The Effect of Both Vitamin E and Thymoquinone on Monoamine Neurotransmitter Changes Induced by Nicotine Treatment and Withdrawal in The Cortex and Hippocampus of Rat Brain

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ABSTRACT

Both vitamin E and thymoquinone have been used in the treatment of many neurodegenerative disorders. This study aims to investigate the effect of vitamin E or thymoquinone on the alterations in monoamine neurotransmitters induced by nicotine treatment and withdrawal in adult male albino rats. Animals were divided into control group (0.9% NaCl saline solution), nicotine-treated group (1mg/kg B.W.), nicotine (1mg/kg B.W) + vitamin E (75 mg/kg B.W.) treated group and nicotine (1mg/kg B.W) + thymoquinone (5 mg/kg B.W.) treated group. Animals were sacrificed after 14 and 28 days of daily treatment and after 3 and 7 days of stopping the treatments that persisted for 28 days. The brain was dissected to obtain the cerebral cortex and hippocampus and the levels of dopamine, norepinephrine and serotonin were determined by spectrofluorimeter. The results obtained have shown that the combined treatment of nicotine with vitamin E or thymoquinone alleviated the changes in monoamine neurotransmitters induced by nicotine during the treatment and withdrawal periods. The prominent effects of vitamin E or thymoquinone were observed during nicotine withdrawal. This was evident from the restoration of almost all the neurochemical changes induced in the hippocampus and cortex in the monoamine neurotransmitters to nearly control-like values. Thus it could be suggested that the administration of either vitamin E or thymoquinone during smoking could reduce the neurochemical changes induced by nicotine and the withdrawal symptoms induced by nicotine cessation.

Key words: Nicotine - Monoamine Neurotransmitters - Vitamin E - Thymoquinone - Cortex - Hippocampus

Introduction

Nicotine, the primary psychoactive component of tobacco, elicits a variety of behavioral, physiological and biochemical responses. It is believed that the dopamine systems of the brain mediate a number of the behavioral responses to nicotine, including particularly the locomotor stimulant and “rewarding” properties of the drug (Corrigall et al., 1992). Nicotine acutely stimulates dopamine transmission after systemic administration in rats naive to nicotine (Benwell and Balfour, 1992). Nicotine not only increase dopamine in areas usually associated with reward or drug preference, but also in other brain areas usually associated with cognitive processes. Shearman et al. (2008) reported that the changes induced by nicotine in monoamine neurotransmitters and in the levels of several transmitters were altered by nicotine in a regionally heterogeneous manner. Nicotine-induced increase in dopamine level in the dorsal and ventral hippocampus, prefrontal and medial temporal cortex, and superior cerebral peduncle.

The central nervous noradrenergic system is involved in stress related responses and memory function (Bremner et al., 1996). Nicotine has been reported to induce norepinephrine release in several brain regions, both in vivo and in vitro (Matta et al., 1995). Systemically administered nicotine has been reported to stimulate norepinephrine release in the hippocampus, paraventricular nucleus of the hypothalamus, amygdala and the cerebral cortex (Summers and Giacobini, 1995; Fu et al., 1998).

There are several behavioral effects of nicotine that seem to be mediated by effects on the serotonergic system. The effects in the cortex, hippocampus, and dorsal raphe nucleus involve stimulation of serotonergic receptors, which play a role in mediating the anxiolytic effects of nicotine. In addition, the serotonergic receptors in the dorsal hippocampus and lateral septum mediate the anxiogenic effects of nicotine (Seth et al., 2002). Systematically administered nicotine (0.2 mg/kg sc) significantly increased cortical serotonin release in awake, behaving rats (Summers and Giacobini, 1995), whereas a higher dose (1.2 mg/kg sc) had no effect. In vivo microdialysis study, chronic treatment with nicotine (0.4 mg/kg sc for 21 days) decreased serotonin...
concentration in the dorsal hippocampus (Ridley and Balfour, 1997). In contrast, Takada et al. (1995) reported increased serotonin concentration after chronic nicotine treatment (0.4 mg/kg/day sc for 14 days).

Smoking cessation is known to produce an aversive withdrawal syndrome in humans (Hughes et al., 1991). This syndrome arises, at least in part, because of the reduction in nicotine intake in nicotine-dependent individuals. The aversive aspects of the nicotine withdrawal syndrome are thought to be powerful motivational factors contributing to the maintenance of the tobacco habit. This nicotine withdrawal syndrome is comprised of somatic and affective components (Malin et al., 1992).

The mesolimbic dopamine system is involved in mediating aversive behavioral states associated with drug withdrawal (Stinus et al., 1990). The reduction in dopamine output observed during nicotine withdrawal may be involved in mediating the increase in anxiety associated with nicotine withdrawal (Weiss et al., 1996). On the other hand, the increase in anxiety observed in rats undergoing nicotine withdrawal suggests that there is enhanced serotonergic transmission during nicotine withdrawal (Cheeta et al., 2001). In addition, there is now a considerable amount of evidence suggesting that noradrenaline plays a major role in mediating somatic signs in rats undergoing opiate withdrawal. Therefore, it is possible that noradrenaline may play a role in mediating somatic signs in rats undergoing nicotine withdrawal (Delfs et al., 2000).

There is a close relationship between the changes in monoamine neurotransmitter contents and the state of oxidative stress induced by nicotine treatment. This relationship is supported by the study of Blum et al. (2001) who found that nicotine evokes the release of dopamine and norepinephrine which are pro-oxidant neurotransmitters suspected to contribute to cell death in neurodegenerative diseases. In addition, the increased dopamine in the extracellular space leads to the formation of oxidative products of dopamine; the neurotoxin 6-hydroxydopamine that is another toxic by-product of dopamine (Seiden and Vosmer, 1984). Moreover, serotonin or its metabolites are likely to enhance plasma lipid peroxidation via changes in the redox potential and lipid peroxidation chain reaction (Aviram et al., 1991) where high serotonin levels were found to cause oxygen formation (Lee et al., 1998) and hydrogen peroxide as a by-product (Abell and Kwan, 2001).

Vitamin E is essential for neurological functions and has shown some promise in the treatment of neurodegenerative disorders that involve free radical processes and oxidative damage, like Alzheimer's and Parkinson's diseases (Vataattlesy, 1992). This fact, together with a growing body of evidence indicating that neurodegenerative processes are associated with oxidative stress, lead to the convincing idea that several neurological disorders may be prevented and/or cured by the antioxidant properties of vitamin E (Ricciarelli et al., 2007). In addition, Vitamin E protected the brain against the seizures and neuronal damage and also reduced percentage of neuronal cell death (Barros et al., 2007).

A larger number of medicinal plants and their purified constituents have shown beneficial therapeutic potentials. Seeds of Nigella sativa, known as black seed or black cumin, have been employed for thousands of years. The oil and seed constituents, in particular thymoquinone, have shown potential medicinal properties in traditional medicine (Mohamed, 2005). Thymoquinone has a protective effect against lipid peroxidation in the brain (Hosseinzadeh et al., 2007). Also, thymoquinone is effective in protecting rats against transient forebrain ischemia-induced damage in the rat hippocampus; this protection was evident from the significant reduction in neuronal cell death in the hippocampal region. This spectacular protection makes thymoquinone a promising agent in pathologies implicating neurodegeneration such as cerebral ischemia (Al-Majed et al., 2006).

Therefore, the aim of the present study was to evaluate the neurochemical effects of nicotine administration and withdrawal alone or in combination with either vitamin E or thymoquinone on the levels of monoamine neurotransmitters in the cortex and hippocampus of rat brain.

Materials and Methods

Experimental Design:

One hundred and sixty adult male Wistar albino rats, weighing 150-200 g, were used in the present study. The animals were obtained from the Animal House Colony of the National Research Center, Giza, Egypt. On arrival, animals were housed ten individuals per cage in stainless steel cages with ad libitum access to standard laboratory diet (composed of 10% casein, 4% salt mixture, 1% vitamin mixture, 10% corn oil, 5% cellulose and completed to 150 g with corn starch) and tap water in a temperature-controlled (20-25°C) and artificially illuminated (12 hs. dark/12 hs. light cycle) room free of any chemical contamination. Animals were allowed to acclimate 10 days before they were used. All animals received human care in compliance with the guidelines of the Animals Care and Use Committee of the National Research Center, Egypt.

Animals were divided into four main groups each one of forty animals: 1- control group that received continuous daily subcutaneous injections of isotonic saline solution 0.9% NaCl (1ml/kg B.W.), 2- nicotine-treated group that received continuous daily subcutaneous injections of nicotine as nicotine hydrogen tartrate salt (purchased from BDH Chemicals Ltd, Poole England) dissolved in saline solution (1mg/kg B.W.) (Rezvani and Levin, 2001; Hernandez and Terry, 2005), 3- nicotine + vitamin E-treated group that received continuous
daily subcutaneous injections of nicotine (1mg/kg B.W.) and oral administration of vitamin E (75 mg/kg B.W.) (Erat et al., 2007) and 4- nicotine + thymoquinone-treated group that received continuous daily subcutaneous injections of nicotine (1mg/kg B.W.) and oral administration of thymoquinone (5mg/kg B.W.) (Paget and Barnes, 1964).

Each group was subdivided into four subgroups of ten animals each; the first and second were sacrificed after 14 and 28 days of daily treatment respectively. The third and the fourth subgroups were sacrificed after 3 and 7 days of stopping treatments that persisted daily for 28 days to study the withdrawal effect of nicotine.

**Handling of Tissue Samples:**

Animals were killed by sudden decapitation after being fasted for 12 hours. The brain of each animal was quickly removed and rapidly transferred to an ice-cold Petri dish and dissected to obtain the cerebral cortex and hippocampus according to Zeman and Innes (1963) and Glowinski et al. (1966). Each brain area was weighed and frozen at -20°C until analyzed.

**Determination of monoamine levels in different brain regions:**

The quantitative determination of monoamine levels (dopamine, norepinephrine and serotonin) was carried out using spectrofluorometer (Jasco F777, with a source of xenon arc lamp 150 Watt, Jasco Ltd., Tokyo, Japan) according to the method described by Ciarlone, 1978).

**Statistical analysis:**

The data were expressed as means ± S.E.M. Data were analyzed by analysis of variance (ANOVA) followed by the Tukey multiple range test when the F-test was significant (p < 0.05). All analyses were performed using the Statistical Package for Social Sciences (SPSS) software in a PC-compatible computer.

**Results:**

As shown in figure (1a), the daily nicotine treatment for 14 and 28 days induced a significant increase in the cortical dopamine level. This increase was restored to non significant changes from control values after 14 and 28 days of daily treatment of nicotine + thymoquinone and after 28 days of nicotine + vitamin E.

On third and seventh day of stopping nicotine, nicotine + vitamin E and nicotine + thymoquinone treatments non significant changes were observed in the cortical dopamine levels.

Cortical norepinephrine level showed a significant increase and non significant changes after 14 and 28 days of daily nicotine treatment, respectively. The combined administration of nicotine with vitamin E but not with thymoquinone returned the increase in norepinephrine after 14 days to non significant change. After 3 and 7 days of stopping nicotine, nicotine + vitamin E and nicotine + thymoquinone treatments that persisted for 28 days a significant decrease in the cortical norepinephrine level was recorded (figure 1b).

The daily nicotine treatment induced a significant increase in cortical serotonin level after 28 days which was restored to non significant changes by the combined treatment of nicotine + vitamin E but persisted after nicotine + thymoquinone. Moreover, the reduced serotonin level induced after 3 days of nicotine stopping was restored after 3 days of stopping treatment of nicotine + vitamin E and nicotine + thymoquinone (figure 1c).

Figure (2 a) showed that a significant increase in the hippocampal dopamine level was observed after 14 and 28 days of daily nicotine treatment. This increase in dopamine level persisted with the combined daily administration of nicotine + vitamin E and nicotine + thymoquinone for 14 days and returned to control like value after 28 days of the combined treatment of either nicotine with vitamin E or thymoquinone.

After 3 days of stopping nicotine and nicotine + thymoquinone treatments a significant decrease in dopamine level was observed while non significant changes occurred after stopping nicotine + vitamin E.

The daily nicotine treatment for 14 days induced a significant increase in hippocampal norepinephrine level followed by non significant changes after 28 days. The daily combined treatment of nicotine with either vitamin E or thymoquinone restored the increase in norepinephrine to control-like value. On stopping the treatments non significant changes in norepinephrine level were observed (figure 2d).

No significant changes in the hippocampal serotonin level were observed throughout the experiment (figure 2c).
The sign * indicates a significant value in comparison to control value

**Fig. 1:** Effect of nicotine, nicotine + vitamin E and nicotine + thymoquinone on the levels of dopamine, norepinephrine and serotonin (μg/g fresh tissue) in the cortex of rat brain.
Discussion:

Nicotine is a psychoactive ingredient in tobacco products and its effect upon the central nervous system is the prime reason why people continue to smoke (Wise and Rompne, 1989). Once in the blood stream, nicotine is
quickly distributed throughout the body, reaching the brain in 7-8 seconds (Russell and Feyerabend, 1978) where it is briefly concentrated (Larson and Silvetle, 1975).

The present study revealed a significant increase in the concentration of dopamine after 14 and 28 days of daily nicotine treatment in both the cortex and hippocampus. The results are in agreement with those of Kubo et al. (1989) who found that 1mg/kg of nicotine resulted in an increase in dopamine content in eight brain regions including the cortex and hippocampus.

It has been reported that nicotine stimulates dopamine transmission in specific brain regions where dopamine is involved in nicotine's discriminative stimulus properties, nicotine-induced facilitation of intracranial self-stimulation, intravenous self-stimulation, nicotine- conditioned place preference and nicotine-induced disruption of latent inhibition (Di Chiara, 2000) since nicotine depends on dopamine for those behavioral effects that are most relevant for its reinforcing properties and are likely to be the basis of the abuse liability of tobacco smoke.

Nicotine is known to promote dopamine synthesis and release (Di Chiara and Imperato, 1988) by activating tyrosine hydroxylase, the first major rate-limiting enzyme in dopamine synthesis (Smith et al., 1991). In addition, nicotine not only increases gene expression of tyrosine hydroxylase but also other subsequent catecholamine biosynthetic enzymes (dopamine β-hydroxylase and phenyl ethanolamine-N-methyltransferase) in the periphery and many catecholaminergic regions of the central nervous system (Serova et al., 1993). The dopamine-secreting neurons that project from the ventral tegmental area and their projections to the prefrontal cortex and hippocampus are key players in dopamine release (Riegel et al., 2007).

Thus it could be concluded that the cortical and hippocampal significant increase in dopamine level that was recorded after 14 and 28 days of daily nicotine treatment may be attributed to the increased synthesis of dopamine and the stimulatory effect of nicotine on the dopaminergic neurons that project to the cortex and hippocampus.

Stopping nicotine treatment for 3 days revealed a decrease in dopamine content that was significant in the hippocampus. Several studies have recorded a reduction in dopamine content in the nucleus accumbens (Fung et al., 1996) and in the striatum (Duchemin et al., 2009). Nicotine cessation after chronic use causes various withdrawal symptoms including a collection of affective and somatic symptoms that emerge a few hours after nicotine abstinence and reflect the imbalance in brain neurochemistry created by the absence of nicotine. There is evidence that the dysfunction of the brain dopaminergic system might be responsible for some nicotine withdrawal symptoms, where the decreased dopamine levels after nicotine abstinence is the cause of nicotine withdrawal somatic signs (Ohmura et al., 2011).

The hypodopaminergic state associated with withdrawal is produced by both reduction in dopamine release and an increase in dopamine re-uptake (Duchemin et al., 2009). Synaptic vesicles play a major role in synaptic transmission by sequestering neurotransmitters for storage and subsequent release. The vesicular monoamine transporter-2 is responsible for packaging newly synthesized or recaptured dopamine into the synaptic vesicles and therefore controls the concentration and disposition of cytoplasmic dopamine within the nerve terminals. Increased expression of vesicular monoamine transporter-2 in dopaminergic neurons during nicotine withdrawal was reported by Duchemin et al. (2009).

Accordingly, the reduced dopamine content in the hippocampus and cortex due to stopping nicotine could be explained by the reduction in dopamine release and increase in the reuptake of dopamine. This decrease in dopamine level may mediate many of the withdrawal symptoms arising from nicotine cessation.

The combined treatment of nicotine with either vitamin E or thymoquinone did not alter the increased dopamine level induced by nicotine in the cortex and hippocampus after 14 days. However, non significant changes in dopamine were observed after 28 days of daily administration of either vitamin E or thymoquinone with nicotine. Furthermore, after 3 days of stopping nicotine + vitamin E and nicotine + thymoquinone, the significant decrease in hippocampal dopamine content induced by stopping nicotine was restored to non significant changes. This effect was more prominent in the case of the animals treated with nicotine + vitamin E.

It is clear from the present data that the restoration of dopamine content in the hippocampus of rats treated with nicotine + vitamin E or nicotine + thymoquinone may have a role in relieving many of the complications arising from nicotine administration and withdrawal. Thus, it could be suggested that both vitamin E and thymoquinone can be used as an adjuvant therapy for smoking addiction as dopamine underlies many of nicotine's effects induced in the central nervous system.

In the present study, the levels of norepinephrine in both the cortex and hippocampus revealed a significant increase after 14 days of nicotine treatment, while daily treatment of nicotine for 28 days returned the level of norepinephrine in both brain areas to control-like values.

The increased norepinephrine release after nicotine treatment was also demonstrated in the cortex and hippocampus (Fu et al., 1998).

The increase in norepinephrine in some cognitive areas such as the cortex and hippocampus raises the possibility that stimulation of cognitive mechanisms via increased noradrenergic activity may stimulate reward
mechanisms as in case of nicotine self-administration where norepinephrine has an important role in reward and learning (Yamamoto and Hornykiewicz, 2004).

The principal noradrenergic innervation to forebrain arises in locus coeruleus, where norepinephrine is secreted by neurons projecting from locus coeruleus (Balfour, 1982). Nicotine increases norepinephrine release by binding to nicotinic receptors located in the locus coeruleus, stimulating noradrenergic neurons to fire and increase the concentrations of norepinephrine. There is evidence that the norepinephrine-secreting neurons that project to the hippocampus from the locus coeruleus express nicotinic receptors on both the nerve terminals and somatodendritic membrane of the cells (Fu et al., 1998).

Accordingly, the present increase in norepinephrine levels in the cortex and hippocampus after 14 days of daily nicotine treatment could be mediated by nicotine-induced stimulation of nicotinic receptors in noradrenergic neurons in the locus coeruleus. In addition, the activation of tyrosine hydroxylase, the rate limiting enzyme in monoamine biosynthesis, by nicotine could have a role in the elevation of norepinephrine levels recorded in the present study in the cortex and hippocampus.

The levels of norepinephrine after 28 days of nicotine treatment returned to control-like value, which may be related to desensitization of nicotinic receptors located on the noradrenergic neurons.

It has been proposed that receptor desensitization on noradrenergic neurons may reduce the amount of norepinephrine released and play a role in the tranquilizing effects of cigarette smoke reported by many smokers (Wonnacott et al., 2005). Similarly, desensitization of norepinephrine release was investigated with repeated intravenous infusions of nicotine by Fu et al. (1998) who mentioned that with repeated administration of nicotine it is likely that there is a generalized desensitization of norepinephrine systems throughout the brain.

Animal research and human studies indicated that adaptation to many effects of nicotine developed with repeated exposure gradually leads to reduced magnitude of its effects including subjective effects (Schultz et al., 1998).

Thus, the restoration of norepinephrine level after 28 days in the present study may underlie reduced nicotine effects. This in turn may explain the increase in the number of smoked cigarettes in cigarette-smokers after a period of time where smokers overcome the receptor desensitization by increasing the nicotine concentration to satisfy the subjective effects induced by nicotine.

Stopping nicotine treatment for 3 and 7 days reduced the cortical norepinephrine level significantly. However, a non significant decrease was recorded in the hippocampal norepinephrine.

The present decrease in norepinephrine levels after nicotine withdrawal may be attributed to the decrease in monoamine oxidase activity. This enzyme plays a vital role in the control and regulation of monoamine neurotransmitter concentration (Nagatsu, 2004).

The action of catecholamines in the synaptic cleft is terminated by selective re-uptake of the neurotransmitter back into the presynaptic terminals via Na-dependent transporters. Once inside the terminals, these neurotransmitters are largely reloaded into synaptic vesicles, but may also be degraded by monoamine oxidase. The role of monoamine oxidase activity in reducing the level of norepinephrine was supported by the study of Villegier et al. (2006) who reported that monoamine oxidase inhibitors have been shown to prolong behavioral sensitization to nicotine and enhance the rewarding effects of nicotine. In addition, activation of monoamine oxidase prolonged place aversion conditioning associated with nicotine withdrawal.

Although the behavior of norepinephrine in the cortex and hippocampus was similar in response to nicotine, the change in norepinephrine was more remarkable in the cortex. This may be due to the interactions between dopamine and norepinephrine in the cortex.

The noradrenergic and dopaminergic projections that arise from the locus coeruleus and the ventral tegmental area, respectively, converge in the medial prefrontal cortex and the interaction between dopamine and norepinephrine neurotransmission in this area is attributed to at least two modulating processes, heteroreceptor and heterotransporter regulations (Pan et al., 2004).

It has been reported that dopamine outflow is regulated by noradrenergic terminals and the norepinephrine transporters due to the lack of dopamine transporters (Sesack et al., 1998). This mechanism plays a significant role in the clearance of extracellular dopamine in the prefrontal cortex (Yamamoto and Novotney, 1998).

Accordingly, the remarkable effect of nicotine on cortical norepinephrine may be due to the competition between norepinephrine and dopamine for the heterotransporter in the cortex where there is a lack of dopamine transporters.

The present data showed that the treatment of nicotine-treated rats with vitamin E or thymoquinone restored the changes in norepinephrine levels induced in the hippocampus and cortex after 14 days of nicotine treatment to non significant changes from control values.

It is worthy of notice that the ability of both vitamin E or thymoquinone to return the changes in norepinephrine to control value was more prominent in the hippocampus than cortex. This may be due to the drastic increase in cortical norepinephrine under the effect of nicotine.
As the cortex has been implicated in various types of behavior such as cognitive processes, response to stress and reward-oriented behavior (Schultz et al., 1998), it could be suggested that the combined treatment of nicotine with vitamin E or thymoquinone may reduce the evolution of addiction process induced by nicotine. The inability of the combined administration of nicotine with either vitamin E or thymoquinone to restore the withdrawal effects of nicotine on cortical norepinephrine level may require the continuation of vitamin E or thymoquinone treatment for a long time after the withdrawal of nicotine.

The present investigation showed non-significant changes in the hippocampal serotonin level during the treatment and withdrawal periods. However, in the cortex a significant increase in serotonin was recorded after 28 days of daily nicotine treatment. Moreover, stopping nicotine treatment for 3 days reduced the cortical serotonin level significantly.

The serotonergic system has been implicated in the pharmacological effects of nicotine (Olausson et al., 2001). Increased cortical serotonin after nicotine administration was reported by Summers and Giacobini (1995). It has been reported that the increase in serotonin release in the cortex is likely to be due to stimulation of nicotinic receptors located on cortically projecting cell bodies in the dorsal raphe nucleus (Summers and Giacobini, 1995).

Thus, the stimulation of serotonin release from serotonergic neurons projecting from the raphe nucleus to the cortex under the effect of nicotine treatment may underlie the present increase in cortical serotonin level. The increase in cortical serotonin was recorded after prolonged treatment (28 days) which may be related to the accumulation of high concentration of nicotine in the cortex.

Supporting this explanation is the study of Summers and Giacobini (1995) who reported that cortical serotonin levels were unaltered when nicotine was applied directly to cortical tissue through dialysis probe. However, administration of high concentration of nicotine through dialysis probe in the cingulate and frontal cortices resulted in elevated levels of serotonin (Toth et al., 1992).

This does not necessarily mean that nicotine was acting on a receptor located on serotonergic terminal, as the effect could have been mediated indirectly via the release of another neurotransmitter (Seth et al., 2002).

The non-significant changes in hippocampal serotonin due to nicotine treatment in the present study were reported by several investigators (Lendvai et al., 1996; Balfour and Ridley, 2000; Reuben and Clarke, 2000). They reported that chronic exposure to nicotine caused a reduction in serotonin concentration in the hippocampus. This reduction is limited strictly to the hippocampus and is associated with reduced rates of serotonin synthesis.

Therefore, the decrease in the hippocampal serotonin level observed in the present study could be attributed to the stimulation of serotonergic autoreceptors which in turn inhibit the serotonin biosynthesis. The present findings indicate a significant decrease in the cortical serotonin level after 3 days of nicotine cessation which are in agreement with the study of Benwell and Balfour (1979) who found a reduction in serotonin tissue content following nicotine withdrawal. It has been reported that nicotine withdrawal has an inhibitory influence on somatodendritic serotonin autoreceptors located within the raphe nuclei and thereby decreases serotonin release into forebrain and limbic site (Ridley and Balfour, 1997). This study was supported by the observation of Cheeta et al. (2001) who found that the administration of nicotine directly into the dorsal raphe nucleus at a concentration that activates somatodendritic serotonin receptors, reversed the increase in anxiety observed in rats undergoing nicotine withdrawal.

Thus, the reduced cortical serotonin level after 3 days of nicotine withdrawal in the present study could be mediated by the inhibitory effect of nicotine withdrawal on the somatodendritic serotonin autoreceptors in the raphe nuclei. The concomitant treatment of nicotine with either vitamin E or thymoquinone did not abolish the cortical increase in serotonin level induced by nicotine after 28 days. However, both vitamin E and thymoquinone restored the significant decrease in cortical serotonin level induced by nicotine withdrawal to control-like value.

It is clear from the present findings that the combined treatment of nicotine with vitamin E or thymoquinone may alleviate the neurochemical changes induced by nicotine during the treatment periods. The most prominent effects of both vitamin E or thymoquinone were observed during nicotine withdrawal. This was indicated from the restoration of almost all the neurochemical changes induced in the hippocampus and cortex in the monoamine neurotransmitters to nearly control-like values.

In the light of the data obtained from the present study, it could be suggested that the administration of either vitamin E or thymoquinone during smoking could reduce the neurochemical changes induced by nicotine.
and relieve the withdrawal symptoms observed after nicotine cessation. This in turn may help smokers to stop smoking.

References


