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Cocaine-Induced Elevation of Plasma Corticosterone is Mediated by Different Neurotransmitter Systems in Rats

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SARNYAI, Z., É. BÍRÓ AND G. TELEGDY. *Cocaine-induced elevation of plasma corticosterone is mediated by different neurotransmitter systems in rats.* PHARMACOL BIOCHEM BEHAV 45(1) 209–214, 1993.—It has previously been demonstrated that cocaine stimulates the hypothalamic-pituitary-adrenal (HPA) axis through hypothalamic corticotropin-releasing factor (CRF) secretion. The role of different neurotransmitters in mediation of the cocaine-induced elevation of plasma corticosterone (CORT) were investigated in rats by using transmitter antagonists. Peripheral (IP) pretreatment with a dopaminergic antagonist, pimozide (0.01–1.0 mg/kg, IP), a noradrenergic blocker, phenoxybenzamine (1.0–4.0 mg/kg, IP), a β-adrenergic blocker, propranolol (0.2–10 mg/kg, IP), an opiate antagonist, naloxone (1.0–4.0 mg/kg, IP), and a muscarinic cholinergic antagonist, atropine (1.0–4.0 mg/kg, IP), inhibited the cocaine-induced CORT response dose dependently. A similar dose-dependent inhibition of the plasma CORT response induced by cocaine was observed after the ICV route of administration of these antagonists in microgram quantities. None of the investigated IP or ICV doses of transmitter antagonists altered the basal CORT level. These results suggest that the activation of multiple neurotransmitter systems, including catecholaminergic, opiate, and cholinergic systems, might be responsible for the cocaine-induced HPA axis activation, probably through the specific receptors located in the CNS.

Cocaine Corticosterone Pimozide Propranolol Phenoxybenzamine Naloxone Atropine ICV

COCAINE is known to interact with dopaminergic, noradrenergic, and serotonergic neurotransmission, inhibiting the reuptake of monoamines (17,23,37). Cocaine inhibits the firing of dopamine (DA) neurons in the ventral tegmental area and the nucleus accumbens and of the noradrenaline (NA) neurons in the locus coeruleus, suggesting an increased synaptic concentration of monoamines (24). In parallel with the behavioral action, cocaine elicits an increase in nucleus accumbens DA levels (4). Most of the behavioral effects of cocaine, such as its psychomotor stimulant, stereotypic and euphoric effects, and its rewarding properties, are believed to be related to its inhibitory action on monoamine reuptake [cf. (14)]. The role of endogenous opiate systems in the mediation of the effects of cocaine have also been demonstrated. Effects of cocaine on rewarding brain stimulation (1) and cocaine self-administration were attenuated by an opiate antagonists (11). Cocaine treatment altered the β-endorphin immunoreactivity (46) and opiate receptor binding (18) in critical reward regions. The effects of nicotinic cholinergic drugs in the modulation of the lethal effect of cocaine (50) and the alteration of the acetylcholine metabolism in the hippocampus (40) have also been described.

Cocaine has been shown to act on the hypothalamic-pituitary-adrenal (HPA) axis activation, increasing the plasma concentrations of corticotropin (ACTH) and corticosterone (CORT) in rats and humans (3,30,29,39). Cocaine-induced activation of the HPA axis could be inhibited by corticotropin-releasing factor (CRF) antiserum and CRF receptor antagonists, suggesting the critical role of endogenous CRF release (39,42). Further, cocaine has been reported to stimulate CRF release from the hypothalamus in vitro (9). Inhibition of cocaine-induced ACTH and CORT secretion has also been demonstrated by pretreatment with dopamine receptor antagonists (both D_1 and D_2), 5-hydroxytryptamine (5-HT) receptor blockers, and the neurochemical lesion of the serotonergic tract (3,25). All neurotransmitters that are thought to participate in the mediation of the effects of cocaine contribute to regulation of the HPA axis, probably through the modulation of CRF release. CRF release is stimulated by noradrenaline (36,48), adrenaline (5,36), dopamine (8), and morphine and endogenous opioids (5), as well as acetylcholine (36,48).

In the present study, we set out to investigate the role of different neurotransmitters, including the dopaminergic, noradrenergic, adrenergic, opiate, and cholinergic systems, in the

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cocaine-induced elevation of the plasma CORT. As the results indicated the role of these mechanisms in the cocaine-induced CORT response to peripheral administration of the transmitter antagonists, we investigated further whether these actions are mediated by CNS target sites.

METHOD

Male rats of the Wistar strain (LATI, Gödöllö, Hungary) weighing 180–200 g were used. Five animals were housed per cage and kept at room temperature under a constant light-dark cycle (lights on between 6:00 a.m. and 6:00 p.m.). Five days prior to the experimental session, animals were subjected to the surgical procedure. For the ICV injection, animals were operated under sodium-pentobarbital (Nembutal, CEVA, Paris, France, 40 mg/kg, IP) anesthesia using a stereotaxic apparatus. A 23-ga steel guide cannula was inserted unilaterally into the right lateral cerebral ventricle. Thus, the tip of the cannula rested 1 mm above the intended site of injection. Cannula placement was verified by visual inspection following injection of blue dye through the cannula after the experiments. Only data from animals with accurate placement were considered for further investigations. The ICV treatments were performed by Hamilton microsyringe (Hamilton Co., Reno, NV) in a volume of 2 μl/animal with a 2 min/injection velocity.

For determination of the effect of cocaine on the plasma CORT level, 30 min after the cocaine or vehicle treatment animals were decapitated, the trunk blood was collected in a heparinized glass tube, and the plasma CORT level was measured by fluorimetry as described earlier (13,51).

Pretreatments with the transmitter antagonists were performed 30 min before the cocaine or vehicle treatment. Antagonists were dissolved in 0.9% NaCl for the IP administration and in artificial cerebrospinal fluid (CSF) for the ICV treatment. The following receptor blockers were used throughout the experiments: pimozide (Janssen Pharmaceuticals, Beerse, Belgium), propranolol HCl (Imp. Chem. Indust. Ltd., GB), phenoxybenzamine HCl (Smith, Kline and French, UK), naloxone HCl (Sigma Chemical Co., St. Louis, MO), and atropine sulfate (EGYT, Budapest).

Statistical analysis was performed by one-way analysis of variance (ANOVA), followed by Dunnett's and Tukey's test for multiple comparisons. A probability level of 0.05 or less was accepted as a significant difference.

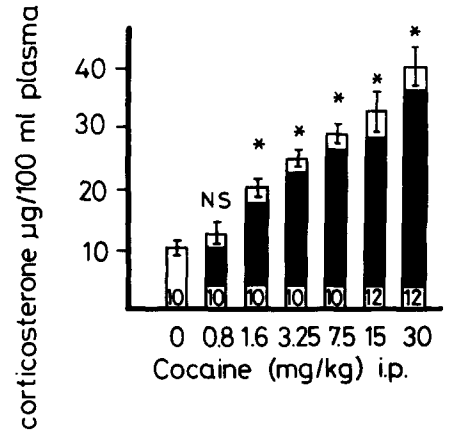

FIG. 1. Effect of different doses of cocaine (intraperitoneally, i.p.) on plasma corticosterone level in rats. $*p < 0.05$ compared to saline-treated (0 cocaine) control. Number in bars represent the number of animals.

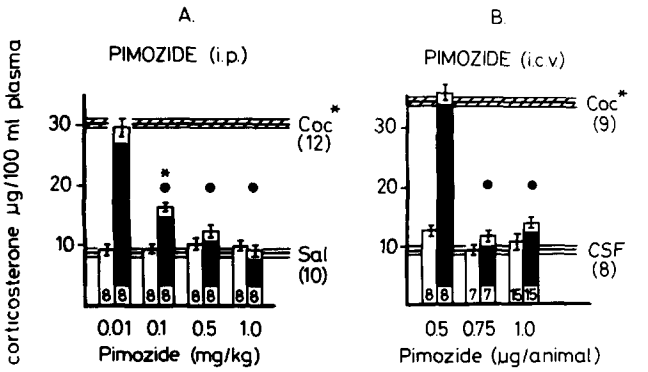

FIG. 2. Effect of peripheral (i.p.) and central (i.c.v.) administration of a dopaminergic antagonist, pimozide on the cocaine-induced elevation of plasma corticosterone level. Sal, 0.9% NaCl; Coc, 7.5 mg/kg cocaine, i.p.; CSF, arteficial cerebrospinal fluid. $*p < 0.05$ compared to Sal- or CSF-treated groups, $\bullet p < 0.05$ compared to Coc-treated group.

RESULTS

Different doses (0.8–30 mg/kg) of cocaine elicited a dose-dependent increase in CORT level 30 min after IP administration (Fig. 1). Although the 0.8-mg/kg dose was without effect, the higher doses (1.6–30 mg/kg) significantly increased the circulating CORT levels relative to saline controls [significant main effect of dose for CORT, $F(6, 97) = 371.2$, $p < 0.0001$]. In all subsequent antagonist experiments involving cocaine, animals were treated with a submaximal dose (7.5 mg/kg) 30 min before trunk blood collection.

Pretreatment with a dopamine receptor antagonist, pimozide (0.01, 0.1, 0.5, and 1 mg/kg, IP), inhibited the cocaine-induced elevation of CORT dose dependently, $F(9, 76) = 155.43$, $p < 0.0001$, as shown in Fig. 2A. As shown in Fig. 3A, doses of a noradrenergic blocker, phenoxybenzamine (2 and 4 mg/kg, IP), attenuated the cocaine-induced CORT response, $F(7, 68) = 128.1$, $p < 0.0001$. Pretreatment with a

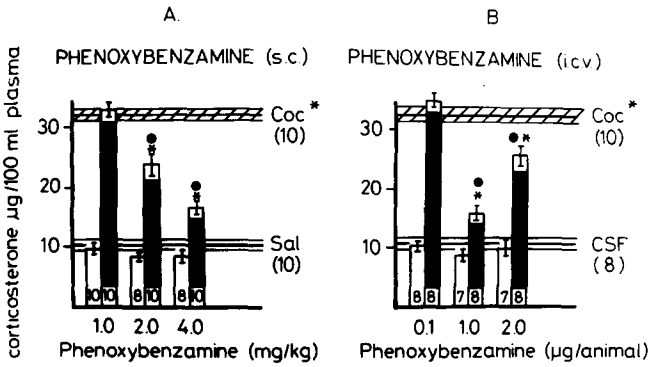

FIG. 3. Effect of peripheral (i.p.) and central (i.c.v.) administration of a noradrenergic antagonist, phenoxybenzamine on the cocaine-induced elevation of plasma corticosterone level. Abbreviations see in Fig. 2.

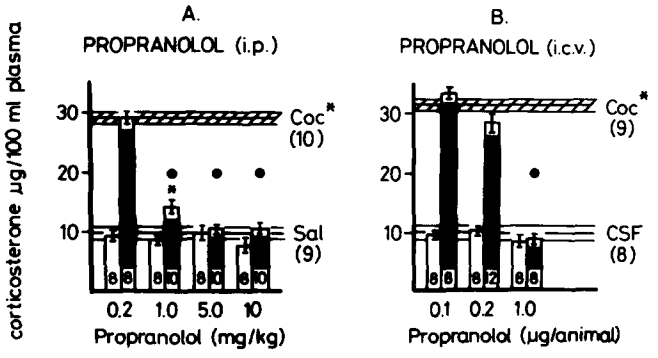

FIG. 4. Effect of peripheral (i.p.) and central (i.c.v.) administration of a β-adrenergic blocker, propranolol on the cocaine-induced elevation of plasma corticosterone level. Abbreviations see in Fig. 2.

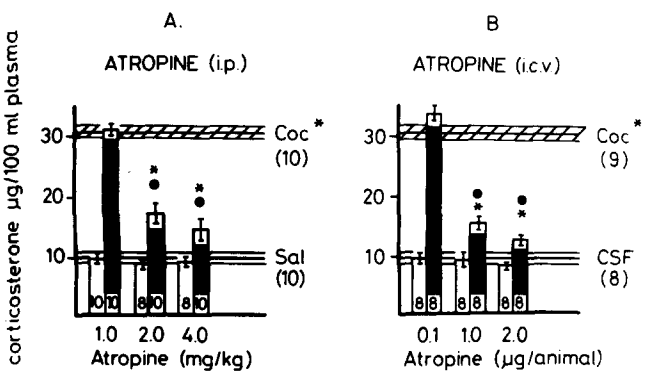

FIG. 6. Effect of peripheral (i.p.) and central (i.c.v.) administration of a cholinergic blocker, atropine on the cocaine-induced elevation of plasma corticosterone level. Abbreviations see in Fig. 2.

β-adrenergic blocker, propranolol (0.2, 1.0, 5.0, and 10.0 mg/kg, IP), inhibited the cocaine-induced elevation of CORT in a dose-dependent manner, $F(9, 79) = 102.69, p < 0.0001$ (Fig. 4A). An opiate receptor antagonist, naloxone (1.0, 2.0, and 4.0 mg/kg, IP), produced a dose-dependent attenuation in the CORT level elevation induced by cocaine, $F(7, 66) = 118.5$, $p < 0.0001$ (Fig. 5A). Pretreatment with a muscarinic cholinergic antagonist, atropine (1.0, 2.0, and 4.0 mg/kg, IP), attenuated the cocaine-induced CORT elevation dose dependently, $F(7, 68) = 106.04, p < 0.0001$, as shown in Fig. 6A.

To investigate the sites of action of neurotransmitter antagonists, the ICV application of receptor blockers was used. ICV pretreatment with pimozide significantly inhibited the CORT response induced by cocaine at the higher doses studied, $F(7, 69) = 203.04, p < 0.0001$ (Fig. 2B). The 1-µg dose of propranolol (ICV) completely abolished the effect of cocaine on the CORT level in the plasma, $F(7, 61) = 203.03$, $p < 0.0001$ (Fig. 3B). ICV pretreatment with phenoxybenzamine (1.0 and 2.0 µg/animal) attenuated the CORT response, $F(7, 56) = 227.9, p < 0.0001$ (Fig. 4B). As shown in Fig. 5B, the 0.1- and 1.0-µg doses of naloxone (ICV) attenuated but the 2.0-µg dose completely inhibited the cocaine-induced CORT elevation, $F(9, 80) = 128.2$, $p < 0.0001$. Atropine pretreatment in the same doses ICV dose dependently attenuated the CORT response induced by cocaine, $F(7, 57) = 253.9$, $p < 0.0001$ (Fig. 6B).

As shown in all figures, none of the doses of any of the receptor blockers altered the basal CORT level, independently of the route of administration ($p > 0.05$).

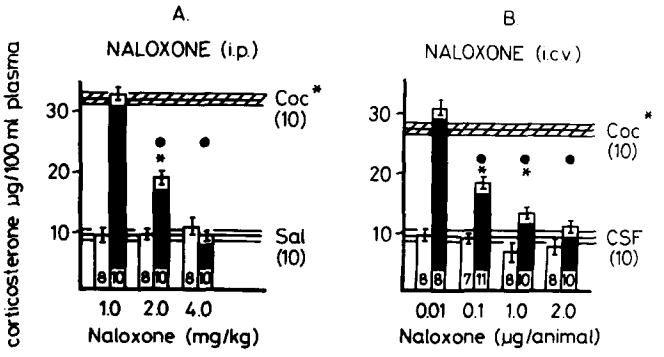

FIG. 5. Effect of peripheral (i.p.) and central (i.c.v.) administration of an opiate antagonist, naloxone on the cocaine-induced elevation of plasma corticosterone level. Abbreviations see in Fig. 2.

DISCUSSION

The present results demonstrate that the acute systemic administration of cocaine produced a dose-dependent elevation of the plasma CORT level, supporting the previous results (3,30,39). The role of dopaminergic, noradrenergic, β-adrenergic, opiate, and cholinergic neurotransmissions in the mediation of the CORT response induced by cocaine have also been shown.

Cocaine-induced activation of the HPA axis is mediated through the release of hypothalamic CRF (39,42). The pituitary and the adrenal gland could be excluded as potential target sites for cocaine, suggested by data that a) cocaine-induced ACTH secretion could be blocked by peripheral administration of CRF antiserum (39), b) ICV administration of CRF antiserum and receptor antagonists blocked cocaine-induced CORT response (42), c) cocaine does not act on the pituitary to stimulate ACTH secretion in vitro (39), d) cocaine stimulates CRF secretion from the hypothalamic explant in vitro (9), e) cocaine alters the levels of immunoreactive CRF in the hypothalamus and in limbic forebrain structures in vivo (41). Based upon these data, we hypothesized that neurotransmitter antagonists were used that may alter the hypothalamic CRF secretion induced by cocaine.

Pimozide, a DA receptor antagonist, has been shown to block cocaine-induced conditioning (2), cocaine reinforcement (12), and cocaine-induced inhibition of α-MSH release in rats (43), suggesting the role of dopaminergic neurotransmission in these effects of cocaine. The dose-dependent inhibition of cocaine-induced CORT elevation by pretreatment with pimozide shows the involvement of a DAergic mechanism. Our present results concerning the role of the dopamine system are highly consistent with the data of Borowsky and Kuhn (3), who first described the critical role of dopaminergic activation in the HPA axis-activating effect of cocaine on the basis of the fact that haloperidol and specific D_1 and D_2 antagonists were effective in attenuating the effects of cocaine on the HPA axis in rats. In contrast, the D_1 antagonist SCH23390 was incapable to block cocaine-stimulated hypothalamic CRF secretion in vitro (9). ICV administration of pimozide in a 10^3 times lower concentration, in which amount the antagonist was ineffective when administered IP, produced a dose-

dependent inhibition of the cocaine-induced CORT response. This observation indicates that the proposed cocaine-dopamine interactions involved in activation of the HPA axis might be localized in the CNS. Centrally mediated activation of the HPA axis by cocaine has been demonstrated previously by the effects of ICV-administered cocaine on plasma CORT and ACTH (25).

Anatomic data demonstrated the presence of dopaminergic fibers and terminals in the parvicellular part of the paraventricular nucleus (PVN) in rats (6,10,26). Direct DAergic innervation of CRF-containing neurones of the PVN has also been proved (27). DA stimulates CRF secretion from the rat hypothalamus in vitro, which could be antagonized by the compound SCH23390, a D_1 receptor antagonist, but not by phentolamine, suggesting that the stimulatory effect of DA upon CRF secretion was receptor mediated and not due to the conversion of this neurotransmitter into norepinephrine (NE) or epinephrine (E) (8).

Our present data on the inhibitory effects of peripherally and centrally applied pimozide on cocaine-induced CORT response together with anatomic and biochemical evidences strongly suggest that cocaine acts on HPA axis activation, at least in part, through DA-CRF interaction in the hypothalamus.

In the present experiments, two other catecholaminergic mechanisms (as potential mediators of the effects of cocaine on the plasma CORT) were also investigated by using an α-noradrenergic blocker, phenoxybenzamine, and a β-adrenergic blocker, propranolol. Phenoxybenzamine attenuated and propranolol inhibited the CORT response elicited by cocaine. Borowsky and Kuhn (3) described the lack of effect of an α_1-adrenergic antagonist, prazosin, and a β-adrenergic antagonist, propranolol, in the HPA activation by cocaine. The discrepancy between their results and our present observations could be explained by the difference in the doses of cocaine and in the time of pretreatment with antagonists used. They applied a 15-mg/kg dose of cocaine to activate the HPA axis and a 60-min pretreatment time. It is possible that the stronger stimulus and the longer time of pretreatment with the antagonists in their experiments may mask the possible effects of the antagonists. The effects of phenoxybenzamine and propranolol administered ICV indicate the role of the CNS in the cocaine-catecholamine interactions.

Noradrenergic neural inputs innervate all parts of parvicellular parts of the PVN (35). Liposits et al. (28) obtained clear evidence of the close relation of phenylethanolamine-*N*-methyltransferase-positive (and thus E synthesizing) afferent catecholaminergic fibers to the CRF neurone in the PVN. Adrenergic receptors have been demonstrated in the PVN (35). Pharmacological studies have shown that ICV-infused adrenaline and noradrenaline induced ACTH surges in rats, which could be blocked by CRF antiserum (47). The α-antagonist phenoxybenzamine consistently inhibits ACTH response to stress (19). The β-adrenergic blocker propranolol blocked ACTH release induced by ICV infusion of adrenaline in rats (46). Stimulatory effects of NE and E on CRF secretion in the hypothalamus have also been demonstrated in vitro (8). These data concluded that central NE and E activate the HPA axis by the stimulation of hypothalamic CRF secretion. Cocaine acts on monoaminergic nerve terminals to inhibit their uptake processes, which, in turn, increase the synaptic availability of these transmitters (23). Based upon our present data and upon previous evidences about the stimulatory role of central catecholamines on CRF secretion, we could hypothesize that noradrenergic and/or adrenergic neurotransmission may also be involved in cocaine-induced activation of the HPA axis in rats.

Involvement of an opiate mechanism in the cocaine-induced CORT response was demonstrated by the inhibitory effect of an opiate (mainly μ-receptor) antagonist, naloxone, on the cocaine action. A CNS target site of this action was suggested because the ICV injection of naloxone in microgram quantities blocked the CORT response elicited by cocaine. It has been demonstrated recently that buprenorphine, a mixed opiate agonist/antagonist, effectively inhibits ACTH secretion induced by cocaine in cocaine-dependent men (29).

The effects of opioids on the HPA axis are currently controversial. In the rat, while chronic administration of morphine has long been known to inhibit the adrenocortical response to stress, and acute naloxone stimulates the secretion of ACTH, acute administration of morphine increase both ACTH and CORT secretion (22). Buckingham and Cooper (5) demonstrated that morphine enhanced basal and stress-induced activity of the HPA system in vivo. It also stimulated the secretion of CRF by hypothalami in vitro. Naloxone did not affect resting HPA activity but reduced markedly the stress-induced release of ACTH, suggesting the stimulatory role of opiates on CRF secretion and subsequent activation of the HPA axis (5). In contrast, Tsagarakis et al. (49) demonstrated an inhibitory effect of morphine on CRF secretion stimulated by NA, acetylcholine (ACh), and 5-HT in vitro. Naloxone pretreatment had no significant effect on basal CRF secretion but reversed the inhibitory effect of morphine on NA-induced CRF secretion (49). It is possible to explain these divergent data if it is postulated that the CRF complex, measured in Buckingham's study, contains an inhibitory factor that is also suppressed by morphine; such a factor has been suggested by previous studies in rats (15). It is also possible that ACTH release induced by opiate agonists is independent to CRF (31), or, as postulated by Buckingham (5), the inhibitory opioid receptors effecting CRF release may lie on neurones (e.g., GABAergic) that inhibit tonically the CRF neurones.

There is some evidence of the involvement of the cholinergic system in the mediation of the effects of cocaine (40,50). In the present study, the muscarinic cholinergic antagonist atropine attenuated the plasma CORT elevation induced by cocaine administered both peripherally and ICV, suggesting a centrally mediated action.

Several lines of experimental evidence suggest that ACh is excitatory to the HPA axis. Implantation of atropine pellets rostrally to the PVN inhibited the ACTH response to stress (20,21), showing that atropine decreased plasma AVP, postulated that atropine worked by inhibitory hypothalamic CRF secretion. Recently, it has been demonstrated that ICV injection of ACh increased the CRF level in hypophyseal portal blood that was attenuated by pretreatment with either muscarinic or nicotinic receptor antagonists (36). In vitro CRF secretion from the rat hypothalamus has also been stimulated by ACh, mediated through both muscarinic and nicotinic receptors (7,48). These data are consistent in terms of the stimulatory role of cholinergic neurotransmission on hypothalamic CRF secretion and subsequent ACTH and CORT release.

It has been shown recently that CORT administration increases the reinforcing potency of psychostimulants (33) and has an intrinsic reinforcing effect measured by the self-administration method (34). It is interesting to note that pimozide, propranolol, naloxone, and atropine were found to be effective to inhibit the reinforcing effect of cocaine in experimental animals (1,12,16) in the same dose ranges in which

these antagonists inhibited the cocaine-induced CORT response demonstrated in our present study. These data suggest that CORT released by cocaine could be an important contributor of reward/reinforcement processes related to psychostimulants.

In summary, the present results confirm the role of the dopaminergic mechanism in the CORT response elicited by cocaine. This is the first demonstration of the involvement of noradrenergic, β-adrenergic, opiate, and cholinergic neurotransmission in mediation of the cocaine-induced elevation of the plasma CORT, which might proceed through a centrally mediated mechanism. These data indicate a multiple neurotransmitter regulation of cocaine-induced HPA axis activation in rats.

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