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Bupropion Versus (+)OH-Bupropion Efficacy Upon Dopaminergic Activities in the Ventral Tegmental Area: An *In Vivo* Electrochemical Study in Rodents

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ABSTRACT

Nicotine induces neurochemical and behavioral changes similar to those induced by the commonly abused drugs and the mesolimbic dopamine pathway, specifically originating from the Ventral Tegmental Area (VTA) and projecting to the Nucleus Accumbens may be an important component in the neural circuitry of reward. Various classes of amine carrier blockers have been studied for potential therapeutic application in drug addiction. One of these compounds, i.e. bupropion, has been shown to be effective for smoking cessation via its effect upon dopaminergic activities. Such effects are mediated via its metabolites and in particular (+)hydroxybupropion. In rat, bupropion has a different metabolism with no formation of (+)OH-bupropion metabolite making it a good species for comparing the effect of exogenous (+)OH-bupropion versus exogenous bupropion itself. Therefore, we have examined the acute effect of these two compounds upon the DA system via concomitant Differential Pulse Voltammetric measurements of DA levels and electrophysiological recordings of the firing rates within the VTA.

Keywords: Bupropion; (+)Hydroxybupropion; Ventral Tegmental Area; Rat; *In Vivo* Electrochemistry

Introduction

A majority of habitual tobacco smokers find it very difficult to quit the habit because they become addicted to the nicotine present in tobacco smoke. Nicotine increases dopamine release in the principal terminal field of the mesolimbic system, the nucleus accumbens, and there is evidence that this mediates the "rewarding" properties of the drug which reinforce it self administration [1,2]. Many observations provide considerable support for the hypothesis that the mesolimbic dopamine pathway, specifically originating from the Ventral Tegmental Area (VTA) and projecting to the Nucleus Accumbens (NAc), may be an important component in the neural circuitry of reward [3,4]. The effects of systemic nicotine on DA overflow in the NAc have been shown to depend mainly upon stimulation of nicotinic receptors in the VTA [5,6]. These results imply that nicotine exerts its effects on DA overflow by influencing impulse flow from VTA to the accumbal terminal field [1,7]. It has been widely reported that nicotine induces neurochemical and behavioral changes similar to those induced by the commonly abused drugs [8-10] and that different classes of amine carrier blockers have been studied for potential therapeutic application in drug addiction [11-13]. One of these compounds i.e. bupropion, has been shown to be effective for smoking cessation, its primary action is via inhibition of dopamine reuptake into neuronal synaptic vesicles, shows a weak inhibition of noradrenaline reuptake while having no or little effect on the serotonin system [14,15].

This therefore suggests that the blockade of catecholamine carriers may be useful also for the nicotine dependence [16-20]. Moreover, four active bupropion's metabolites have been identified in human and mouse plasma and some of them, in particular the (+)OH-bupropion, have been shown not only to have amine carrier blocker properties, but also to reach higher plasma concentrations compared to bupropion itself [21-23]. Indeed, bupropion undergoes metabolic transformation to this metabolite through hepatic cytochrome P450-2B6 (CYP2B6) [24]. In rat, bupropion has a different metabolism with no formation of (+)OH-bupropion metabolite [25-28] making it a good species for comparing the effect of exogenous (+)OHbupropion versus exogenous bupropion itself. Therefore, we have examined the acute effect of these two compounds upon the DA system via Differential Pulse Voltammetric (DPV) measurements of DA levels as well as electrophysiological recordings of the firing rates within the VTA.

Methods

Animals

Male adult rats (Wistars, 220–250 g) were supplied by Charles-River (Italy) and kept in temperature- and humidity controlled rooms (22°C, 50%). All animal procedures were carried out in accordance with the Italian law (Legislative Decree no. 116, 1992) which acknowledges the European Directive 86/609/EEC. Furthermore, all efforts were made to minimize the number of animals and their suffering. Four different groups of rodents were employed and treated with : (+)OH-bupropion, bupropion or vehicle: saline (NaCl 0.9%), respectively.

Combined *In Vivo* Electrophysiological and Voltammetric Analysis

Anaesthetised (urethane 1.5g/kg i.p.)) rodents have been prepared for combined *in vivo* electrophysiological and DPVoltammetric analysis as described earlier [29]. In particular a single micro-biosensor (carbon fibre micro-electrode: mCFE) has been used for both measurements [30]. The mCFE (30µm diam, 100µm length) was first electrically and chemically treated with Nafion in order to be selectively sensitive to nanomolar concentration of catecholamines [31]. Then it was inserted stereotaxically under light microscopy into the VTA following Paxinos atlas coordinates [32]. The data obtained from all the experiments were analysed with STATISTICA software version 6.0 using ANOVA to evaluate significant differences between mean values produced by drug treatments versus control (vehicle treatment). Statistical significance was set at a probability level of $p < 0.05$.

Results

Concomitant Voltammetry and Electrophysiology in Ventral Tegmental Area

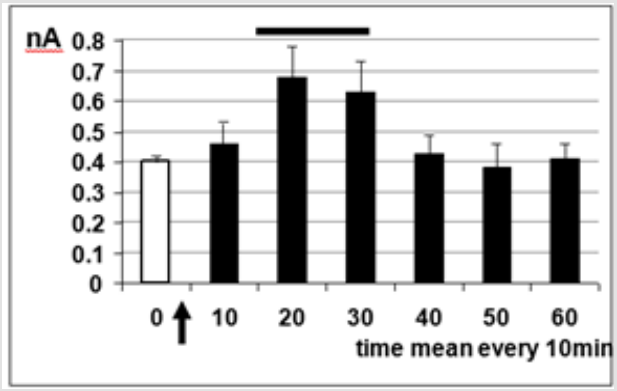

Figure 1: DPV analysis in VTA: effect of injection (arrow) of (+)OH-bupropion (4mg/Kg i.v.dissolved in saline, n=4) following a control period of 10 min recording. The voltametric levels of extracellular DA are measured in nanoAmperes (nA), they are monitored every 5 min and presented as mean every 10min (± s.e.m.). Bar: p<0.05.

(+)OH-Bupropion Treatment: Concomitant DPVoltammetric and electro-physiological measurements (Ephys) were performed in VTA of anaesthetised rats (n=4). After a control period (30min) (+)OH-bupropion was injected (4mg/Kg i.v.) and this increased the voltammetric levels of extracellular DA to approx. 170% of controls within 20min (Figure 1). This dose of (+)OH-bupropion has been selected as it is significantly active within the short term nicotine release test [33,34]. Concomitantly, Ephys firing increased to 150-180% of control within 20-50min, respectively (Figure 2). This data is in accord with those obtained with similar doses of (+)OH-bupropion as described in similar studies [35].

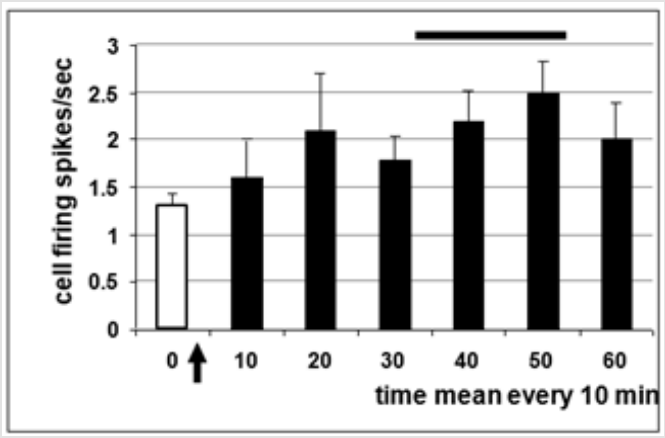

Figure 2: Electrophysiology: cell firing in VTA, effect of injection (arrow) of (+)OH-bupropion (5mg/Kg i.v. dissolved in saline, n=4) following a control period of 10 min recording. Data are mean every 10min (± s.e.m.) of continuous cell firing recordings. Bar: $p<0.05$. This data is in accord with those obtained with similar doses of (+)OH-bupropion as described in similar studies [35].

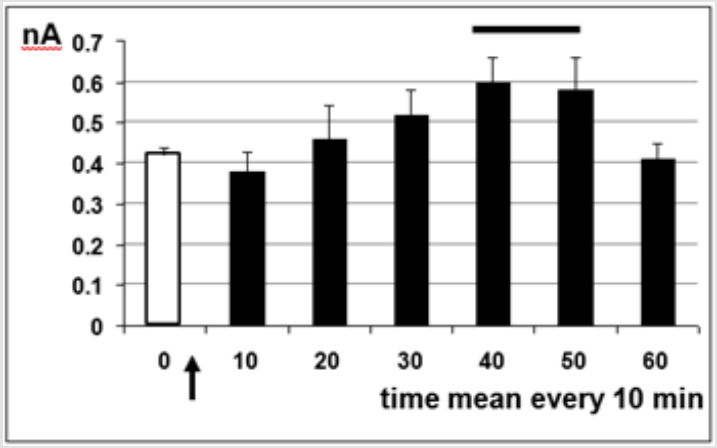

Figure 3: DPV analysis in VTA: effect of injection (arrow) of Bupropion (50mg/Kg i.v.dissolved in saline, n=4) following a control period of 10 min recording (white column). The voltammetric levels of extracellular DA are measured in nanoAmperes (nA), they are monitored every 5 min and presented as mean every 10min (± s.e.m.). Bar: $p<0.05$.

Bupropion Treatment: Experiments with bupropion 5mg/kg i.v. (n=4) or 50mg/Kg i.v. (n=4) have been performed in anaesthetised rats prepared for voltametric measurements of DA for concomitant voltammetry– electrophysiology analysis in VTA as described earlier [29-31]. Bupropion 5mg/kg i.v. was unable to modify significantly cell firing and voltametric extracellular DA levels in VTA (data not shown). In contrast Bupropion 50mg/kg i.v. did increase firing in VTA (approximately up to 160% of control levels). Concomitant DPVoltammetric extracellular DA levels appeared to be increased up to approx. 150% of controls within 40-50 min. (Figures 3 & 4).

Vehicle Treatment: In a control group (n=4) treatment with saline (NaCl 0.9%) was without significant effect upon DPV as well as cell firing levels in VTA (data not shown).

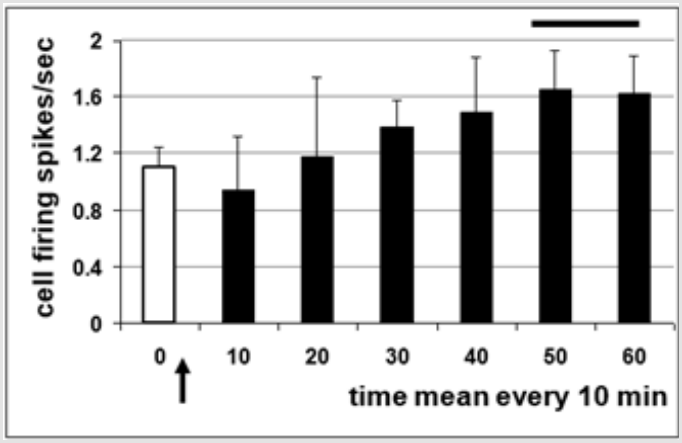

Figure 4: Electrophysiology: cell firing in VTA, effect of injection (arrow) of Bupropion (50 mg/Kg i.v. dissolved in saline, n=4) following a control period of 10 min recording (white column). Data are mean every 10min (± s.e.m.) of continuous cell firing recording. Bar: $p<0.05$.

Discussion

Bupropion, the first non-nicotine based drug for smoking cessation exerts its effect primarily through the inhibition of dopamine reuptake into neuronal synaptic vesicles. It is also a weak noradrenalin reuptake inhibitor and has no or little effect on the serotonin system. It also attenuates the stimulant effects of nicotine on the nicotinic acetylecholine receptors [36]. The present data concerning bupropion influence upon DA activity within the VTA are in accord with previous reports showing that pre-treatment of brain slices with a clinically relevant concentration of bupropion [24] reduces GABAergic transmission to DA neurons. This results in reduction of tonic inhibition of these neurons with the consequent increase of DA neuron excitability [37]. These effects are mediated via its metabolites and in particular (+)hydroxybupropion [38]. Indeed, bupropion undergoes metabolic transformation to this metabolite through hepatic cytochrome P450-2B6 (CYP2B6) [24]. As already mentioned in the Introduction, in rat, bupropion has a different metabolism with no formation of (+)OH-bupropion metabolite [25-28] making it a good species for comparing the effect of exogenous (+)OH-bupropion versus exogenous bupropion itself. Therefore, we have examined the acute effect of these two compounds upon the DA system via Differential Pulse Voltammetric (DPV) measurements of DA levels as well as electrophysiological recordings of the firing rates within the VTA. The data gathered indicate similar efficacy of these two compounds upon the dopaminergic activities in VTA, however (+)OH-bupropion appeared to stimulate DA firing and release at the dosage of 5mg/kg while this dosage was ineffective when using bupropion. Only when the dosage was increased to 50mg/kg the effect of this chemical was significant upon DA activities in VTA. These data confirm the reported difference in efficacy between Bupropion and its metabolite (+)OH-bupropion supporting the latter as best treatment in helping people quit tobacco smoking.

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