Research Article

Evidence of the dopamine-2 receptor mediated inhibition of the hypothalamic-pituitary-adrenal system; a rodent model of hypercortisolism in chronic neuropsychiatric disorders

Balázs Thurzó, Miklós Jászberényi*, Zsolt Bagosi, Imre Pataki, Eszter Kádár, Gyula Szabó and Gyula Telegdy

Department of Pathophysiology, University of Szeged, Szeged, Hungary

Abstract

The purpose of this study was to examine the role of dopaminergic mediation in the hypothalamic-pituitary-adrenal (HPA) response challenged by ether stress. First the effects of the D1 selective (SCH-23390) and the D2 selective (haloperidol) dopamine antagonists on ether stress evoked corticosterone responses were tested. The activation of the HPA axis was assessed by measuring plasma corticosterone levels. Low doses of haloperidol (25 nmol/kg, intraperitoneally) failed to affect either basal or stimulated corticosterone secretion, while SCH-23390 elicited moderate inhibition of stimulated release. However, to our surprise higher doses of haloperidol (250 nmol/kg) raised basal secretion and even potentiated the HPA response evoked by ether stress. Therefore to elucidate the role of D_2 mediation, the intrinsic activity of the D_2 antagonist was tested in further experiments. Haloperidol (from 25 nmol/kg to 2.5 mmol/kg) alone elicited a dose-dependent activation of the HPA system reflected by both corticosterone and ACTH serum levels. This D_2-antagonist-evoked HPA activation could be prevented by pre-administration of the CRH antagonist, α-helical CRH_{9-41}. These findings provide unequivocal evidence that D_2 receptor can exert inhibitory control over the HPA axis.

Introduction

Although dopaminergic neurons interconnect several brain centers and modulate a plethora of functions, the activities and disorders of three specific systems represent the most important physiologic and pathophysiologic phenomena in monoaminergic neurotransmission [1,2]. The nigrostriatal, mesocorticolimbic and hypothalamic-tuberoinfundibular neural networks predominantly manage inherited, instinctive, neuroendocrine programs (extrapyramidal modules, holokinetic movements, postural reflexes, and hormonal responses), but the modulation and fine-tuning provided by them also have impact even on the most intricate and flexible cognitive processes [3,4].

The complexity of these neural circuits is further multiplied by an arsenal of dopaminergic receptors [5,6], which explains the complex pathology of these systems (schizophrenia, attention-deficit hyperactivity disorder, Parkinson's disease, Parkinson's dementia, Lewy body dementia (LBD), various endocrine disorders), and the unpredictable effects and side effects (toxicity and withdrawal symptoms) of dopaminergic pharmacological agents [5-8]. Further, it is well known that, in both endogenous monoaminergic and addictive disorders, the pathological activity of the HPA system can be observed. Most commonly it is represented by either an over-activation or a decreased resilience of the HPA system reflected by resistance to dexamethasone suppression [9]. However, the role of different dopaminergic pathways and receptor classes in the control of the HPA axis is poorly understood. The only aspect, upon which even recent publications agree, is the stimulus dependent role of various dopaminergic pathways in the transmission of the stress response [10].

First, Jezova reported [11] that non-selective dopaminergic agonists (apomorphine, pergolide) evoked significant elevations in ACTH secretion in the rat. According to them, this response could be completely abolished by preadministration of the selective D_2 inverse agonist, haloperidol [11]. Moreover, Hennig *et al.* [12], demonstrated that the human cortisol response to heat stress can be prevented by haloperidol pretreatment.

The next major contribution to the field of dopaminergic control of the HPA axis was the clarification of the central stimulatory activity of cocaine [13-16]. The cocaine-elicited HPA response [13-19] is now generally considered to represent dopaminergic activation [20-21] of corticotropin-releasing hormone (CRH) secretion [16]. However, the specific roles of the D_1-like (D_1 and D_5) and the D_2-like families (D_2, D_3 and D_4) of pre- and postsynaptic dopamine receptors in these processes has not yet been clarified. Further, Goebel *et al.* even reported clear-cut evidence of the central stimulatory action of the D_2 antagonist, haloperidol, on corticosterone secretion [23]. This finding is in sharp contrast with that of Jezova [11] and is in complete agreement with several clinical symptoms of dopaminergic deficit. In major depression, bipolar disease, Parkinson's dementia and, especially, in LBD (LBD completely eradicates the dopaminergic cells in the nervous

Correspondence to: Miklos Jaszberenyi, Department of Pathophysiology, University of Szeged, H-6701, Szeged, Hungary, Tel: + 36 62 545993; Fax: + 36 62 545710; E-mail: jaszberenyi.miklos@med.u-szeged.hu

system) cessation of the circadian rhythm of the HPA axis and overall hypercortisolism are almost unequivocal universal findings [24-27]. Goebel tried to explain this contradiction with a peripheral stimulatory action of prolactin on the adrenal gland [23], however we surmised a dose and challenge dependent role of dopamine in the regulation of the stress response.

Our earlier publications have clearly demonstrated the stressor specificity of the HPA response [28,29], which supports the aforementioned hypothesis. Further, in the case of pharmacologic challenges, the relative contributions of D_1 and D_2 receptors are still debated and the experimental findings are inconsistent. Zhou *et al.* [30] found that in the hypothalamus, neither of these receptors influenced CRH expression, while D_2 receptors appeared to curb cocaine-binge elicited transcription of proopiomelancocortin (POMC). However, recently Gozzi *et al.* reported a profound inhibitory activity of D_1 receptor antagonism on the orexin positive stress and arousal pathways [31]. Therefore, these contradictory findings necessitate stressor specific evaluation of the role of D_1 and D_2 receptor families in HPA activation.

Consequently, our experiments first investigated the dopaminergic mediation of ether induced HPA activation by using two selective inhibitors of dopaminergic transmission: the D_1 receptor antagonist, SCH-23390, and the D_2 dopamine receptor antagonist, haloperidol. However, because we observed a profound additive activity of D_2 receptor inhibition on the endocrine response, the mediation of the intrinsic effect was evaluated by measuring plasma levels of adrenocorticotropic hormone (ACTH) and corticosterone and by applying the corticotropin-releasing hormone (CRH) receptor antagonist, α-helical CRF_{9-41}.

Materials and methods

Animals

The animals were maintained and handled during the experiments in accordance with the Council Directive of the European Economic Community regarding the protection of animals for experimental and other scientific purposes (86/609/EEC). Male Wistar rats weighing 150-250 g upon arrival were used and they were between 2.5-3 months old at the time of the experiments. The rats were kept in their home cages at a constant room temperature on a standard illumination schedule, with 12-h light and 12-h dark periods (lights on from 6.00 a.m.). Commercial food and tap water were available *ad libitum*. The rats were allowed a minimum of 1 week to acclimatize before surgery. To minimize the effects of nonspecific stress, the rats were handled daily. All experiments were carried out between 8:00 a.m. and 10:00 a.m.

Surgery

For icv. administration, the rats were implanted, under pentobarbital (Nembutal, Phylaxia-Sanofi, Budapest; 35 mg/kg, intraperitoneal (ip.)) anesthesia, with a stainless steel, Luer cannula (10 mm long) aimed at the right lateral cerebral ventricle. The stereotaxic coordinates were 0.2 mm posterior, 1.7 mm lateral to the bregma, and 3.7 mm deep from the dural surface, according to a rat brain atlas [32]. Cannulas were secured to the skull with dental cement and acrylate. The rats were used for studies after a recovery period of at least 5 days. After the experiments to verify the permeability of the cannulas, methylene blue was injected into each decapitated head and the brains were dissected. Only the data obtained from animals which manifested a diffusion of methylene blue into all the ventricles were used for statistical analysis.

Treatments

The animals were subjected to pretreatment with either the D_1 receptor selective dopamine blocker, SCH-23390 (Tocris, Bristol, UK), or the D_2 dopamine receptor antagonist, haloperidol (Richter, Budapest, Hungary). All compounds were dissolved in 0.9% saline. The initial concentrations of the antagonists were doses we found to be most effective in previous experiments [33,34], but which *per se* did not affect hormone levels. Different doses of haloperidol (from 25 nmol/kg to 2.5 mmol/kg) and SCH-23390 (25-250 nmol/kg) were dissolved in 0.5 ml saline and administered ip. to conscious rats. The same volume of saline was administered to the controls ip. To evaluate the mediation of the intrinsic activity of haloperidol, combined treatment with a CRH antagonist was performed. Thirty minutes prior to haloperidol treatment, 5 nmol/kg CRH antagonist, α-helical CRH_{9-41} (Bachem, Germany) was administered icv. in a volume of 2 μl.

Ether stress

Thirty minutes after the above treatments the animals were exposed to ether stress in the following manner. Rats were removed from their cages and placed individually for 1.5 min in a large closed jar containing a diethyl-ether (Reanal, Hungary) dampened paper towel at the bottom. Unconsciousness always occurred within this period of breathing the ether-saturated atmosphere [28,29].

Determination of plasma corticosterone

Thirty min after the ether stress, the rats were sacrificed by cervical dislocation and decapitation, and approximately 3 ml of trunk blood was collected in heparinized tubes for corticosterone assay. The plasma corticosterone concentration was measured by fluorescence assay [36,37].

Determination of plasma ACTH

The most effective doses of haloperidol found in the corticosterone or saline alone (control animals) assays were injected ip. into conscious rats. Fifteen min after this treatment, the animals were sacrificed and 2 ml of blood was collected in EDTA-containing tubes. The ACTH concentrations of the samples were determined by a solid-phase two-site sequential chemiluminescent immunometric assay (Immulite 2000, Diagnostics Products Corporation, Los Angeles, USA). The analytical sensitivity of the assay is 5 pg/ml, whereas the intra-assay and inter-assay precisions are 6.8% and 8.2%, respectively.

Statistical analysis

Values are presented as means ± S.E.M. Statistical analysis of the data was performed by general linear model (GLM). The differences between groups were examined by Tukey's *post hoc* comparison test, and a probability level of 0.05 or less was accepted as indicating a statistically significant difference. Data reductions and statistical analyses were performed by SigmaPlot 12.0 (Systat Software, Inc., Chicago, IL) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY).

Results

As expected, ether stress caused a marked increase in plasma corticosterone (Figure 1; $F_{(1, 106)}=134.97$, $p<0.01$ vs. control). Pretreatment with antagonists also proved to be effective (Figure 1; $F_{(4, 106)}=25.102$, $p<0.01$). According to Tukey's *post hoc* comparisons, SCH-23390 slightly attenuated the HPA response at the highest dose (Figure 1; $p<0.01$ for 250 nmol SCH-23390 *vs.* saline). Haloperidol
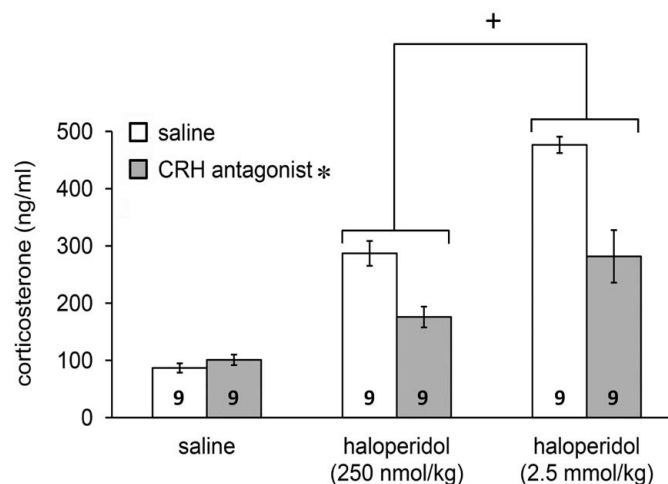
pretreatment in a dose of 25 nmol/kg showed a tendency to increase the basal but did not influence the ether induced corticosterone secretion. In contrast, a higher dose of haloperidol (250 nmol/kg) elevated the basal plasma corticosterone level and the same pretreatment even augmented the ether induced response (Figure 1; $p<0.05$ vs. saline for 25 nmol/kg haloperidol and $p<0.01$ vs. saline for 250 nmol/kg).

In further experiments we established that the stimulatory effect of haloperidol is dose-dependent on both the ACTH (Figure 2; $F_{(3, 21)}=3.2$, $p<0.05$ for 2.5 mmol/kg haloperidol vs. saline with Tukey's *post hoc* test) and corticosterone responses (Figure 2; $F_{(3, 21)}=18.85$, $p<0.01$ for both 250 nmol/kg haloperidol vs. saline and 2.5 mmol/kg haloperidol vs. saline with Tukey's *post hoc* test).
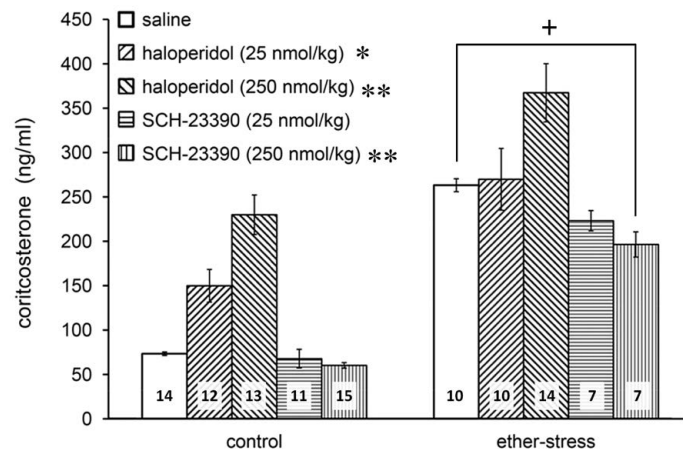
In the third set of experiments the D_2 antagonist evoked response (Figure 3; $F_{(2, 48)}= 80.901$, $p<0.01$ vs. saline) could be partially attenuated by pretreatment with the CRH antagonist α-helical CRH$_{9-41}$ (Figure 3; $F_{(1, 48)}=28.171$, $P<0.01$ vs. saline). The revealed interaction between the two treatments ($F_{(2, 48)}=11.0$, $P<0.01$ vs. saline) suggested specificity of the CRH antagonist.

Discussion

The results obtained from our experiments with ether stress and selective dopaminergic antagonists refine the proposed

Figure 1. Effects of the D_1 antagonist, SCH-23390, and D_2 antagonist, haloperidol, on ether stress evoked corticosterone release. Data are expressed as means ± S.E.M. Numbers within bars are the numbers of animals used. Symbols: *=$p<0.05$ vs. saline, **=$P<0.01$ vs. saline, +=$p<0.01$ ether vs. control.
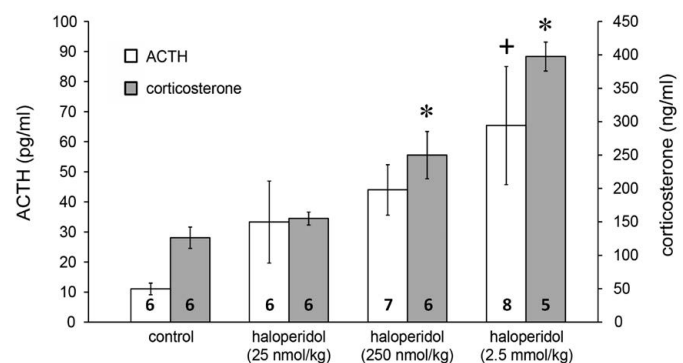
Figure 2. Effects of haloperidol on ACTH and corticosterone release. Data are expressed as means ± S.E.M. Numbers within bars are the numbers of animals used. Symbols: *=$p<0.01$ vs. saline; +=$p<0.05$ vs. saline.

Figure 3. Inhibitory action of the CRH antagonist, α-helical CRH$_{9-41}$, pretreatment on haloperidol-evoked corticosterone release. Data are expressed as means ± S.E.M. Numbers within bars are the numbers of animals used. Symbols: *=$p<0.01$ for CRH antagonist vs. saline; +=$p<0.05$ for haloperidol vs. saline.

oversimplified model of dopaminergic mediation in the control of the HPA axis [11,38,39]. Selective D_1 inhibition by SCH-23390 did not have a significant impact on basal secretion and appeared slightly antagonistic on stimulated activity of the HPA axis, which supports the observations of Zhou *et al.* regarding cocaine challenge [30]. However, to our surprise, haloperidol at higher doses even augmented the ether evoked corticosterone response. Because the available literature reflects conflicting data regarding the action of antipsychotics on the HPA axis [23,30,40], in separate, dose-response experiments, the intrinsic activity of D_2 antagonism on the HPA system was investigated. It was not only the inconsistent literature but the increasingly recognized importance of the CRH positive neural networks in the development of dopaminergic system-related disorders [23,35,41-45] that motivated us to investigate this question. Nevertheless, our results unambiguously revealed that the dopamine D_2 receptor blockade by haloperidol *per se* increased both ACTH and corticosterone secretion and the response could also be inhibited by pretreatment with the CRH antagonist, α-helical CRH$_{9-41}$. These findings argue for two important conclusions. First, in the regulation of the HPA axis the activity of D_2 receptors predominate and that of the D_1 family is negligible. Second, the D_2-family exerts tonic inhibitory control over HPA stimulation and blockade of the receptors leads to profound augmentation of the stress response. Our findings somewhat correspond to those of Zhou but unlike cocaine-binge [23] ether stress appears to rely on CRH, not POMC, transcription. Taking into account the effectiveness of haloperidol and, that the tuberoinfundibular system mainly expresses D_2 and D_3 receptors [46-49] it appears that the D_2-like family exerts tonic inhibitory control over HPA activation in the hypothalamus. Earlier studies clearly demonstrated that ether stimulates directly the hypothalamic CRH secretion [28,29], because it proved effective despite complete hypothalamic deafferentation [50-52] or olfactory bulbectomy [53]. Therefore, haloperidol apparently interrupts centrally, in the hypothalamus the feedback regulation exerted by presynaptic D_2 autoreceptors on dopamine synthesis and release. Further, at the same time, it may also disinhibit the action of D_2/D_3 receptors on postsynaptic adenyl-cyclase which, in turn, increase the level of cAMP [1,46]. Since, in our studies, the CRH antagonist attenuated the haloperidol-evoked response it seems that this effect, to some extent,

is independent of the direct action of dopaminergic neurons of the arcuate nucleus on POMC-positive cells of the pituitary. Further, not completely excluding the potential influence of some regions of the mesolimbic system, such as the nucleus accumbens [49], we propose that it is the dopaminergic and peptidergic inputs from the arcuate nucleus [54] that may play significant roles in the central processing of ether-induced HPA activation [28,29]. This way, our experiments provided *in vivo*, functional evidence for D_2 mediated disinhibition of CRH and ACTH secretion. This has not been previously clarified, unlike the dopaminergic control of prolactin secretion, which is also inhibited by a D_2 receptor pathway [55,56]. Nevertheless, our findings may reflect ether-challenge specific features of HPA signaling.

Therefore, decreased activity in the dopaminergic system may lead to a two-pronged endocrine response in the form of CRH and prolactin secretion. This may favor the integrity of the individual (HPA response, self-maintenance) at the expense of inhibition of gonadotropins (reproduction) by prolactin [56] in a stressful environment. Perhaps kisspeptin and other RFamides may play a crucial, integrative role in these processes influencing dopamine and then, in turn, CRH and prolactin release [57-60]. Moreover, dopamine receptor down-regulation, and consequent hyperprolactinemia may also aggravate HPA stimulation [23].

Nonetheless, further pharmacodynamic studies would be necessary to clarify this bewilderingly complex picture and the individual contributions of hypothalamically expressed D_2 and D_4 receptors. Moreover, serotonin and noradrenaline and those pharmacologic agents, which influence their levels (monoamine oxidase inhibitors, tricyclics and selective serotonin reuptake inhibitors), play equally ambiguous [9,61,62] roles in the regulation of the HPA axis and mood disorders [61-64]. To clarify the mediation of their activity, and to shed light on their similarly unpredictable and dangerous side-effect spectrum [64,65] further studies are also required.

Acknowledgment

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