evidence that BDNF expression and signaling within the striatum promotes—rather than brakes, as in the case of Arg—psychomotor sensitization to cocaine.<sup>54</sup>

A role for cell adhesion and growth factor signaling in acute reactivity, and subsequent vulnerability, to cocaine is still being established, but what our previous report,<sup>16</sup> as well as others,<sup>12-14</sup> suggest is that disturbances in the processes that act to stabilize synapses, spines and dendritic arbor engender vulnerability to both the rewarding and deleterious properties of repeated psychostimulant exposure. That *arg*<sup>-/-</sup> mice also lack sensitivity to haloperidol on orbitofrontal-dependent behavioral tasks raises the possibility that adolescent-onset vulnerabilities relate to frontal dopamine D2 receptor expression patterns.<sup>16</sup> These findings also have implications for efficacy of antipsychotic drugs acting on the dopamine system, as neuroplasticity within the orbital cortex may be associated with therapeutic-like outcomes.<sup>55</sup>

The median age of first illicit drug use among psychostimulant addicts is 16 years, with few adult addicts having first administered their drug of choice after the age of 20.<sup>56</sup> Given that cortical development culminates during these adolescent and peri-adolescent periods, further characterization of the molecular mechanisms that regulate cortical neuronal shape and complexity and their impact upon sensitivity to drugs of abuse may provide a significant advance towards a more comprehensive view of the cyclical behavioral patterns that characterize addiction, as well as insight into early intervention techniques and pharmacotherapies.



**Figure 2.** Arg deficiency confers vulnerability to cocaine and cocaine-induced deficits in a reversal task. (A) Arg-deficient mice show heightened psychomotor sensitivity to cocaine, as indicated by greater photobeams broken in a locomotor monitoring apparatus after low-dose (10 mg/kg, i.p.) cocaine administered across several days. Locomotor activity in the absence of cocaine is unchanged (not shown; <sup>5,16</sup>). Because repeated breaking of the same photobeam constituted the largest difference between wt and *arg*<sup>-/-</sup> mice, these specific counts (suggestive of stereotypy) are shown here. (B) During a reversal test in which mice must redirect responding from a previously reinforced operant aperture to a previously non-reinforced aperture, *arg*<sup>-/-</sup> mice initially generate more “perseverative” errors than wild type (wt) counterparts (left), consistent with cortical dendritic simplification in these mice. *arg*<sup>-/-</sup> mice acquired the reversal with repeated training (middle), but repeated exposure to low-dose cocaine greatly exacerbated perseverative errors (right), despite a prolonged washout period prior to test. \**p* ≤ 0.05; \*\**p* < 0.001.

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