New Options in the Treatment of Cocaine Dependency

The Antiepileptic Gamma Vinyl-GABA (GVG)

The National Institutes of Health (NIH) suggests that gamma vinyl-GABA (GVG), a drug used to treat epilepsy, may prove to be an effective treatment for cocaine addiction. Researchers from New York University School of Medicine and Brookhaven National Laboratory in Upton, New York, reported in a small, preliminary clinical trial conducted in Mexico that this drug could cut cocaine use dramatically in people who had used cocaine daily for at least 3 years [80]. GVG reduced levels of dopamine, the "*feel-good*" chemical that floods the brains of cocaine users, providing the "*high*" they crave (Fig. 50). Using GVG to temper the dopamine system may very effectively block the addiction-related effects of cocaine. The people who completed the study said their craving for the drug was eliminated after 2–3 weeks of continuous GVG administration, the authors report. In addition, those who completed the trial also showed improved self-esteem, re-established healthy family relationships, went to work, or actively sought work. Such preliminary finding has important implications for our medications development program.

GVG, also known as Vigabatrin®, is approved in many countries as a treatment for epilepsy. Its main effect is that it increases the amount of another brain chemical involved in nerve cell communication, GABA, and thus helps moderate seizures. The US Food and Drug Administration has not approved GVG for treating epilepsy or any indication because of concerns about the relatively high incidence of tunnel vision that has occurred in people given the drug over many months or years. Vigabatrin® (or CPP-109, Catalyst Pharmaceutical Partners/USA) has been tested in regard to potential side effects, especially on vision impairment, and none of the eight people who completed the pilot study reported vision changes of any kind.

Cocaine normally results in an increased concentration of dopamine in the brain causing the "high" or exaggerated sense of pleasure associated with drug abuse. This is where CPP-109 sets in by indirectly lowering the level of dopamine in the brain via GABA (gamma-aminobutyric acid), is a neurotransmitter in the brain, which inhibits the release of dopamine. GABA, however, is broken down by GABA transaminase (GABA-T). CPP-109 works by inhibiting GABA-T and

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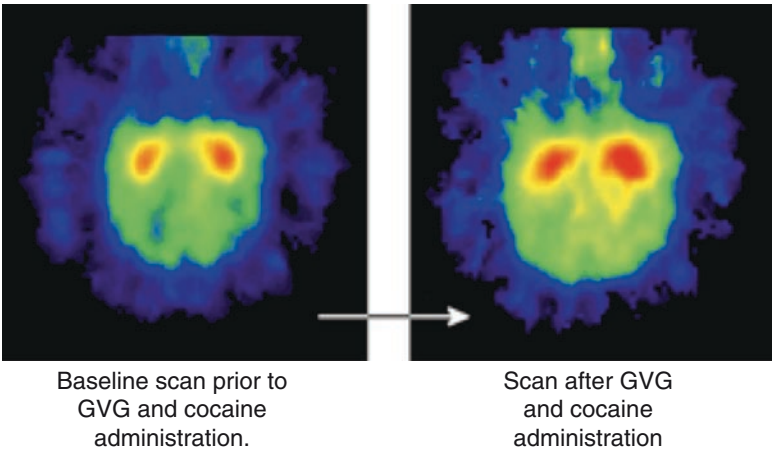

Fig. 50 GVG increases the amount of the neurotransmitter GABA in the brain and reduces the level of dopamine in the region of the brain that is thought to be involved in addiction

consequently increasing the level of GABA, which then lowers the level of dopamine and turns off the "*high*". CPP-109 seems to work without the apparent side effects typically associated with GABA agonists. Thus targeting brain GABAergic systems with drugs such as CPP-109 is a potentially effective treatment for cocaine, methamphetamine and other substance dependencies. Previous studies in established animal models of addiction, involving both rats and primates, have shown that Vigabatrin® interrupts the neural mechanisms essential for addiction (Fig. 50). In preclinical studies, Vigabatrin® prevented the characteristic drug-seeking behavior of addicted animals. Meanwhile three human trials of Vigabatrin® have been completed in Mexico with patients addicted to cocaine or methamphetamine, including a US Phase II, double-blind, placebo-controlled trial in 103 patients, which was completed in 2007. Data from these three trials provide clinical evidence of Vigabatrin®s potential as a safe and effective treatment for patients with these addictions (Fig. 51). By 2008, the company Catalyst initiated enrollment of patients for a US Phase II 180-patient, multicenter, double-blind, placebo-controlled clinical trial evaluating the use of CPP-109 in treating patients with cocaine addiction.

Disulfiram (Antabuse®)

Disulfiram is a drug normally used to help patients with alcohol disorders to remain sober. Patients taking disulfiram and who ingest even small amounts of alcohol develop a reaction that produces nausea, flushing, vomiting, and throbbing headache. At times, this reaction can be severe and can lead to critical illness, such as severe respiratory or circulatory problems. In combination with cognitive behavioral

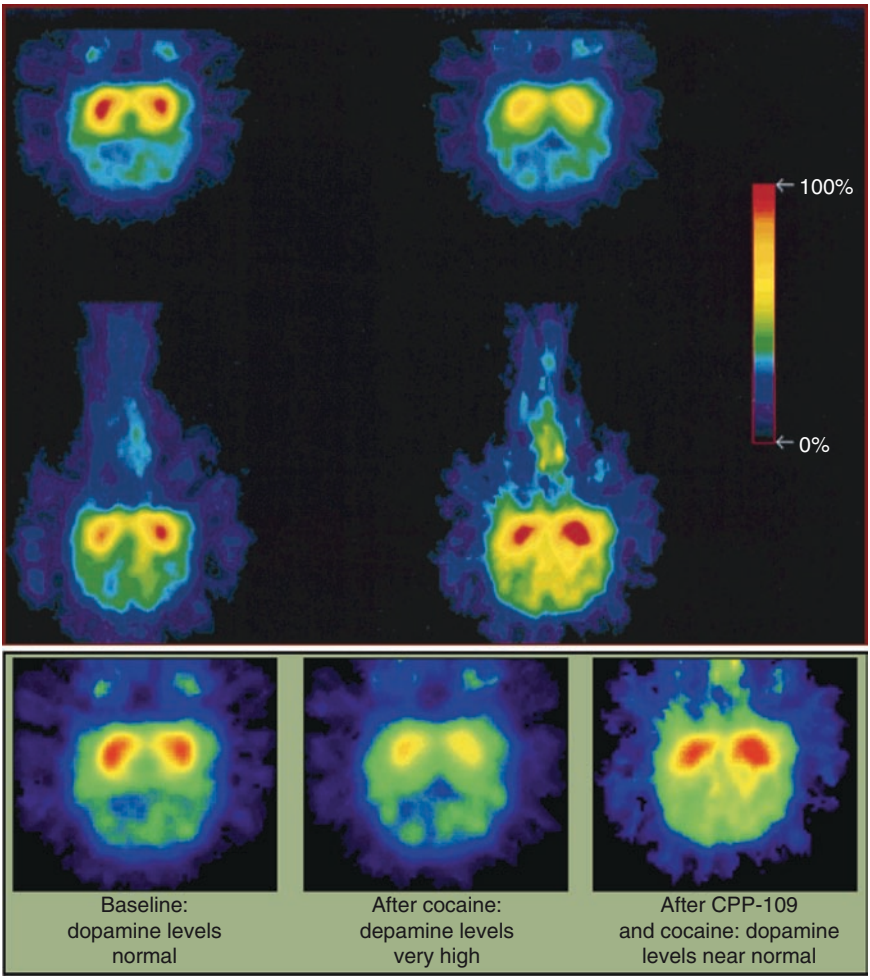

Fig. 51 Composite brain scans on receptor availability before, during cocaine use, and following treatment with CPP-109 in the corpus striatum of baboons (red indicates higher availability vs. magenta indicating a lower receptor availability). Cocaine decreases receptor availability (*top right*) compared to baseline values (*top left*). When pretreated with GVG, however, cocaine did not alter receptor availability (*lower right*) compared to baseline values (*lower left*)

therapy (CBT) disulfiram appears to be effective in reducing cocaine use, especially among cocaine users who are not dependent on alcohol. Since alcohol is a powerful "cue" for using cocaine, and can impair judgment and lower resistance to cravings for cocaine, researchers hypothesize that by reducing alcohol use with disulfiram, users might be less likely to abuse cocaine. However, use of disulfiram has not been evaluated in general populations of cocaine users. A study in randomly 121 cocaine-dependent adults (average age 34.6 years) were assigned to receive either disulfiram

or placebo over a 12-week period. Participants were also randomized to participate in either cognitive behavioral therapy (CBT) or interpersonal psychotherapy (IPT), a less structured form of behavioral therapy. Participants assigned to disulfiram reduced their cocaine use significantly more than those assigned to placebo, and those assigned to CBT reduced their cocaine use significantly more than those assigned to IPT [81]. This first placebo-controlled trial demonstrates that disulfiram therapy is especially effective for nonalcoholic cocaine users, as the effects of disulfiram treatment were most pronounced in participants who did not meet the criteria for current alcohol abuse or dependence and in those who abstained from alcohol during the trial.

Use of an Anti-cocaine Vaccine

Normally, the dopamine D2-receptor receives signals in the brain triggered by dopamine, a neurotransmitter needed to experience feelings of pleasure and reward. Without receptors for dopamine, these signals get "jammed" and the pleasure response is blunted. Previous studies in animals have shown that chronic abuse of alcohol and other addictive drugs increases the brain's production of dopamine. Over time, however, these drugs deplete the brain's D2-receptors and rewire the brain so that normal pleasurable activities that stimulate these pathways no longer work, leaving the addictive drug as the only way to achieve this stimulation. A study demonstrating dramatic reductions in alcohol use in alcohol-preferring rats infused with a gene inducing dopamine D2-receptor activation hypothesized that the same would hold true for cocaine-dependent individuals, who may have their need for cocaine decreased if their D2 levels are boosted. Researchers tested this hypothesis by injecting a virus that had been rendered harmless and altered to carry the D2-receptor gene directly into the brains of experimental rats that were trained to self-administer cocaine, a technique used in the earlier alcohol study. The virus acted as a mechanism to deliver the gene to the nucleus accumbens, the brain's pleasure center, enabling the cells in this brain region to make receptor proteins themselves. An animal study examined how the injected genes affected the rats' cocaine-using behavior after they had been taking cocaine for 2 weeks. Having received the D2 receptor treatment, the rats showed a 75% decrease in self-administration of the drug. This effect lasted 6 days before their cocaine self-administration returned to previous levels.

Vaccination of the Cocaine User

TA-CD is an active vaccine developed by the Xenova Group/USA, which is used to negate the effects of cocaine, making it suitable for use in the treatment of addiction, and is made by combining norcocaine with inactivated cholera toxin. It works in much the same way as a regular vaccine. A large protein molecule attaches to cocaine, stimulating the response for antibodies, which then destroy the molecule.

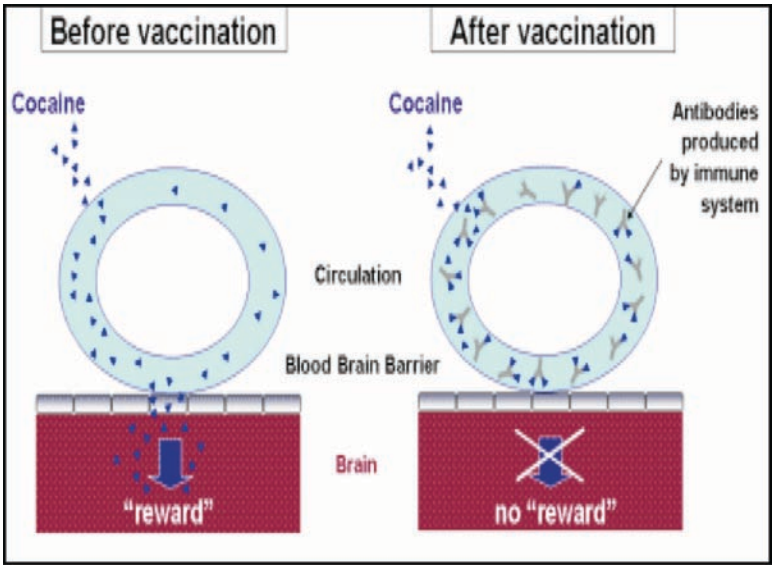

Fig. 52 Principles of vaccination preventing further use of cocaine and avoiding relapse

This also prevents the cocaine from crossing the blood-brain barrier, negating the euphoric high and rewarding effect of cocaine caused from stimulation of dopamine release in the mesolimbic reward pathway (Fig. 52). This anti-cocaine vaccine is in early testing stages. Reports indicate that the vaccine successfully mounted an antibody response against free cocaine in the blood that lasted nearly 3 months. It is believed that antibodies to other stimulants might also be developed [62]. In addition, TA-CD also has been shown to lower the effect of cocaine on the heart.

Newer Dopamine Reuptake Inhibitors

GBR-12909 (Vanoxerine)

Vanoxerine is a selective dopamine uptake inhibitor. Because of this action, it reduces cocaine's effect on the brain, and may help to treat long-term cocaine addiction. Preliminary studies have shown that GBR 12909, when given to primates, suppresses cocaine self-administration. As of 2006 clinical studies phase 2 are in progress.

Venlafaxine (Effexor®) and Ecopipam

Although not a dopamine reuptake inhibitor, venlafaxine is a serotonin/norepinephrine reuptake inhibitor that has been successfully used to combat depression

caused by cocaine withdrawal and to a lesser extent, the addiction associated with the drug itself. Further clinical studies, especially in regard to side-effects are planned to prove its usefulness.

Recently reported research demonstrated that the selective dopamine D1/D5 receptor antagonist ecopipam diminished the euphoric and anxiogenic effects of cocaine, and stemmed craving [82]. It has been suggested that low doses of the antagonists might be useful in blocking relapse or blunting effects of relapse when it occurs. D3 receptor partial agonists also have been effective in reducing cocaine craving, so a combination of drugs acting on D1 and D3 receptors might prove particularly powerful for treating cocaine addiction [83].

Outlook Regarding Therapy in Cocaine Abuse

One of the biggest challenges in treating drug addiction is the danger of relapse after quitting. Drug-associated cues can trigger persistent drug cravings that grow stronger the longer the abstinence, but what mediates the increasing reactivity of the brain to these cues is not well understood. It is known that cocaine-seeking also depends on activation of a subgroup of glutamatergic receptors in the nucleus accumbens. Recently researchers have shown that rats that undergo prolonged withdrawal from cocaine show an increase in the numbers of this type of synaptic APMA (α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid) receptors. This, in return, leads to the increased reactivity of nucleus accumbens neurons to cocaine-related cues and an increase in drug-seeking by the animals. Thus, the AMPA receptors in the nucleus accumbens present a new approach to tackle the problem of cocaine-related relapse [84].

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