because neovascularization is crucial to tumor growth and rheumatoid arthritis progression. Could elevated levels of angiogenic markers such VEGF be a marker of hemophilic arthropathy? Nonetheless, despite the promise of this investigation, the exact mechanism underlying hemophilic joint disease remains unknown and although the contributions of iron deposition, inflammatory cell recruitment, and cytokine/growth factor production to hemophilic joint disease have individually been demonstrated, no linchpin for this process has been demonstrated. Collection of cytokine and growth factor samples from subjects on prophylaxis and with joint disease should be considered as a first step to more clearly define the etiology of hemophilic arthropathy. Until more data are obtained, VEGF and other angiogenic mediators remain a cog in this complicated pathway.

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VASCULAR BIOLOGY

Comment on Yao et al, page 2538

Cocaine and the blood-brain-barrier

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Cocaine is one of the most abused street drugs; according to the National Survey on Drug Abuse, 15% of Americans have used cocaine at least once in their lifetime. Cocaine has been shown to alter behavior and mood, causing feelings of euphoria. One of the most damaging effects of cocaine abuse is that it compromises judgment capacity leading to risky sexual behavior, thereby increasing chances of contracting HIV infection.

In this issue of *Blood*, Yao et al present evidence that cocaine alters blood-brain-barrier (BBB) permeability via a mediator: platelet-derived growth factor (PDGF).[1] Previously, it has been reported that cocaine as well as HIV can down-regulate tight junction proteins.[2-4] It is well established that blood microvascular endothelial cells structurally and functionally control the BBB; this report now shows that cocaine—via binding to its cognate σ receptors—elicits a signaling cascade, leading to the induction of PDGF-B chain which is a key mediator of increased endothelial permeability. Yao and colleagues show that the activation of mitogen-activated protein kinase and transcription factor (Egr1) pathways lead to an activation of increased expression of PDGF-BB. Earlier studies have also shown that the Egr-1 pathway is involved in neuronal plasticity and may possibly be involved in regulating apoptosis via the phosphatase and tensin homolog pathway.[5,6] The findings in the present report were further validated in mice pretreated with anti–PDGF-BB neutralizing antibodies. This treatment led to abrogation of subsequent possible cocaine-mediated induction of permeability.

The findings in this report have significant implications for our understanding of molecular mechanisms leading to leaky vessels in the brain. A synergistic action of cocaine and HIV-1, as shown by Yao et al, will go a long way to explaining an accelerated neuroprogression of HIV-1 infection among cocaine abusers. Moreover, these findings are important in opening newer avenues in our understanding of cocaine-mediated functions in the central nervous system. Despite combined anti-retroviral therapy, HIV-associated neurocognitive disorders (HAND) continue to afflict approximately 60% HIV-infected individuals, most likely because of partial or complete inability of antiretroviral drugs to go across the BBB. The findings in this report may lead to initiatives seeking alternatives to treat HAND and the development of novel interventions, as well as continuation of the search for methods of reversing cocaine-mediated increased permeability. It will also be of great interest to investigate whether cocaine-induced increased permeability can be reversed by stopping cocaine addiction. Moreover, recent reports suggest that gold nanoparticles can inhibit microvascular endothelial growth factor–induced vascular permeability in retinal endothelial cells.[7] Although the mode of action of gold nanoparticles in retinal endothelial cells may follow a different pathway, such studies need to be carried out if similar phenomenon can occur in the brain microvasculature.

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2011 117: 2303
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