Psychotropic substance-seeking: evolutionary pathology or adaptation?

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ABSTRACT

According to a conventional evolutionary perspective, the human propensity for substance use is the product of a 'mismatch' between emotional mechanisms that evolved in a past without pure drugs or direct routes of drug administration, and the occurrence of these phenomena in the contemporary environment. The primary purpose of this review is to assert that, contrary to the conventional view, humans have shared a co-evolutionary relationship with psychotropic plant substances that is millions of years old. We argue that this 'deep time' relationship is self-evident both in the extant chemical–ecological adaptations that have evolved in mammals to metabolize psychotropic plant substances and in the structure of plant defensive chemicals that have evolved to mimic the structure, and interfere with the function, of mammalian neurotransmitters. Given this evidence, we question how emotional mechanisms easily triggered by plant toxins can have evolved. Our argument is also supported with archeological and historical evidence of substance use in antiquity suggesting that, for people in the past, psychotropic plant substances were as much a mundane everyday item as they are for many people today. Our second, and more speculative objective is to suggest provisional hypotheses of human substance-using phenomena that can incorporate the evolutionary implications of a deep time relationship between psychotropic substances and people. We discuss hypotheses of selective benefits of substance use, including the idea that neurotransmitter-analog plant chemicals were exploited as substitutes for costly, nutritionally constrained endogenous neurotransmitters. However, even if substance seeking was adaptive in the environment of our hominid ancestors, it may not still be so in the contemporary environment. Thus, the implications of our argument are not that the mismatch concept does not apply to human substance-using phenomena, but that it must be reconsidered and extended to incorporate the implications of a substance-rich, rather than substance-free, evolutionary past.

KEYWORDS Alkaloids, anthropology, biological adaptation, central nervous system stimulants, evolution, medicinal plants, motivation, neurotransmitters, reinforcement (psychology), substance-related disorders.

INTRODUCTION

According to what we will call the 'conventional' evolutionary perspective, the human propensity for substance use is the product of a 'mismatch' between emotional mechanisms that evolved in a past without pure drugs or direct routes of drug administration, and the occurrence of these phenomena in the contemporary environment (Tooby & Cosmides 1990; Nesse 1994; Nesse & Berridge 1997; Smith 1999). Consequently, psychoactive substances can 'short-circuit' the adaptive functions of positive emotions and instead 'directly stimulate the brain

mechanisms that regulate pleasure' (Nesse 1994). Nesse & Berridge (1997) contend that 'drugs of abuse create a signal in the brain that indicates, falsely, the arrival of a huge fitness benefit'. Similarly, drugs are used to block painful feelings or affect states, short-circuiting the adaptive functions of negative emotions.

The primary purpose of this review is to assert that, contrary to the conventional view, humans have shared a co-evolutionary relationship with psychotropic plant substances that is millions of years old. We argue that this 'deep time' relationship is self-evident both in the extant chemical–ecological adaptations that have evolved in mammals to metabolize psychotropic plant substances and in the structure of plant defensive chemicals that have evolved to mimic the structure, and interfere with the function, of mammalian neurotransmitters. Given this evidence, we question how emotional mechanisms easily triggered by plant toxins can have evolved. Our argument is also supported with archeological and historical evidence of substance use in antiquity suggesting that, for people in the past, psychotropic plant substances were as much a mundane everyday item as they are for many people today.

Our second objective is to suggest provisional hypotheses of human substance-using phenomena, that can incorporate the evolutionary implications of a deep time relationship between psychotropic substances and people. We argue that, during a 200 million-year relationship, mammals may have evolved not just defensive mechanisms for detoxifying plant chemicals, but adaptations to counter-exploit their adaptive potential. From this perspective, aspects of human substance-seeking behavior in the present may be considered the evolutionary sequelae of adaptive benefits derived from the exploitation of those plants in our evolutionary past. We discuss provisional hypotheses of such selective benefits, including the idea that neurotransmitter-analog plant chemicals were exploited as substitutes for costly, nutritionally constrained endogenous neurotransmitters.

However, even if substance seeking was adaptive in the environment of our hominid ancestors, it may not still be so in the contemporary environment. Thus, the implications of our argument are not that the mismatch concept does not apply to human substance-using phenomena, but that it must be reconsidered and extended to incorporate the implications of a substance-rich, rather than substance-free, evolutionary past.

Before proceeding, a few caveats are necessary. The conventional evolutionary explanation for human substance-using phenomena is based on the assumption that the human central nervous system is inherently vulnerable to psychotropic substances. Accordingly, the conventional view tends to focus on pathological rather than mundane substance use. The focus of our discussion, on the other hand, is the origin of mundane and ubiquitous human substance-using behavior: we are interested in why people everywhere choose to seek out substances *in the first instance*, not to explain why a minority go on to gross, habitual substance use. Therefore, our preference is for the neutral terms 'substance seeking' and 'substance use', rather than 'addiction' and 'substance abuse'. Finally, this discussion is focused primarily on evolutionary theoretical perspectives: a necessary limitation given the vast scope and diversity of theoretical perspectives in the literature of drug-using phenomena.

HISTORICAL AND ARCHAEOLOGICAL EVIDENCE OF UBIQUITOUS SUBSTANCE USE IN ANTIQUITY

Archaeological evidence and historical accounts of substances used by indigenous peoples at European contact (Fig. 1) provide some insight into psychotropic substance use in prehistory. It is important to consider that as the origin of these practices is unknown, their actual antiquity is on an open-ended time scale.

In the case of *Areca catechu* (betel nut), today the fourth most used drug in the world after nicotine, ethanol and caffeine (Marshall 1987), archaeological evidence suggests that it was being chewed approximately 13 000 years ago in Timor (Glover 1971, 1977) and 10 700 years ago in Thailand (Gorman 1970; Yen 1977). At the time of European contact, Aborigines were exploiting the indigenous plant pituri (*Duboisia hopwoodii*) for its nicotine content in western Queensland, and an indigenous *Nicotiana* in central Australia (*N. gossei*) (Watson 1983; see also Feinhandler *et al*. 1980). As Aborigines had lived in Australia for at least 40 000 years before the arrival of colonists (see Bellwood 1985), the antiquity of the exploitation of these native plants may be considerable. Tobacco species (*N. tabacum* and *N. rustica*) were spread throughout most of the Americas by the time of conquest, and were 'one of the oldest of the New World cultigens' (Schultes 1979). Similarly, the use of khat (*Catha edulis*) in Ethiopia and north-east Africa was already an 'ancient' practice before the arrival of colonists (Weir 1985). According to Plowman (1984), coca (*Erythroxylum coca*) was being domesticated in the western Andes by 7000 years ago, and archaeological artifacts date the use of coca in Ecuador to at least 5000 years ago (Balick & Cox 1997).

Route of administration

At the time of first European contact, as today, betel nut, khat, tobacco and coca were chewed in the buccal cheek cavity. The buccal mucosa is a blood-rich tissue that

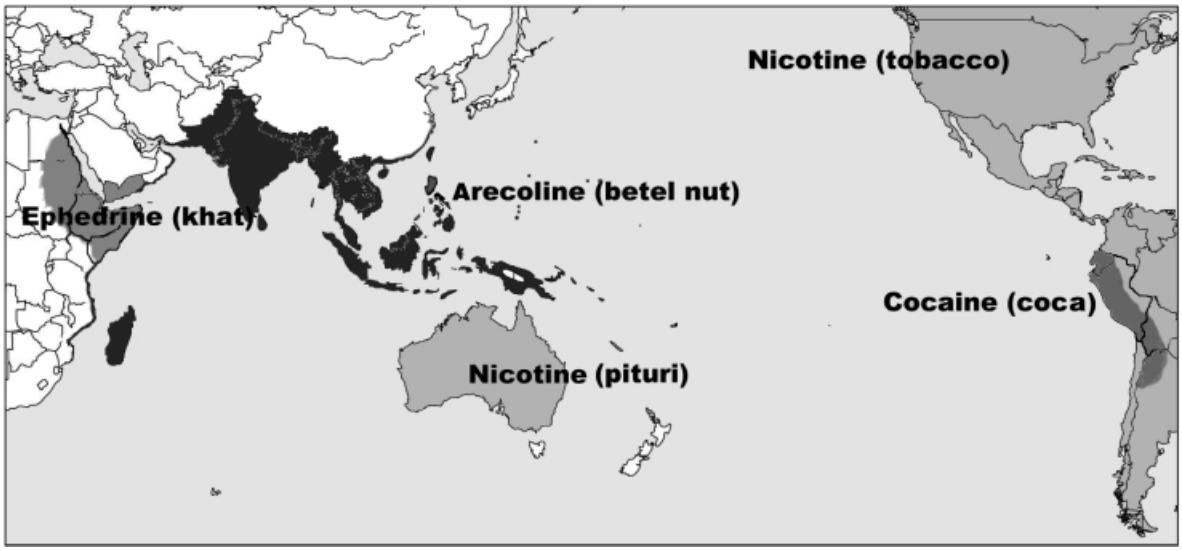

Figure 1 Examples of ubiquitously exploited allelochemicals in the precolonial world

allows the passage of these substances directly into the blood stream, avoiding the elimination that occurs via the intestine and liver when a drug is introduced orally (first-pass metabolism). This process is facilitated, with the exception of khat, by mixing the substance with an alkali (lime or wood ash) that converts it into the free base (pituri: Watson 1983; tobacco: Furst 1976; McKim 1991; betel nut: Johnston *et al.* 1975; Wink 1998c; coca: Balick & Cox 1997; Wink 1998c). That people in the past used alkalis to free base psychotropic substances is evident in the alkali-bearing vessels found in the archaeological record (Fox 1970; Balick & Cox 1997). This combination of physiological and cultural processes produces a pure drug introduced into the body by a direct route.

Although a universally used method, the buccal route was only one of several direct routes of administration used in antiquity. For example, the smoking of tobacco and the administration of psychedelics nasally and rectally were common in the Americas (McKim 1991).

Pharmacology and potency

The nicotine-bearing plants used by indigenous people at European contact tend to be more potent than the commercial *N. tabacum* used today (up to approximately 1.5% nicotine: Goodman, Gilman *et al.* 1985). The *N. rustica* used by indigenous Americans ranges up to 8% nicotine, and the pituri used by aboriginal Australians ranges between 3.5% and 5% nicotine (Watson 1983).

Despite being one of the most commonly used drugs globally, betel nut is virtually unknown in the west and is rarely mentioned in texts describing commonly used drugs. Chewing a betel nut in combination with the conventional pepper leaf and lime exerts potent parasympathetic effects in the intolerant user, including: salivation, sweating, tremor, nausea, bronchoconstriction and vasodilation (see Goodman, Gilman *et al.* 1985; Chu 1993, 1995; Rooney 1993). The betel nut's most abundant alkaloidal constituent is arecoline (Farnworth 1976), a non-selective muscarinic agonist that readily crosses the blood–brain barrier (Asthana *et al.* 1996), and increases brain levels of acetylcholine in animals by 150–250% (Shannon *et al.* 1994).

Khat's active constituents include cathine (norpseudoephedrine) and ephedrine (Luqman & Danowski 1976), both central stimulants structurally similar to noradrenaline (Julien 1985). Cathine is a sympathomimetic that increases the release of serotonin, noradrenaline and dopamine and inhibits their re-uptake (Schmeller & Wink 1998). Ephedrine inhibits the re-uptake of norepinephrine (Wink 1998b) and is a drug of frequent abuse elsewhere (Julien 1985; Mattoo *et al.* 1997). The spectrum of khat's pharmacological action is estimated to be between amphetamines and caffeine (see Halbach 1972; Luqman & Danowski 1976).

Cocaine, the active alkaloid in *E. coca,* is a central stimulant exerting its pharmacological action by preventing the re-uptake of norepinephrine and dopamine (Julien 1985; Wink 1998b). The approximately 15 million regular coca chewers in South America consume around 50 g of fresh leaves per day each, equivalent to 0.4 g of cocaine (Mann 1992; Wink 1998c).

Drugs as food

It is pertinent to consider what 'drugs' represented for people in the ancestral environment. The ways in which indigenous people perceive traditionally used psychoactive and/or 'medicinal' plants are different from pharmaceutical concepts understood in the industrial

west. Today, when we think of 'drugs', we visualize processed commodities such as packaged cigarettes, pills or powders. These processed products had no counterpart in the environments of indigenous peoples or in the ancestral environment: 'drugs' were plants, and thus were eaten as food (Etkin 1994; Balick & Cox 1997). While researching the effects of betel chewing on people with schizophrenia in Micronesia (Sullivan *et al*. 2000), the first author found that betel nut was not perceived as a drug in the western sense. Rather, it is chewed in the manner of a food, is conceived as imparting energy and sustenance in the manner of a food, and comes from a palm that is tended and grown around dwellings in the manner of a food-bearing plant. Moreover, when chewers were questioned about their perceptions of the effects of chewing, the response was invariably that the nut was chewed for energy or to prevent fatigue, rather than for its psychotropic effects.

Similar accounts of a blurred distinction between drugs and food can be found in the ethnomedical and anthropological literatures. Marshall (1981) relates that, in Yap and Chuuk, tobacco is considered akin to a strength-imparting food or drink and is governed by similar taboos & restrictions. Etkin & Ross (1982) found that of the 107 plant species used for gastrointestinal disorders by the Hausa of Nigeria, 50% (53) are also used in dietary contexts where they are regarded solely for their nutritive value. Moerman (1994) found that a large number of plant species used by Native North Americans were used as both food and medicines. Of the 2646 utilized species, 1222 were used exclusively as medicines, 745 were used exclusively as foods and 679 were used as both food and medicines. Thus, roughly half of all food plants (48%) were also medicinal. He concluded that 'people have, over the millennia, sought out *as foods* those species that were likely to contain disproportionate quantities of secondary chemicals, many of which are poisonous' (emphasis added, Moerman 1994; but see Dufour & Wilson 1994).

Describing drugs as food does not necessarily constitute a metaphor, as many ubiquitously used substances have considerable nutritional value. For example Balick & Cox (1997) note that the calcium, phosphorus, iron, vitamins A, B2 and E in 100 g of Bolivian coca leaf exceeds the daily recommended US dietary allowance. Khat contains vitamin C (150 mg/100 g of fresh leaves) and trace amounts of thiamine, niacin, riboflavin, carotene, as well as iron and amino acids (Luqman & Danowski 1976). Moreover, as many alkaloids are based chemically on tryptophan or tyrosine (Dalton 1979; Waterman 1998), these essential proteins may become available after oral consumption.

Although the evidence presented above is not proof of ubiquitous substance use in the ancestral environment, it is sufficient to give pause to some of the assumptions of the conventional model and is suggestive of further research. The information presented in Fig. 1 is necessarily a work in progress, owing to the inherent difficulty of elucidating the past use of drugs in the anthropological and historical literature (for example, see Marshall 1987 for a review of the debate on the origins of tobacco use in Oceania). However, archaeological and historical data are not the only sources of insight into the relationship between drugs and people in the past.

ALLELOCHEMICALS THAT MIMIC MAMMALIAN NEUROTRANSMITTERS ARE EVIDENCE OF A DEEP-TIME RELATIONSHIP BETWEEN PSYCHOTROPIC PLANTS AND MAMMALS

Chemical analogs of mammalian neurotransmitters—psychoactive substances—were ubiquitous in the ancestral environment, as they are nowadays, in the form of plant allelochemicals: toxic metabolites deployed by plants to dissuade herbivores and pathogens (Johns 1990; Wink 1993). Over hundreds of millions of years, plants have evolved allelochemicals that mimic the structure of mammalian neurotransmitters (NTs), and bind at receptors in the nervous systems of plant predators (Wink 1993, 1998a, 1998c). This process is demonstrated in the structure–function relationship between ergot alkaloids & the neurotransmitters serotonin, dopamine and noradrenaline (Fig. 2). In this case, the ergot alkaloid has evolved a single molecular structure that binds to any of three monoamine neurotransmitter receptors. Ergot alkaloids interfere with the central nervous system (CNS) neurotransmission of grazing animals, exerting a range of effects from vasoconstriction to hallucination (Wink 1998b).

This molecular co-evolutionary relationship between plants and their mammalian predators, what we will term the allelochemical–CNS phenomenon, represents our second source of evidence that psychotropic substances were a recurrent feature of the ancestral environment, and had been so for a great deal of time before the emergence of hominids. The allelochemical–CNS phenomenon is not idiosyncratic, but encompasses many of the known CNS-signaling pathways to the extent that, with the exception of alcohol, allelochemicals constitute all of the most commonly used psychotropic substances (Table 1). Moreover, it is noteworthy that the discovery of several mammalian NT systems has followed observations of the psychotropic effects of allelochemicals and of their site of action in the CNS. As Deakin (1980: 40) has observed, 'the development of the opiate receptor concept begged

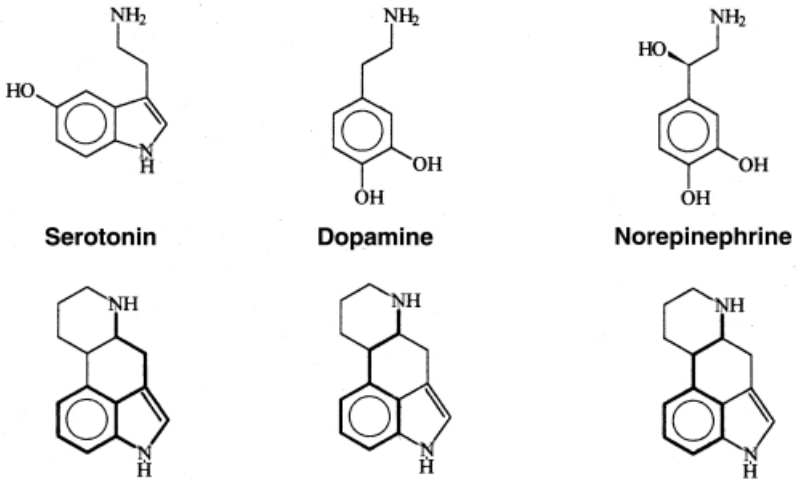

Figure 2 Structure–function relationship of ergot alkaloids with the neurotransmitters serotonin, dopamine and norepinephrine (Wink 1998b).

Table 1 Examples of allelochemicals that interfere with mammalian neurotransmission (after Wink 1998b).

Receptor	*Neurotransmitter*	*Allelochemical/alkaloid*	*Occurrence and products*
1. Acetylcholine receptor			
Nicotinic receptor	Acetylcholine	Nicotine	*Nicotiana* (tobacco)
		Nicotine	*Duboisia hopwoodii* (pituri)
Muscarinic receptor	Acetylcholine	Arecoline	*Areca catechu* (betel nut)
		Muscarine	*Amanita, Inocybe, Clitocybe*
2. Adrenergic receptors	Norepinephrine/epinephrine	Ergot alkaloids	*Claviceps*
		Ephedrine, norpseudoephedrine	*Catha edulis* (khat)
		Cocaine	*Erythroxylum* (coca)
3. Serotonin receptor	Serotonin	Ergot alkaloids	*Claviceps*
		Mescaline	*Lophophora* and other cacti
4. Dopamine receptor	Dopamine	Ergot alkaloids	*Claviceps*
		Cocaine	*Erythroxylum* (coca)
5. Adenosine receptor	Adenosine	Caffeine	*Coffea, Carmellia* (coffee)
		Caffeine, theophylline, theobromine	*Camellia sinensis* (tea)
		Theobromine	*Theobromine cacao* (chocolate)
6. Opioid receptor	Endorphins	Morphine	*Papaver somniferum* (opium)
7. Cannabinoid receptor	Anandamide	Δ9-THC	*Cannabis sativa* (marijuana)

the teleological question of the reason the brain contains a set of receptors for substances derived from plants'. Other receptor systems named for their allelochemical NT analogs are the nicotinic & muscarinic cholinomimetics, and the recently described cannabinoid system (Ameri 1999).

MAMMALIAN CHEMICAL-ECOLOGICAL ADAPTATIONS ARE EVIDENCE OF A DEEP-TIME RELATIONSHIP BETWEEN PSYCHOTROPIC PLANTS AND ANIMALS

The third source of evidence of a co-evolutionary relationship between mammals and plant chemicals is manifest in the many existing physiological and behavioral mammalian adaptations for defeating plant chemical defenses (Johns 1990). Among what could be called chemical–ecological adaptations, the most relevant are the cytochrome P-450 and other liver enzyme systems, which have evolved specifically with the function of metabolizing allelochemicals by oxidation, hydrolysis or reduction (Johns 1990; Wink 1998a). Other examples of physiological chemo-ecological adaptations are gustation, olfaction and the direct expulsion of the toxins by vomiting (Johns 1990; Wink 1998a). It is also interesting to consider whether the buccal membrane is a functional mammalian adaptation to exploit nutrients and plant chemicals, or whether it is an evolutionarily neutral structure that has been serendipitously exploited.

Associated with these physiological functions are several behavioral adaptations, such as detoxication induction behaviors, sensory-specific satiety and neophobia (Johns 1990). The seeking and ingestion of soils, clay and charcoal to bind dietary allelochemical toxins, or geophagy, is a behavioral adaptation employed by humans (Johns 1990), chimpanzees (Mahaney *et al.* 1996), monkeys (Oates 1978; Cooney & Struhsaker 1997) and other animals and birds (Wink 1998a). Cultural practices developed by *H. sapiens* over thousands of years to remove plant chemicals from foods can also be considered behavioral chemo-ecological adaptations and include: heating, solution leaching, drying, fermentation, adsorption and physical processing (Johns 1990). Selectivity is also an important process in that only a few of 300 000 plant species are exploited as food (Johns 1990; Wink 1998a), and only a tiny fraction of the known allelochemicals are exploited by humans and animals (Schmeller & Wink 1998; Wink 1998c).

To summarize, we have presented evidence that questions the mismatch assumption that pure psychoactive chemicals were *not* recurrent features of the ancestral environment. In contrast, we have argued that there has been a deep-time relationship between drugs and people evident in the allelochemical–CNS phenomenon, and in extant behavioral and physiological chemical–ecological adaptations for managing allelochemicals.

Although pure drugs in the sense of allelochemicals with structurally enhanced potency (e.g. heroin from morphine) were obviously not present in the past, NT-analog allelochemicals that interfere significantly with CNS signaling processes were recurrent features of the ancestral environment. For an unknown time period, people have enhanced the natural potency of allelochemicals by free basing constituent psychotropic agents in the buccal cavity.

QUESTIONS ABOUT THE MISMATCH MODEL

In positing the reasons for substance abuse, the conventional perspective is logically dependent on a mismatch between an emotional reinforcement mechanism that evolved in a past without pure drugs or direct routes of administration and the novel occurrence of these phenomena in the contemporary environment. However, the evidence presented above positing a deep-time relationship between psychotropic chemicals and people undermines the logical consistency of the conventional view.

When interpreted as a cognitive model, the emotional reinforcement mechanism implicit in the mismatch perspective is a generalized content-*independent* mechanism: a punishment/reward mechanism that mediates learning independently of innate content about the environment in which the mechanism has evolved. This 'reward' model has much in common with proximate, or non-evolutionary, models of the acute drug state (Di Chiara *et al.* 1993; Koob & Nestler 1997; Robbins & Everitt 1999). However, plants have evolved defensive chemicals to substitute endogenous NT acting at specific receptor sites (Wink 1998b), *not* to activate a generalized reward mechanism. The function of these evolved plant defenses is to discourage plant predators (Johns 1990; Wink 1993, 1998a, 1998b). A generalized mechanism that blindly reinforces positive or negative feedback would either be exploited quickly by rapidly evolving allelochemical plant defenses, or could encourage rather than discourage consumption of the plant. In short, the evidence that plants have evolved chemical defenses targeting the mammalian CNS makes it unlikely that a content-independent mechanism, triggered easily by plant toxins, can have evolved in mammals.

First experiences of commonly used drugs are often aversive

The strongest logic supporting the evolutionary interpretation of the reward model is that drugs are consumed serendipitously, and are reinforced immediately by a hedonic euphoria. Accordingly, the mismatch model tends to be applied to the pathological use of highly purified or synthetic euphoric drugs. However, a *very small* proportion of human substance use fits this scenario. For example, the stable incidence of 'heavy use' of the most widely used refined drug, cocaine, is less than 650 000 people in the United States (Smith 1999), or <0.3% of the population. In comparison, the most widely used drugs in prehistory and by perhaps one-quarter of the *global* population today, the cholinergic stimulants nicotine and betel nut, are sought in the unrefined state, or are used in products of comparable potency to that of the unrefined plant. These mundane substances do not have an immediate hedonistic 'hit'; on the contrary, they are unpleasant to the new user who must persist for a significant period of time until a tolerance to the drug's unpleasant side-effects are achieved.

A recent review of research investigating the motivation for contemporary nicotine use also questions the importance of hedonic feedback. Eissenberg & Balster (2000) report that data from retrospective adolescent studies indicate that the first smoking experience is often aversive. For example, in one study (N = 386) 88% of subjects reported aversive responses to their first cigarette, with dizziness reported by 44%, sickness by 38%, headache by 33% and nausea by 23% (Hirschman *et al.*

1984). In addition to little evidence for a rewarding initial smoking experience, Eissenberg & Balster (2000) found that 'pleasurable effects of smoking are, at best, of moderate importance in maintaining smoking behavior' (see also Rothman & Glowa 1995).

AN ALTERNATIVE MODEL AND PROVISIONAL HYPOTHESES

We have argued that the operation of a content-independent generalized reward mechanism is not consistent with the evidence of co-evolution between allelopathic plants and the mammalian CNS. An alternative cognitive model used to explain many facets of evolved human behaviour is the content-*dependent* domain-specific model. If we were to propose an opposing hypothesis to the mismatch model, that a substance-seeking function was selected for in the ancestral environment, such a model can accommodate the evidence we have presented here: the content-dependent mechanism has co-evolved with and therefore incorporates innate information about plants in the ancestral environment; this information is managed within a cognitive domain of chemical–ecological adaptation that has evolved in 'competition' with allelopathic plant defenses.

Can we even consider that substance seeking, or use, is the product of an adaptive evolutionary process? Evolutionary theorists have tended to discount this possibility in adherence to the mismatch model (Nesse 1994; Cosmides & Tooby 1999). For example, Nesse (1994: 343) posits that '[t]he seeking of certain chemicals is one manifestation of the generally adaptive tendency to repeat behaviors that bring pleasure. In this sense, trying to explain why humans use drugs is like trying to explain why people eat. The difference of course is that food intake is useful and selection has shaped specialized brain mechanisms that regulate food intake, while no mechanisms have evolved specifically to regulate psychotropic drug intake'. Given that the mismatch perspective is based on what we have argued are erroneous assumptions, we assert that a provisional discussion of just such an alternative model is warranted. We acknowledge at the outset that such a discussion will necessarily be speculative and intended as the basis for critique and further research.

Citing discrete pharmacological actions such as analgesia, stimulation and sedation, Smith (1999) has suggested that 'it is relatively easy to imagine the fitness-enhancing aspects of psychotropic substances in our evolutionary past' (see also Siegel 1989). However, such discrete properties are unlikely to account for the evolution of a complex species-level behavioral adaptation. From an adaptationist perspective, behavioral mechanisms have evolved to solve a recurrent adaptive problem in the ancestral environment (Williams 1966; Tooby & Cosmides 1990, 1992; see also Symons 1992). Logical requirements are that there is evidence of suitable background conditions for the putative mechanism to have evolved, that there is evidence of evolved 'design' in structures or behaviors, and that there was a plausible selection pressure (often called an adaptive problem) for the evolution of the putative mechanism in the ancestral environment (Tooby & Cosmides 1990, 1992).

Extant characteristics of the mammalian CNS already meet the first two of these conditions. The biochemical fit between allelochemical NT substitutes and mammalian CNS receptors attests to the existence of appropriate conditions in the past for the evolution of a substance-exploiting mechanism. The examples of behavioral and physiological adaptations for the management of plant chemicals described above are extant evidence of 'design' in a chemical–ecological cognitive domain. Continuing with the biochemical theme, we propose that mammalian NTs that require exogenous nutrition for synthesis provide an example of a recurrent adaptive problem 'solved' by a substance-seeking mechanism under certain conditions. Such a mechanism is activated by NT deficits and initiates the search for compensatory chemicals in the environment. Although a novel concept when applied to human substance-seeking behavior, it is already known that NT processes are homeostatic (e.g. Grace 1995; Chaouloff *et al.* 1999) and that similar exogenously provisioned regulatory processes are content-dependent, e.g. salt, water, mineral and nutritional homeostasis (Beauchamp 1987; Denton 1982; Blundell 1990; Garattini *et al.* 1990). To follow are two adaptive problems associated with NT deficits that may have constituted selection pressures for the evolution of a substance-seeking adaptation in the ancestral environment.

(1) Nutritional constraints on brain-signaling processes

The NTs most implicated in substance use, monoamines and acetylcholine, are nutritionally constrained (the adaptive problem). In the ancestral environment, these constraints equated to myriad costs incurred in the provisioning of high-quality nutrients. In this context we hypothesize that substance seeking evolved to alleviate these constraints on brain-signaling processes. In marginal or highly variable environments, high quality food may have been periodically unavailable. Indeed, the examples of ubiquitous drug use in antiquity all originate in marginal environments—desert (Ethiopia and the Australian interior), arid alpine (Peru) and rain forest

(Indonesia, Malaysia) (Fig. 1). In periods of privation, plant NT-analogs may have been easier to obtain, transport and store than dietary NT-precursors. In such conditions, an endogenous NT could be substituted with its allelochemical analog, overcoming the functional constraint. Consistent with the theme of 'drugs as food' related above, in the ancestral environment, the hominids goal in consuming NT-analog allelochemicals was not to feel good, but to save energy.

Anderson & Johnston (1983) state that 'it is clear that the brain is dependant upon an adequate nutrient supply for normal development and function. Alterations in supply such as those that occur with nutrient deficiencies, food deprivation, and normal fluctuations in neurotransmitter precursor availability are circumstances during which nutrition influences brain function.' Put in evolutionary terms, this means that there are constraints on *normal* brain signaling processes that increase with environmental/nutritional stressors.

The chemical signaling processes in the brain that are most often implicated in substance seeking are also those that are subject to the constraints of external provisioning (norepinephrine, dopamine, serotonin and acetylcholine). Because of their functional importance, we would expect brain signaling processes to be 'cheap' in terms of metabolic and exogenous requirements. This is the case for many NT processes. For example, γ-aminobutyric acid, glutamate and aspartic acid are dietary non-essential amino acids whose production and release are managed endogenously (Anderson & Johnston 1983). In contrast, the precursors for serotonin, norepinephrine, dopamine and, to a lesser extent acetylcholine, must be provisioned externally.

The sensitivity of the CNS to the external provision of NTs is evident in that dietary precursors alone have been used to increase monoamine turnover as a treatment for depression (Chouinard *et al.* 1979; Gelenberg *et al.* 1980; see also Growdon *et al.* 1982 in Parkinson's disease). In addition to the modulation of mood, these NTs affect many critical brain functions including cognition, motor activities, body temperature, sensory perception, endocrine release and ingestive behaviors (Anderson & Johnston 1983). Indeed, depletion of monoamine NTs and their nutritionally sourced precursors is known to initiate food-seeking behaviors of specific food types, that will supply or facilitate transport of the deficient precursors (Blundell 1990; Garattini *et al.* 1990).

The costs in time and energy expended in procuring and processing these essential nutrients cannot be overstated. For human foragers in the ancestral environment, survival was a strategic exercise of extracting the necessary energy, in calorific value, from the environment (Kelly 1995; Hill & Hurtado 1996). If the diet of contemporary hunter/gatherers is analogous to the diet in ancestral environments, meat will comprise about one-third of the diet by weight, and about one-half by calories (Hayden 1981). The current combined daily dietary recommendations of the essential amino acids tryptophan and phenylalanine/tyrosine for a 70-kg adult are a modest 1190 mg, or 6020 mg for all essential amino acids combined (Beers & Berkow 1999). However, variation in foraging returns are known to be high, and understanding the strategies used by foragers to buffer this variation is a central problem in the study of living hunter–horticulturists (Kelly 1995). Recent research demonstrates that even brief periods of food shortage can have a profound nutritional impact on these chronically food-constrained populations (Hagen *et al.* 2001).

(2) Sustaining NT-depleting stress adaptations

Monoamine and cholinergic NTs are activated when people are exposed to physiological and psychological stress. Stress is an adaptive response to challenging environmental contexts that, if sustained, can lead to maladaptive behaviors, exhaustion and death (Griffin & Thomson 1998). It has been proposed that NT depletion is the *cause* of maladaptive behavioral changes in animals, and that treatments which sustain NT release may help animals (including people) avoid the maladaptive 'behavioral sequelae' of stress (Wurtman & Lieberman 1989).

In the case of early humans, the exploitation of exogenous NT-analogs may have prevented NT-depletion, and allowed users to tolerate prolonged stress states in aversive conditions. In this regard, colonial accounts of Aboriginal Australian use of pituri in stressful circumstances are informative. For example Bancroft (1879) (in Watson 1983) reports that '[t]hey never travel without it on long marches, using it constantly to deaden fatigue and cravings of hunger'. Similarly, in the present, all the indigenously used substances detailed in Fig. 1 have been commonly observed to increase tolerance for fatigue, hunger and thermal stress in aversive conditions (betel nut: Rooney 1993; nicotine/pituri: Watson 1983; khat: Luqman & Danowski 1976; Wink 1998c; coca: McKim 1991; Balick & Cox 1997).

Activation of the substance-seeking adaptation by novel phenomena

An NT-modulating behavioral adaptation that has evolved in response to selection pressures in the past will also be activated by novel NT-depleting phenomena in the present. A notable contemporary example of extraordinary substance use in association with NT abnormalities is 'self medication' by people with major mental illnesses including schizophrenia and depression. Although

schizophrenia is common today, its full expression in the ancestral environment may have been rare (Allen 1997; Allen & Sarich 1988). Similarly, although depression is probably an ancestral adaptation to certain social circumstances (Hagen 1999; Nesse 2000), contemporary social dynamics differ radically from those faced by our hominid ancestors. Consequently, depressed affect states may not 'solve' the novel social problems faced by people today, resulting in abnormally prolonged depression. Several models of abnormal NT processes have formed the basis for the pharmacological treatment of schizophrenia (Tandon & Greden 1989; Tandon 1999), and suspected NT-depletion underlies the biogenic-amine hypothesis of depression (Chouinard *et al.* 1979; Van Praag 1981). Moreover, both of these disorders have been associated with psychotropic substance seeking and self-medication (Khantzian 1985, 1997; Sullivan *et al.* 2000).

Even though the clinical manifestations of schizophrenia and depression may well be evolutionary novelties, the NT-deficits associated with these and other mental illnesses will continuously activate an NT-modulating adaptation, hypothetically explaining both the initial substance-seeking impulse and the high frequency of substance-use by people with these disorders.

DISCUSSION

A critique of the mismatch model

In critiquing the mismatch assumption that pure psychoactive chemicals were *not* recurrent features of the ancestral environment, it has not been our intention to construct a strawman. We have no doubt that most advocates of the mismatch model are aware that drugs were used to some extent in prehistory; but that use is often privileged as distinct from the ubiquitous use of the same or similar agents in the present (e.g. betel nut, coca, khat and tobacco).

Although 'pure' drugs in the sense of allelochemicals with structurally enhanced potency were not present in the past, NT-analog allelochemicals that significantly interfere with CNS signaling processes were a recurrent feature of the ancestral environment and could be administered by direct routes. Additional evidence of the recurrent nature of the relationship between drugs and people can be found in the allelochemical–CNS phenomenon, and in extant behavioral and physiological chemical–ecological adaptations for managing the consumption of allelochemicals. Given this evidence, the key issue that needs to be addressed by exponents of the conventional perspective is whether a content-free, or drug-naive CNS could have evolved given that (1) plants have evolved NT analogs to target the mammalian CNS, and that (2) adaptations such as the cytochrome P-450 mechanism have evolved specifically to metabolize plant allelochemicals.

We also questioned the importance of hedonic reinforcement in the etiology of substance use, emphasizing that the first experience of ubiquitously used drugs is often aversive. Related to the bias towards pathology in the mismatch model, we also discussed whether a focus on pathological drug use is appropriate, particularly for a universalistic theory of human substance use, and given that the vast majority of human substance use is mundane exploitation of relatively unrefined plant products. Also in regard to pathology, we emphasized that an 'etic' pathologization of psychotropic plant substances is a western preoccupation that is distinct from the 'emic' inclusion of such substances, often 'as food', in the classifications of indigenous people, and possibly also by our foraging ancestors.

A substance-seeking adaptation?

Over the approximately 200 million-year evolutionary history of *Mammalia*, plants have evolved chemical defenses—neurotransmitter substitutes—that interfere with CNS-signaling processes in plant predators. In turn, mammals have evolved 'counter adaptations' to manage plant chemicals—functional mechanisms that have been interpreted conventionally as performing a defensive role against toxins (Johns 1990; Profet 1992; see also Sherman & Billing 1999). Is it logical to assume that this relationship has resulted in purely defensive mechanisms in mammals? Or is it reasonable to posit that over millions of years mammals, including behaviorally sophisticated hominids, may have evolved adaptations to counter-exploit the potential benefits of psychotropic allelochemicals?

As the basis for both initial critique and further research, we have proposed two provisional hypotheses describing recurrent conditions in ancestral environments in which selection for substance-seeking behaviors may have occurred. These suggest that in some situations it was less costly to consume NT-analog allelochemicals than it was to find and metabolize nutrient NT precursors; and that in aversive environmental conditions, NT-depleting stress adaptations may have been sustained with the consumption of NT-analog allelochemicals.

A controversial aspect of this model is that *H. sapiens* and other mammals may have innate content, or knowledge, about functional psychotropic substances. Although it is a comparatively new area of research, the selective exploitation of allelopathic plants by animals, or zoopharmacognosy, is increasingly well documented (Rodriguez *et al.* 1985; Rodriguez & Wrangham 1993;

Glander 1994; Sauther 1994; Schmeller & Wink 1998). Zoopharmacognosy suggests that animals are content-dependent in regard to flora, while other writers have suggested that humans and other animals are content-dependent in regard to the natural world in general (Atran 1998; Rips 1975; Barrett 1999). The degree to which humans and other mammals may have innate knowledge about psychotropic plants is suggestive of novel and testable research questions. For example: do animals seek out allelochemical NT-substitutes from among a range of consumable choices when chemically deprived of endogenous NT, or when subjected to stressors? Under experimental conditions, do drug-naive human subjects show preferences for commonly exploited allelochemicals?

We would like to emphasize that a consideration of the adaptive benefits of substance seeking in the past does not minimize in any way the enormous societal costs associated with contemporary substance use (see Smith 1999; Soyka 2000). Nor does it mean that there are no novel costs in the use of the 'mundane' substances that were the focus of this discussion. As most people no longer live as foragers, any energetic benefits of using nutrient-constrained NT analogs no longer exist, while the costs in age-related health problems associated with substance dependence (cancer and circulatory diseases) are considerable. However, as hominids have been exposed to psychotropic allelochemicals for millions of years and may have evolved adaptations to exploit NT-substitute plant chemicals, an NT-deficit-triggered *motivation* to seek psychotropic substances may not be pathological. As stated at the outset, the implications of our argument are not that the mismatch concept does not apply to human substance-using phenomena, but that it must be reconsidered and extended to incorporate the implications of a substance-rich, rather than substance-free, evolutionary past. Human substance seeking and the deep time co-evolution of mammals and plant allelochemicals are related and compelling phenomena that merit widespread scientific investigation.

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