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Round table on nicotinic receptors in addiction: summary report

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No report can adequately summarize the spirited 2 h Round Table, which took place at the end of the last day of the scientific meeting on Neuronal Nicotinic Receptors: From Structure to Therapeutics. The participants, Drs. David K. Balfour, Paul B.S. Clarke, Gaetano Di Chiara, Emilio Merlo Pich, and the formal discussant, Dr. Tomoji Yanagita, each presented their points of view and were, in turn, both questioned and given differing opinions by members of the audience. The only conclusion all would agree on is that there is a need for more research.

A specific role of nicotinic acetylcholine receptors in addiction is based on the fact that acetylcholine and choline are important neurotransmitters and/or modulators of many aspects of behavior including those that are pleasurable, reinforcing, habit forming and, in some, addicting. Both muscarinic and nicotinic receptors are involved in central and peripheral mechanisms that involve pleasurable behaviors and substances. It is well documented that many pleasurable substances are readily self-administered by animals and humans. Nicotine is reinforcing in animals as are tobacco products, especially cigarette smoke, in man. Pure nicotine in the form of gum, patches, nasal sprays, and inhalers appears not to be abused by humans even though package inserts warn of their addiction liability. Nicotine administration by different methods of delivery is statistically more effective than placebos in helping tobacco smokers quit. Lam et al. (1987) reported a *meta*-analysis of controlled clinical trials of nicotine gum in specialized clinics in which after 6 months the success rate to quit was 27% with nicotine and 18% with placebo. In 1994, Silagy et al. reported a *meta*-analysis on various nicotine replacement therapies in smoking cessation. After at least 6 months, the odds ratio of abstinence was 1.61 for gum, 2.07 for patch, 2.92 for nasal spray and 3.05 for inhaled nicotine. Hughes et al. (1999) also reviewed a variety of pharmacotherapies of tobacco smoking. They concluded that one third of cigarette smokers who quit and use pure nicotine products for 6 months return to cigarette smoking. Statistically, nicotine replacement clearly is better than a placebo to help smokers quit. However, clinically the success rates for quitting smoking, even with the best of pharmacological therapies, are clinically far from impressive (Domino, 1999). This occurs even when tobacco smokers who desire to quit are given the very best psychological, social and family support. Why is the delivery of nicotine and the thousand other chemicals (mostly very bad for ones' health) so addicting? The Round Table focused on the role of the cholinergic system via its nicotinic cholinergic receptors in the reinforcing effects of addicting substances, mostly nicotine itself. During this excellent meeting, the participants heard of the multiple nicotinic cholinergic receptors and their role in cognition, memory, attention, and anti-anxiety as well as in Alzheimer's disease, Parkinson's disease, epilepsy and schizophrenia. However, there is a ''price'' the tobacco user must pay in activating and desensitizing nicotinic receptors with nicotine; that is, the increased risk of cardiovascular and pulmonary diseases and various forms of cancer. Why do people continue to use tobacco products knowing the health risks? How can we scientists help to develop better strategies to improve the quality of life? Which nicotinic cholinergic receptors are the most important and especially what further research needs to be done? The format of the Round Table was that each speaker gave a brief presentation with enough time for discussion, specific questions, or responses from all the other attendees as the major researchers in this field.

Dr. Balfour pointed out that nicotine shares many properties with other psychostimulants but has a different mechanism of action at the molecular level. Cocaine and amphetamine increase dopamine release via their effects on the presynaptic dopamine transporter, whereas nicotine influences impulse flow to the terminal field by acting on nicotine receptors on or near dopamine cell bodies in the ventral tegmental area (Balfour et al., 1998). Acute nico-

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tine injections to drug-naive animals preferentially increase dopamine overflow in the shell of nucleus accumbens when measured using in vivo microdialysis. Repeated daily injections of small doses of nicotine, however, result in sensitization of its effects on the projections to the core of the accumbens. In nicotine chronically treated animals, dopamine overflow in this subdivision of the accumbens is significantly enhanced. The sensitized response is attenuated if an NMDA receptor antagonist is given prior to the challenge dose of nicotine. These, and other, results suggest that the sensitized response reflects the fact that chronic, but not acute, nicotine increases burst firing of the neurons, which project to the core of the accumbens. Pretreatment with nicotine does not sensitize animals to the effects of three other nicotinic receptor agonists, ABT-418 [(*S*)-3-methyl-5-(1-methyl-2-pyrrolidinyl)isoxazole], epibatidine or lobeline, on dopamine overflow in this region of the brain. Dr Balfour argued that these data, when taken together, are most consistent with the hypothesis that the expression of the sensitized dopamine response to nicotine probably reflects co-stimulation of at least two isoforms of the nicotinic receptor. One of the receptors, putatively containing $\alpha 3$, $\alpha 4$ or $\alpha 6$ subunits, is located on the dopamine-secreting cells; the other, putatively containing $\alpha 7$ subunits, is located on glutamate terminals and facilitates the release of glutamate in the ventral tegmental area. Chronic treatment with amphetamine and cocaine also results in sensitization of their effects on dopamine release in the core of the accumbens (Di Chiara, 1998). In addition, it has been suggested that an ability to elicit sensitized dopamine responses in the nucleus accumbens may be fundamental to the addictive potential of drugs of dependence, being involved with the change from 'drug-liking' to 'drug-wanting' or 'drug-seeking behavior' (Robinson and Berridge, 1993). Since the nucleus accumbens core sends major projections to motor areas of the brain, Dr. Balfour hypothesized that sensitization of the dopamine projections to the core may reinforce specifically drug seeking behavior.

Dr. Changeux asked where receptors involved in the sensitized responses were located. Dr Balfour responded that one important locus was the ventral tegmental area since the response could be evoked by microinjecting nicotine directly into this part of the brain. However, the possibility that other loci might be involved in the response to systemic drug could not be excluded. Dr. Neal commented on the fact that although tobacco smoking seemed to be very addictive, this was not the case for pure nicotine preparations in spite of the fact that they carried a health warning, which covered their potential addictive properties. Dr. Balfour acknowledged that tobacco smoke contained other components, which might also be important to its ability to elicit addiction. This included a component, almost certainly not nicotine itself, which inhibits monoamine oxidase B (Fowler et al., 1996). The degree of enzyme inhibition, evoked by tobacco smoke (approx. 60%) may not, however, be sufficient to elicit a pharmacologically meaningful effect since many pharmacologists argue that up to 80% of the enzyme needs to be inhibited before any significant consequence ensue. Dr Balfour also suggested that other components of the smoke might act as conditioned reinforcers when paired with nicotine.

Dr. Bertand asked if the sensitized dopamine response reflected stimulation or desensitization of nicotinic receptors. Dr. Balfour responded by saying that it was most likely that the increased dopamine overflow reflected stimulation of nicotinic receptors. Dr. Stolerman cautioned that behavioral sensitization to nicotine may not necessarily be relevant to tobacco dependence in humans because there was little evidence for a similar phenomenon in humans. Furthermore, secondary conditioned stimuli seem to play a very important role in maintaining the tobacco smoking habit. Dr. Balfour acknowledged that this was correct but went on to hypothesize that the primary role of extrasynaptic dopamine in the nucleus accumbens may be to facilitate the attribution of incentive salience to the many sensory cues associated with smoking a cigarette. He drew attention to the fact that one of the principal consequences of increased burst firing of dopamine neurons was to cause a marked and sustained increase in extracellular dopamine. In this respect, the response to chronic nicotine resembled that of the other psychostimulant drugs of abuse. He hypothesized that any stimulus experienced during this period of raised extracellular dopamine has the potential to acquire the characteristics of a secondary or conditioned reinforcer and, thus, contribute significantly to the development of dependence. The repetitive nature of the tobacco smoking habit lends itself particularly well to this concept and may explain why cigarette smoke appears much more addictive than the pure nicotine preparations, most of which are designed to maintain the plasma nicotine concentration at a level which avoids withdrawal.

Dr. File pointed out that the rate at which nicotine enters the brain is an important factor in the development of addiction and asked if Dr. Balfour had investigated the responses to i.v. nicotine since this mimicked more closely absorption of nicotine from tobacco smoke inhaled into the lungs. Dr. Balfour agreed that this was an important issue but said that he had not yet explored the effects of i.v. nicotine. However, he said that whereas single injections of s.c. nicotine evoked increased dopamine overflow in the accumbens, this was not seen so clearly in animals given constant infusions of nicotine from osmotic minipumps. Indeed, nicotine delivered in this way antagonizes the response to a nicotine injection.

Dr. Di Chiara gave a most enthusiastic overview of his research, which he summarized in detail earlier in the Symposium. Although he agreed with Dr. Balfour and others on the importance of dopamine release in nicotine dependence, he emphasized the putative role of the shell and core of nucleus accumbens. Data from his laboratory

indicate that acute nicotine given to nicotine-naive rats induces dopamine release primarily in the shell. With repeated nicotine administration, dopamine release in the shell does not change or is down regulated, the same as with morphine administration. He emphasized the difference between explicit expectancy learning and automatic ''habit'' learning. Naive rats given nicotine do not show much dopamine release in the core of nucleus accumbens. Only with repeated nicotine administration is there an increase in release of dopamine in the core. The ratio of core to shell dopamine release is increased with nicotine induced sensitization. Not only is core dopamine release increased, but also shell dopamine release is decreased. This phenomenon is not specific for nicotine but occurs with cocaine and morphine as well as with deprivation of about 85% of normal intake of food on a lean body weight schedule. In addition, repeated mild stress produces the same effect. Dr. Di Chiara's working hypothesis is that dopamine release in the shell is involved in associative stimulus-reward learning and in non-automatic incentive responding. This responding is controlled by its consequences, i.e., by an action–outcome relationship. Dopamine release in the core, instead, is hypothesized by Dr. Di Chiara to be involved in the expression of habit responding, a form of instrumental responding that is relatively independent from its outcome as it is triggered by stimuli that run the response automatically according to a motor plan or to an action scheme. Nicotine addiction is viewed by Dr. Di Chiara as a form of instrumental responding initially controlled by nicotine according to an action–outcome relationship. With training, responding becomes progressively independent from nicotine as it is controlled by stimuli conditioned to nicotine but preceding the response. This change corresponds to a shift from non-automatic to automatic responding as associative learning is shifted from incentive (accumbens shell) to habit learning (accumbens core).

Dr. Merlo Pich recommended caution regarding some of the conclusions by Dr. Di Chiara about the reinforcing properties of nicotine based on results obtained by administering an acute dose of nicotine. This is a paradigm that does not reproduce human smoking. In fact, acute nicotine can produce aversive effects in mammals, and the neurochemical correlates of such administration do not reflect the substrate of the reinforcing effects of nicotine. Only experiments in which nicotine is chronically administered, and possibly chronically self-administered by the experimental animals, can be considered with some degree of correctness as mimicking human smoking. Dr. Ken Lloyd commented that while dopamine release may be necessary and sufficient in the rat, it may not be in humans. Other neurotransmitters, including norepinephrine and serotonin, must be considered, as well as the rewarding properties of other stimuli. Dr. Bertand was intrigued with the role of minimal stress in behavioral sensitization since corticosteroid interactions with nicotinic cholinergic receptors are well known. Furthermore, the role of gender and its hormonal effects needs more research. Dr. Changeux asked if dopamine release in the shell is critical and what is the target of its shell release. Perhaps acetylcholine itself is the major reward substance. Dr. Di Chiara's response was that the shell of the nucleus accumbens and the bed nucleus of stria terminalis involve a terminal dopamine area belonging to the ''extended amygdala'' involving an affective signature of increased stimuli from short term to long term memory. Dr. Sandra File suggested that mild stress and the anxiogenic effects of nicotine are rewarding. Thus, the negative effects of nicotine inducing mild stress may be most important to its addiction liability! Although Dr. Di Chiara disagreed, he did leave the door open to many different possibilities of reward. It was clear that his verbal sparring with Dr. File were both stressful as well as rewarding to him.

Dr. Merlo Pich summarized the role of nicotinic receptors containing β2 subunits in the reinforcing properties of nicotine in genetically modified mice developed at the Pasteur Institute by Changeux et al. (1998). Self-administration of drugs such as cocaine and nicotine is a conditioned operant behavioral paradigm that involves two different associative learning phenomena mixed together. The first is stimulus–response learning, which is the basis of habit forming. The second is stimulus–reward (incentive) learning, which produces an association between the action leading to the delivery of the drug (i.e., lever pressing) and the rewarding effects of the drug. Wild type mice with intact β2 nicotinic receptor subunits, when trained to cocaine, work to nose poke a lever for an i.v. injection of nicotine. Wild type mice trained to nicotine also work when nicotine is replaced by cocaine. When wild type mice trained to nicotine are given saline as a substitute, they bar press for a period of time and then extinguish. When nicotine is given as a substitute for cocaine in β2 knock out mice trained to self-administer cocaine, it is not perceived as reinforcing. The animals continue to work for a time but then extinguish their responding as if given saline. Their initial responding to the substituted nicotine is interpreted as the habit form of learning. It is an artifactual continuation of bar pressing in which the animal is seeking a reinforcement, which it does not obtain because the knock out animals subsequently extinguish. By using a discrimination index between active and inactive drug lever pressing, it was noted that wild type mice easily distinguish and prefer the active lever, whereas the β2 knock out mice lever presses are random. In another experiment using a drug discrimination paradigm with sugar sweetened milk as a reward, wild type mice can be trained to associate nicotine injections with the active lever for sweet milk reinforcement. If the animals are given saline, they learn to press the opposite lever for sweet milk reward. With training, the wild type animals are able to discriminate between the two levers, but the β2 knock out animals cannot. They do not recognize a small dose of

nicotine from saline, in contrast to their wild type controls. Knock out animals only discriminate a large dose of nicotine that would be toxic if given to wild type mice. The large dose nicotine discrimination may be related to some high affinity nicotine binding sites still left in the knock out animals, as described by Dr. Changeux earlier in this meeting. Another important point is that the α7 subunits, as well as other nicotine receptors in brain areas such as the solitary tract and area postrema, are not modified, nor are they in the peripheral nervous system of β2 knock out mice. A peripheral autonomic action of nicotine may be involved. Dr. Merlo Pich also described preliminary data using an immediate early gene transcription factor Fos brain mapping technique in wild type control and β2 knock out mice. Naive mice with an i.v. catheter were yoked to self-administering animals and exposed to passive nicotine infusion. The shell of nucleus accumbens showed half as much Fos activity in the knock out compared to the wild type animals. The core was less activated than the shell, with a similar ratio of reduction in the knockouts. Other brain areas showed complex differential and also no changes between wild type and the β2 knock out mice. For example, the central amygdala and the lateral septum were strongly activated in the wild type but not in the knock out mice, whereas the paraventricular nucleus of the hypothalamus showed no difference in the two types of mice. The wild type animals appeared to be in a situation of mild stress based upon the Fos brain pattern. It is known that acute nicotine, like amphetamine and cocaine, appears to induce a more aversive internal state of anxiety and stress-like changes, whereas the chronic nicotine-treated animals have a less anxiogenic and more reward type pattern of Fos in various brain nuclei. Dr. Balfour asked if this was evidence for mild stress maintaining nicotine responding as per the Sandra File hypothesis. However, Dr. Di Chiara felt it merely confused the issue. In his research, stress decreases dopamine release in the shell and increases dopamine release in the prefrontal cortex, whereas nicotine (except in a large dose) produces the opposite effect. One of the participants stated he is less impressed with nicotine alone as an addictive agent and suggested other ingredients in tobacco must be studied. The animal models described do not adequately mimic craving in humans. Dr. Merlo Pich agreed that animal self-administration of nicotine is not a perfect model for human nicotine addiction because the animal's behavior is not compulsive and appears more a habit which has been learned.

Dr. Lloyd supported the concept of mild stress or sensation-seeking behavior that Dr. File mentioned earlier because the aversive effects of the first cigarette smoked are well known. Dr. Leonard raised the genetic issue in relationship to nicotine and tobacco smoking and its aversive or reinforcing nature. Dr. Stolerman reminded us that acute tolerance occurs to most of the unpleasant effects of tobacco smoking. Dr. Collins' group in Colorado have generated abundant data that genetic aspects of nicotine are important in different strains of mice and, therefore, probably in humans as well. While tobacco smoking involves many secondary reinforcers and stimuli, as well as many other chemicals, it does not negate the critical role of nicotine.

Dr. Le Houezec suggested that none of the animal models duplicate human cigarette smoking which, via inhalation, produces a direct route of delivery of nicotine from the lungs via the heart to the brain. He felt kinetic differences were most important, although Dr. Bertrand felt that the speed of injection of nicotine is only one factor. Dr. Neal commented that after so many years of tobacco use, there seems to be no good answers to simple questions. However, the producers of tobacco know that tobacco cigarettes that contain too little nicotine are not liked by smokers, indicating some nicotine is essential. A nicotine-free tobacco that contains all of the other products of tobacco smoke would answer the question of the importance of nicotine to tobacco use. However, such a tobacco may be impossible to genetically engineer.

The next panel speaker, Dr. Clarke, suggested the reviews by Stolerman et al. (1991, 1995) indicate that nicotine is indeed very important in tobacco. The current dogma, which is widely accepted, is that nicotine is addicting because it releases brain dopamine. With increasingly more research, it is evident that this dogma is changing because things are a lot more complicated than that. Dr. Clarke raised seven major issues: (1) Various stimuli that are either aversive, neutral or rewarding all increase dopamine release in nucleus accumbens. Aversive stimuli shown to increase dopamine release include foot shocks, tail shocks, restraint stress and β-carboline induced anxiety. Neutral stimuli such as intermittent non-correlated tone and light stimuli have no effect, but when the tone precedes the light there is increased dopamine release into the interstitial space of nucleus accumbens, indicating learning may be the important factor. (2) Many of the drugs of abuse in humans, including nicotine, cocaine, amphetamine, and morphine increase dopamine release as well. However, nucleus accumbens dopamine release is better correlated with the ''chase than the capture.'' A male rat separated from a receptive female by a transparent barrier shows increased dopamine release in the accumbens but does not when the barrier is lifted and he ''interacts'' with the female. The release of dopamine is more closely correlated with anticipation of reward. (3) ''Wanting'' or ''liking'' are terms introduced by Robinson and Berridge (1993). They have accumulated evidence that dopamine release may underlie wanting rather than liking. Liking is the immediate hedonic impact, whereas wanting is the anticipation and looking forward to the reinforcer. The immediate hedonic response in rats with interrupted dopamine transmission to taste stimuli is unaltered. (4) Lesioning of the dopamine system will prevent rats from responding to nicotine, amphetamine, etc. This has been

used as evidence for the critical role of dopamine in reward. One of the problems of the microdialysis technique is it tends to extract from the extracellular fluid many substances with a molecular weight lower than the molecular sieve used. Thus, many chemicals are removed, of which only a very few, like dopamine, are measured. (5) Electrophysiologic recordings of dopamine neurons by Schultz et al. (1997) during presentation of unexpected rewarding stimuli indicate these dopaminergic cells transiently increase their firing. On the other hand, a neutral stimulus that precedes the reward in a well-trained animal produces increased neuronal firing, but not to the reward itself. If the conditioned stimulus is present without the reward, then the firing rate of dopaminergic neurons is decreased. Thus, dopaminergic cell firing appears related to discrepancies between the amount of reward delivered and the amount of reward actually obtained. (6) Several reports, principally from the lab of A. Gratton (Richardson and Gratton, 1996) suggest that dopamine release may actually decrease when reward is delivered. This conclusion is based on the use of an in vivo electrochemical technique that monitors catecholamine-related signals in the nucleus accumbens in rats that are bar pressing in order to obtain intermittent rewards. (7) We know very little about what goes on in the brains of tobacco smokers. Quite likely, because of nicotinic cholinergic receptor desensitization, there is very little increase in baseline dopamine release with repeated tobacco smoking throughout the day. Desensitization of nicotinic cholinergic receptors may be an important effect of continued nicotine use.

Dr. Di Chiari took strong exception to Dr. Clarke's remarks, stating that Dr. Clarke's review of the field represented the state of knowledge 2–3 years ago. Since then, the role of the shell response using modern microdialysis techniques has clarified some of the issues Dr. Clarke referred to in which less precise methods were used. Unfortunately, there was no time for further discussion of these issues.

Dr. Yanagita, as the invited discussant, described his view of nicotine dependence and its relationship to other drugs of abuse. He raised two important questions: (1) Is the proposed biological mechanism of nicotine dependence specific to nicotine or common to other drugs of abuse? (2) Does the proposed mechanism of action of nicotine explain its unique dependence profile? The dependence profile of nicotine is characterized by a mild increase of extracellular dopamine in nucleus accumbens, tachyphylaxis, moderate reinforcing effects, mild withdrawal manifestations, no enhancement of the reinforcing effect by pretreatment with repeated administrations of nicotine, and lack of psychotoxicity. It is well known that cocaine or the amphetamines markedly stimulate dopamine release into the extracellular fluid of nucleus accumbens in rat brain. Nicotine also elevates the dopamine concentration in nucleus accumbens but the effect is very weak, particularly in nicotine-naive rats (Yanagita et al., 1995). However, it is not clear to what extent the release of dopamine is relevant to the reinforcing efficacy of drugs. Nicotine develops tachyphylaxis but usually not tolerance. This is clearly demonstrated in intravenous self-administration of nicotine in rhesus monkeys (Yanagita et al., 1974). A gradual increase of drug intake in the first few weeks is observed with morphine, barbiturates, and alcohol but no such increase is observed with nicotine. Dr. Yanagita et al. have shown that the reinforcing efficacy (indicated as a breaking point) for nicotine in a progressive ratio test in self-administration experiments is up to 2690, which is much lower than that of cocaine (12,800) or alcohol (6400). A proposed mechanism should be able to differentiate nicotine from cocaine in this regard. He pointed out that the withdrawal syndrome of nicotine reported in humans consists mainly of psychic symptoms such as irritability, impatience, anxiety, restlessness, and difficulty in concentrating. In rhesus monkeys, no observable withdrawal signs are developed following hourly intravenous administration of nicotine in a dose of 0.25 mg/kg/injection for 4 weeks.

Dr. Yanagita also stressed that although enhancement of the reinforcing effect by pretreatment (development of physical dependence) is observable markedly with opiates and moderately with alcohol, no such enhancement is observable with nicotine, as confirmed in the progressive ratio test even after pretreatment at a maximally tolerable dose regimen.

Cocaine and amphetamines are known to produce marked psychic disorders such as delusion and hallucinations. According to the Diagnostic Criteria of DSM-IV, substances such as cocaine, opioids, and alcohol produce delirium, psychotic disorders, mood disorders, anxiety disorders, sexual disorders, and sleep disorders. None of these symptoms are applicable to nicotine. In fact, in self-administration experiments in rhesus monkeys, he and his colleagues did not observe any unusual behaviors throughout the active nicotine taking period or the withdrawal period. A proposed mechanism of action has to be able to differentiate nicotine from other drugs.

Dr. Yanagita felt that the dependence characteristics of nicotine known in animals may differ from those in humans because some psychological and social factors specific to humans may be involved. Since proposed mechanisms are biologically based, it is not necessary to explain all of the characteristics that are specific to humans. However, they have to explain the biological characteristics of nicotine dependence that are observed in animals. His final point was that there are many factors, including legal status, availability, price, sociological, and psychological issues that add to the unique dependence profile of nicotine in the form of tobacco in humans. Table 1 summarizes the dependence profiles of nicotine, cocaine, and morphine, as viewed by Dr. Yanagita.

It was fitting that the last comment and question was from Dr. Changeux. Perhaps we are anthropomorphizing

Table 1

Drug	Dopamine release in nucleus accumbens	Reinforcing effect	Enhancement of self-administration by repeated administration	Withdrawal	Psychotoxicity
Nicotine	mild	moderate	none	mild	none
Cocaine	marked	marked	none	mild	severe
Morphine	moderate	marked	marked	severe	moderate

too much and assigning human interpretations to animal data. If the only unique mechanism involving nicotine addiction is the dopamine receptor target in the shell of nucleus accumbens, then dopamine antagonists should block nicotine addiction. Dr. Balfour's response was that the dopamine D_3 receptors are expressed primarily in the shell of nucleus accumbens. We need unique new drugs to preferentially target such receptors before we can provide an answer.

In conclusion, it is clear that the brains of mice and rats are very complex, those of humans far more so. A repeated theme throughout the Round Table was that we need to do a great deal more research on the role of specific nicotinic cholinergic receptors in addiction.

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References

Balfour, D.J.K., Benwell, M.E.M., Birrell, C.E., Kelly, R.J., Al-Aloul, M., 1998. Sensitization of the mesoaccumbens dopamine response to nicotine. Pharmacol. Biochem. Behav. 59, 1021–1030.

Changeux, J.-P., Bertrand, D., Corringer, P.-J., Dehaene, S., Edelstein, S., Léna, C., Le Novère, N., Marubio, L., Picciotto, M., Zoli, M., 1998. Brain nicotinic receptors: structure and regulation, role in learning and reinforcement. Brain Res. Rev. 26, 198–216.

Di Chiara, G., 1998. A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. J. Psychopharmacol. 12, 54–67.

Domino, E.F., 1999. Pharmacotherapy of tobacco smoking cessation. JAMA 281, 1984, To the Editor. Letters.

Fowler, J.S., Volkow, N.D., Wang, G.-J., Pappas, N., Logan, J., MacGregor, R., Alexoff, D., Shea, C., Schlyer, D., Wolf, A.P., Warner, D., Zezulkova, I., Cilento, R., 1996. Inhibition of monoamine oxidase B in the brains of smokers. Nature 379, 733–736.

Hughes, J.R., Goldstein, M.G., Hurt, R.D., Shiffman, S., 1999. Recent advances in the pharmacotherapy of smoking. JAMA 281, 72–76.

Lam, W., Sacks, H.S., Sze, P.C., Chalmers, T.C., 1987. *Meta*-analysis of randomized controlled trials of nicotine chewing gum. Lancet 4, 27–29.

Richardson, N.R., Gratton, A., 1996. Behavior-relevant changes in nucleus accumbens dopamine transmission elicited by food reinforcement: an electrochemical study in rat. J. Neurosci. 16, 8160–8169.

Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Rev. 18, 247–291.

Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275, 1593–1599.

Silagy, C., Mant, D., Fowler, G., Lodge, M., 1994. *Meta*-analysis of efficacy of nicotine replacement therapies in smoking cessation. The Lancet 343, 139–142.