Intranasal delivery to the brain

To the Editor:

In his News Feature published in the February issue, Michael Eisenstein outlines several alternative methods of drug delivery[1] and discusses how several targets in the central nervous system "remain difficult to reach, and the brain presents a particular challenge." Although I agree with Eisenstein that successfully crossing the blood-brain barrier (BBB) after infusion is a substantial hurdle for many biologic therapeutics, particularly as "the mechanism underlying this BBB penetration is poorly understood," I would like to alert readers to a simple and direct approach for delivering drugs into the brain that was not mentioned in the article: intranasal drug delivery[2,3].

The use of intranasal delivery to mediate the local, intranasal effects of adrenocorticosteroids and antihistamines has been well documented. But this approach can also exert systemic effects. The nasal mucosal surface has been considered a 'gateway for vaccines'[4] and an efficient method for inducing systemic immune responses[5]. Intranasal drug administration has also been used to deliver peptide hormones to regulate enuresis[6] and renal colic[7].

Several factors are thought to influence drug uptake into the brain by intranasal delivery. First, because the nasal cavity contains a rich vascular bed, intranasal drugs can be readily absorbed by these vessels and enter the systemic circulation. Second, drugs that have entered the circulation can cross the BBB but, as Eisenstein suggests, BBB drug penetration is still poorly understood. And third, it has also been suggested that intranasal delivery can facilitate direct entry into the brain without BBB penetration[8]—a concept that has been effective in the use of dihydroergotamine treatment of migraine[9], theophylline treatment of smell and taste loss[10], and insulin treatment of Alzheimer's disease[11].

To date, the majority of studies investigating this delivery mechanism have looked only at animal models[11], but both short- and long-term effects in humans have also been shown. For example, in the case of melanocortin, systemic effects have been observed within minutes of nasal administration. This peptide hormone also reaches the cerebrospinal fluid within minutes and induces long-lasting mediation of fear and anxiety[11]. In the case of the larger biologic insulin, intranasal administration has not been shown to alter blood insulin or glucose levels but it has been reported to improve attention, memory and cognitive function in patients with Alzheimer's disease[11].

Thus, intranasal administration represents an additional and promising route for drug delivery. Indeed, similar to other approaches, it may be possible to design chemical enhancers or carriers that facilitate the intranasal delivery route. In the meantime, further work will be needed to elucidate the mechanism of entry—one plausible mechanism for intranasal delivery is that drugs are absorbed by the olfactory epithelium and then transported directly across the cribriform plate along the path of the olfactory bulb and thereby directly into the brain.

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Quantitative analysis demonstrates most transcription factors require only simple models of specificity

To the Editor:

Determining the specificity of transcription factors is an important step in understanding regulatory networks and the effects of genetic variations on those networks. To date, attempts to use position weight matrices (PWMs) to assess the DNA-binding specificity of transcription factors from protein binding microarray (PBM) data have suggested that the energetics of transcription factor–DNA recognition fail to follow simple rules. Here we describe a new method for deriving PWMs from PBMs, BEEML-PBM (Binding Energy Estimation by Maximum Likelihood for PBMs). Using this method, we demonstrate that simple PWMs generally do give good approximations of transcription factor specificity, which are reproducible in PBM experiments.

In recent years, several high-throughput approaches have been developed to rapidly and efficiently determine the specificity of transcription factors[1]. One important issue that arises in the analysis of binding data is the complexity of the specificity model needed. It has important implications for both the characterization of specificity and for the prediction of the consequences of mutations. If the recognition mechanism is simple, then the specificity of a transcription factor can be