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REVIEW ARTICLE

ANIMAL MODELS OF TARDIVE DYSKINESIA – A REVIEW

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Abstract : Tardive dyskinesia is a serious motor side effect of long term neuroleptic therapy, with an unknown pathophysiological basis. The leading hypothesis of the pathophysiology of tardive dyskinesia includes dopamine receptor supersensitivity, GABAergic hypofunction, excitotoicity and oxidative stress. Many preclinical models have been developed to identify the underlying pathological processes of tardive dyskinesia, but none has yet produced a parsimonious results. A wide range of animal models, viz. Homologous, analogous and correlational models have been developed to explore the pathophysiology of tardive dyskinesia. Vacuous chewing movements in rodents induced by chronic neuroleptic treatment is the most frequently employed model. As the existing models suffer from several phenomenological and methodological problems, development of new models, highly predictive of pathological basis of tardive dyskinesia can accelerate tardive dyskinesia research for the better understanding of the pathophysiological processes underlying the syndrome and for the discovery of new therapeutic targets for the treatment of tardive dyskinesia.

Key words : tardive dyskinesia, vacuous chewing movements, reserpine, isoniazid, pathophysiology, neuroleptics, animal models

INTRODUCTION

Tardive dyskinesia (TD), a syndrome of potentially irreversible involuntary hyperkinetic disorder that occurs during chronic neuroleptic treatment is a major limitation of chronic neuroleptic therapy (1). The most common clinical presentation is orofacial dyskinesia, which includes opening, protrusion and retrieval of the tongue and closing of the mouth, chewing, licking, sucking, puckering, smacking, panting and grimacing. Abnormal movements associated with the disorder may involve any part of the body, may be ballistic, athetotic, myoclonic, dyskinetic or choriform in nature (2–4).

The first case of TD was reported by Schonecker, who described a lip smacking dyskinetic movement disorder following chlorpromazine treatment (5). The term "tardive dyskinesia" was first coined by Faurbye et al., to describe abnormal

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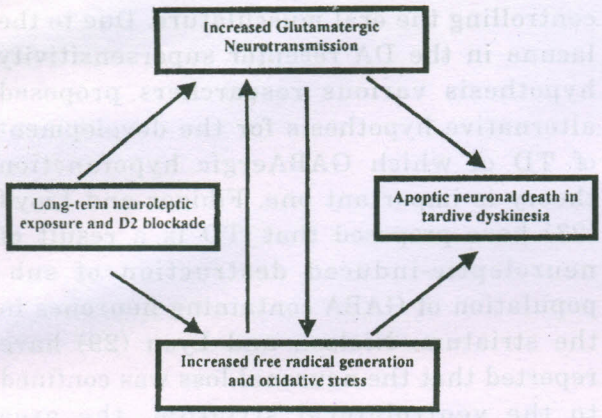


Fig. 1: Hypothetical diagram showing the involvement of neuroleptic-induced process such as increased glutamatergic transmission and oxidative stress in the pathophysiology of tardive dyskinesia.

movements that developed during long term neuroleptic treatment (6). Epidemiological data indicate that neuroleptic exposure was the most significant etiological factor in the development of TD, but number of authors have continued to question this relationship (7, 8). Abnormal movements and spontaneous dyskinesia in psychiatric patients may be a manifestation of subtle brain damage rather than neuroleptic exposure or precipitated by a variety of other drugs besides neuroleptics (4), caffeine, phenytoin, estrogens, tricyclic antidepressants (9, 10), anxiolytics (11), anticonvulsants (12), narcotics and L-dopa (13), amphetamine (14), metaclopramide (15) and antihistaminics (16, 17). Estimates for the prevalence of TD in patients receiving neuroleptic range from 0.5% to 70%. The average prevalence rate is 24% against a background prevalence of spontaneous dyskinesia of about 6% (18–20, 1, 4). Many preclinical models have been developed to identify the underlying pathophysiological mechanisms of tardive dyskinesia, but none has yet produced a greedy explanation.

Pathophysiology of tardive dyskinesia

In spite of enormous frequency of occurrence of TD, relatively little is known about the primary neurological mechanisms responsible for the development of tardive dyskinesia. Since approval of TD as an adverse effect of chronic neuroleptic treatment various attempts of TD as an adverse effect of chronic neuroleptic treatment various attempts were made to unravel the pathophysiological mechanisms underlying the development of TD, but most of these studies are inconclusive. Abnormalities in various neurotransmitter systems have been implicated in the pathophysiology of tardive dyskinesia. These includes dopaminergic, GABAergic, noradrenergic, and serotonergic systems. Recently excitotoxicity and oxidative stress have received much more attention.

The dopamine receptor supersensitivity hypothesis

The dopamine (DA) receptor supersensitivity hypothesis has dominated the conceptual underpinnings of tardive dyskinesia research since the early 1970s. The dopamine supersensitivity theory was first proposed by Klawans et al., in 1970 (21). Based on the similarities between L-dopa induced dyskinesias and TD, he suggested that chronic neuroleptic treatment produced supersensitive postsynaptic striatal dopamine D2 receptors, because all the antipsychotic drugs potently block DA D2 receptors at

therapeutic doses. Since then dopamine receptor supersensitivity theory has been an important theoretical construct guiding TD research. However the dopamine receptor supersensitivity theory is no longer viable (19, 22), as there are several fundamental flaws. Several inconsistencies, however suggests that this hypothesis cannot explain entirely the pathogenesis of TD. Fibiger and Llyod (23) demonstrated that the appearance of abnormal movements in TD shows a poor temporal correlation with dopamine supersensitivity, as supersensitivity occurs with in two to three weeks of initiation of neuroleptic treatment, where as TD develops after long-term use. Finally the dopamine receptor number returns to normal within few weeks after withdrawal, where as TD persists for months or years (24, 25).

It is difficult to reconcile all the clinical data with the dopamine receptor supersensitivity hypothesis. There are virtually no direct data in humans supporting this hypothesis (26). Post-mortem studies have been unable to find differences in D1 or D2 receptors in patients with tardive dyskinesia (27).

The GABA insufficiency hypothesis

The classical dopamine receptor supersensitivity theory has several pitfalls. The dopamine receptor supersensitivity theory fails completely to account for the fact the prevalent and core features of TD is orofacial dyskinesia, or the so called buccolingual-masticatory syndrome (28). The hypothesis also fails to explain the special vulnerability of the neuronal systems controlling the oral musculature. Due to the lacuna in the DA receptor supersensitivity hypothesis various researchers proposed alternative hypothesis for the development of TD of which GABAergic hypofunction theory is important one. Fibiger and Lioyd (23) have proposed that TD is a result of neuroleptic-induced destruction of sub-population of GABA containing neurones in the striatum. Nielson and Lyon (29) have reported that the neuronal loss was confined to the ventrolateral striatum, the area which is concerned with the innervation of oral musculature (28). Investigations in the non-human primates indicate that TD may be associated with decreased glutamic acid decarboxylase (GAD), the GABA synthesising enzyme, in the substantia nigra, medial globus pallidus, and subthalamic nuclei in dyskinetic monkeys compared with similarly neuroleptic treated non tardive dyskinetic monkeys (30). Taken together these studies suggests that long term neuroleptic administration causes, a selective loss of GABAergic neurones along with reduced nigral GAD activity resulting in the development of dyskinesia (31). Data from the clinics are partially supportive of role of GABA in tardive dyskinesia. However, treatment trials with GABA-enhancing drugs have not produced clinically significant or sustained improvement in tardive dyskinesia (1), this raises important question about a primary role for GABA in tardive dyskinesia.

The excitotoxicity hypothesis

Excitotoxicity hypothesis of tardive dyskiensia was first proposed by McGeer and McGeer (32), they suggested that

striatal excitotoxicity might play a role in TD, this was further outlined by DeKeyser, who proposed that long-term neuroleptic treatment could increase the striatal release of glutamate from cortico-striatal terminals, leading to striatal excitotoxicity and TD (33). Number of studies have shown that long-term neuroleptic treatment increases striatal glutamate release and thereby the possibility of excitotoxicity (34–37). Gunne and Andren hypothesised that neurodegeneration of striatonigral and striatopallidal GABAergic afferents, due to the excitotoxic mechanisms after chronic neuroleptic treatment might be the potential mechanism for the development of TD (38). The involvement of excitotoxicity in acute neuronal damage is now well understood, but the exact mechanism for the proposed excitotoxicity in chronic neurodegeneration and TD are still unclear (39).

The free radical hypothesis

Oxidative stress has been proposed as a pathogenetic mechanisms in TD (40–42). Neuroleptics induce an increase in furnover of dopamine (43), which may lead to the formation of reactive oxygen species such as hydrogen peroxide, superoxide radical and hydroxyl radical (44). This increased levels of reactive oxygen species might negatively affect both neurotransmission and cellular viability. Oxygen free radicals are also reported to diminish the dopamine transporter function (45) further increasing the extracellular dopamine levels. Elkashef and Wyatt, have reported that rats with vacuous chewing movements had significantly higher thiobarbituric acid reactive substances (TBARS) in the striatum (44), suggesting increased lipid peroxidation and free radical production. Free radicals are thought to play a significant role in ageing process, and age is one of the most prominent risk factor for the development of TD. Support to the free radical hypothesis comes from *in vitro* studies where haloperidol induced oxidative stress (46–48) and vitamin E attenuated neuroleptic-induced vacuous chewing movements. It is highly possible that different mechanisms may play a significant role in TD. Excitoxicity and oxidative stress may very well act together, since these are closely related processes (42). All these accumulating evidences strongly supports the free radical hypothesis of TD. Two issues remained unanswered by free radical theory. The first was why the severity of TD tended not to progress over time and the second was why all the patient exposed to neuroleptics are not developing TD.

Other neurochemical abnormalities

It is well approved that neuroleptic drugs apart from dopamine also antagonises many other receptor subtypes. There for it is possible that some other neurotransmitter systems may also play a key role in the pathophysiology of tardive dyskinesia. Therapeutic success of clozapine and other atypical antipsychotics has focused attention on the serotonergic system involvement in the pathophysiology of schizophrenia and extrapyramidal side effects (EPS). However, to date there are no consisting findings of alterations in serotonin parameters, nor have there been effective selective serotonin treatment approaches for tardive dyskinesia. Another hypothesis regarding TD was noradrenergic overactivity with the suggestion that beta-hydroxylase activity

was greater in patients with tardive dyskinesia (1). Alterations in the neuropeptide level such as Substance P (49, 50), opioid peptides like dynorphin and enkephalin (51), cholicystokinin (CCK) (52), and neurotensin (53, 54), also implicated in the pathophysiology of tardive dsyskinesia.

Animal models of tardive dyskinesia

Tardive dyskinesia research in humans has many limitations. Challenging normal subjects with neuroleptic drugs, especially if this has to be done repeatedly pose many ethical constraints. Its investigation in psychiatric patients is complicated by the presence of agitation in the psychiatric disorder per se. Studies in humans also precludes investigations that are invasive and could possibly endanger health. In search of animal models for tardive dyskinesia, some basic requirements of an animal model for a neuropsychiatric disorder are, symptom similarity, pharmacological isomorphism and cross-species biochemical processes (55). The model should have face construct and predictive validity. While idelly a homology should be aimed for, isomorphic models may be useful for certain investigations (56, 57).

Several animals models have studied to explain the development and persistence of tardive dyskinesia (22, 26, 39, 41). Three general types of animal models have contributed to our knowledge about the TD. These models can be described as homologous, analogous, and correlational models (58). The homologous model requires that all the critical factors of tardive dyskinesia be highly similar to the clinical picture of TD. This includes the aetiology, biological basis, symptoms, response to treatment, course and out come as well as unique features such as individual vulnerability (26). Homologous model is best represented by long-term neuroleptic studies in non-human primates (58, 59). The most frequently employed model is analogous model. This model requires some of the critical features be similar, but other features may not be similar. This is best represented by vacuous chewing movements

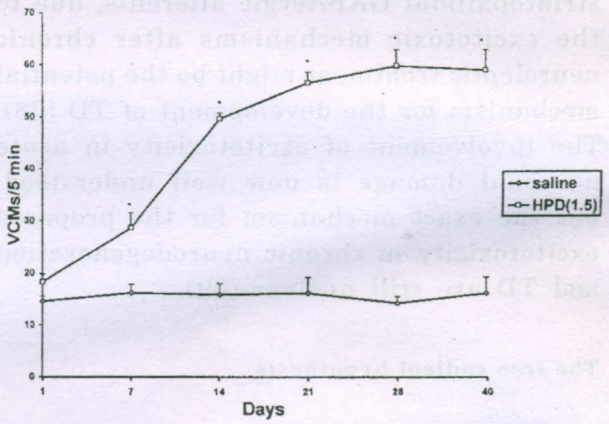


Fig. 2: Figure showing the time dependent increase in haloperidol (HPD) induced vacuous chewing movements as compared to vehicle treated group, reaching maximum level after 21 days. *P<0.05 as compared to first day treatment (ANOVA followed by Dunnet's test).

(VCMs) in rodents treated for brief to extended periods of time (60–64). The correlational model requires few or no factors between the preclinical and clinical observations be similar, but the results of the preclinical model are highly predictive of clinical picture. Potential examples of this model includes the possible correlation between the future likelihood of specific antipsychotic drugs to cause tardive dyskinesia and (1) acute extrapyramidal side

effects (EPS) induced by neuroleptics or (2) responses to dopamine agonists following brief neuroleptic treatment in rodents (1, 26, 58). The most valuable and highly predictive of clinical picture of TD is the homologous model, as it fit all the critical criteria for TD in patients, especially the factor of individual vulnerability. The only limitation of this model is the it is very expensive and time consuming. The most frequently employed model in the laboratory is the analogous model (VCMs in rodents),

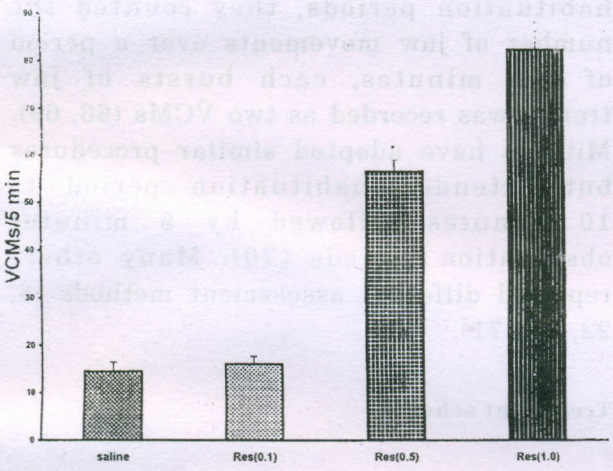


Fig. 3 : Dose dependent differences in the development of vacuous chewing movements in reserpine (Res) treated animals. *P<0.05 as compared to vehicle treated group (ANOVA followed by Dunnett's test).

due to certain advantages over homologous model. This model is relatively efficient, inexpensive and less time consuming. The clear advantage of the correlational model is the efficiency and relatively low cost of conducting acute studies that have high predictive power for chronic treatment outcomes. Even though most widely employed model, this model also has certain set backs, as the results appear to be strain dependent (62). The results are not of highly predictive in nature, and this model also not fulfil the individual vulnerability criteria, as all the rodents treated with neuroleptics develops dyskinetic symptoms.

The characteristic of tardive dyskinesia to be approximated by an animal model of syndrome include 1) irregular, but continuous movements of the oral region, extremities or trunk 2) delayed development of these movements after prolonged neuroleptic treatment with a protracted course after drug cessation 3) antagonism by dopamine receptor antagonists 4) resistance to suppression with anti-cholineric agents and 5) exacerbation by stress or activity (62). The animal models of tardive dyskinesia have number of methodological and phenomenological problems.

Neuroleptic-induced orofacial dyskinesia

One of the most frequently employed model of TD is neuroleptic-induced perioral movements. Rats treated chronically with neuroleptics often develops spontaneous mouth movements (22, 65, 66), such movements has been described as "vacuous chewing movements" (VMCs) and reliable techniques were described to quantify them. There are disagreements in the literature about the similarities of these movements to TD and its validity as an animal model of tardive dyskinesia.

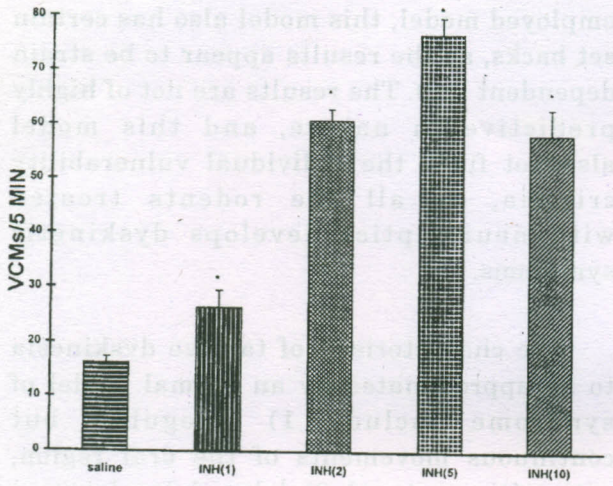


Fig. 4 : Diagram showing dose dependent increase in vacuous chewing movements in isoniazid (INH) treated animals as compared to vehicle treated group, showing ceiling effect at 5 µmol/rat (i.c.v.). *P<0.05 as compared to vehicle treated group (ANOVA followed by Dunnett's test).

Phenomenology

Glassman and Glassman used "oral dyskinesia" as the general descriptor to refer vacuous chewing movements, not directed to any physical material. They are characterised by up-down jaw movements with occasional tongue protrusions (67). Gunne et al., have used "oral dyskinesia" and "spontaneous chewing" as general descriptor in referring to quick single mouth openings in a vertical plane, with bursts of jaw tremor and masseter twitching (61, 66). Similarly Rupniak and colleagues have used "perioral movements" as their descriptor of purposeless chewing jaw movements with occasional tongue protrusions, but with no wide openings (68). From the above analysis, the most consistently reported phenomenology is that of vacuous (or abortive or spontaneous) chewing, where by what appears to be robust chewing sequences are manifested, but are not directed to any evident physical material.

Mode of assessment and quantification of orofacial movements

Various procedures are used by different authors for the quantification of orofacial movements. Gunne et al., and Johansson et al., have transferred animal to small prespex cage with a mirror placed behind to improve visibility. After two minutes habituation periods, they counted the number of jaw movements over a period of two minutes, each bursts of jaw tremor was recorded as two VCMs (66, 69). Mithani have adopted similar procedures but extended habituation period to 10 minutes followed by 5 minutes observation periods (70). Many others reported different assessment methods (8, 22, 68, 71).

Treatment schedule

The duration of neuroleptic treatment for the development of oral movements also different from one to another study, several authors have reported the gradual emergence of orofacial movements during several months of long-term treatment with neuroleptics (72, 73). Where as Rupniak et al., reported the emergence of orofacial movements very early in the course of neuroleptic treatment (68). Early onset of orofacial movements have been reported in modest number of studies (74, 75), in the absence of any obvious methodological differences on comparison with the majority of studies reporting late onset movements, these phenomena remain enigmatic.

In summary the conclusion of different investigators are not entirely consistent with respect to susceptibility, movement type or severity and persistence after withdrawal. Thus, there remains a question about the utility of this neuroleptic-induced VCMs as an animal model of TD.

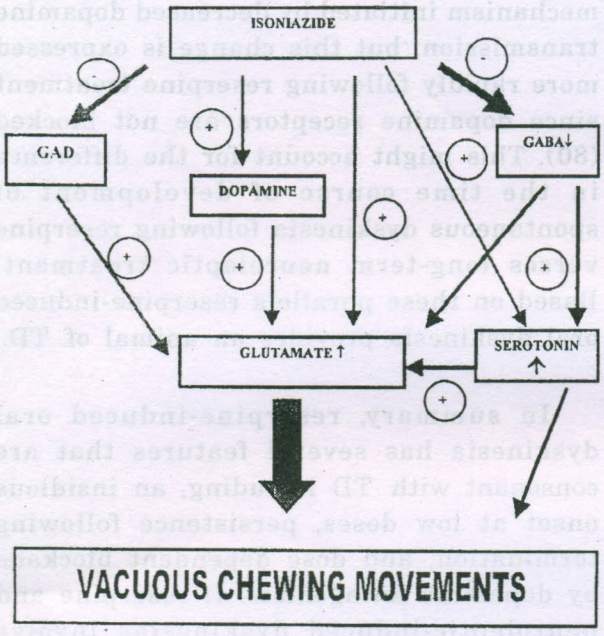
Reserpine-induced orofacial dyskinesia

Another analogous model of TD which is recently gaining impetus is reserpine-induced orofacial dyskinesia. Reserpine is a monoamine depleting agent and non selectively depletes dopamine, serotonin and norepinephrine. Although reserpine is not classified as neuroleptic, it has been used as an antipsychotic agent and had been associated with the development of TD (5, 76). Repeated administration of reserpine in rats produced spontaneous oral dyskinesias similar to the symptoms of TD in humans, including twitching of oral musculature, jaw movements and tongue protrusions (77, 78). The behaviour was not observed after the initial treatment, but developed after 3 days of treatment and persisted for at least 60 days post treatment. Sussman et al., recently reported that acute reserpine injection elicited long term oral dyskinesia in rats that persisted for 84 days post injection (79). One characteristic of reserpine-induced oral dyskinesia that is inconsistent with TD is that, the response develops rapidly, reaching maximum with in 3 days. In contrast TD typically develops after months or years of neuroleptic treatment. It is possible that both neuroleptic and reserpine treatment produce orofacial dyskinesia through a similar mechanism initiated by decreased dopamine transmission, but this change is expressed more rapidly following reserpine treatment since dopamine receptors are not blocked (80). This might account for the difference in the time course of development of spontaneous dyskinesia following reserpine verses long-term neuroleptic treatment. Based on these parallels reserpine-induced oral dyskinesia provides an animal of TD.

In summary, reserpine-induced oral dyskinesia has several features that are consonant with TD including, an insidious onset at low doses, persistence following termination, and dose dependent blockade by dopamine antagonists. If reserpine and neuroleptic-induced dyskinesias involve similar mechanisms, then the rapid development of reserpine-induced oral dyskinesia at higher doses offers a tremendous advantage over long-term neuroleptic administration.

Isoniazid-induced orofacial dyskinesia

Isoniazid besides a GABA depletor (81), is an inhibitor of glutamic acid decorboxylase (GAD) enzyme (82), a GABA synthesising enzyme. Nigral GABAergic hypofunction was reported to be involved in the pathophysiology of TD (23, 83). In rats decreased GAD activity significantly correlated with emergence of VCMs (84, 85). In a serious of experiments conducted in our laboratory, intracerebroventricular (i.c.v.) administration of isoniazid (1, 2, 5 and 10 µmol/rat) dose dependently induced vacuous chewing movements, showing a ceiling effect at 5 µmol/rat. The peak effect was observed after 30 minutes of isoniazid



Fog. 5 : Hypothetical diagram showing the possible involvement of different neurotransmitter systems in isoniazid-induced vacuous chewing movements.

administration and the effect was sustained for 60 minutes. Vacuous chewing movements in these animal was persistent for more than 30 days, above the control levels. Acute treatment with dopamine antagonists such as haloperidol significantly reversed isoniazid-induced VCMs.

Vacuous chewing movements induced by isoniazid shows several similarities with that of neuroleptic-induced VCMs, as the persistence of VCMs after the drug cessation and reversal by acute treatment with dopamine antagonists. One character that is inconsistent with TD is the rapid development of vacuous chewing movements.

In summary, if isoniazid-induced VCMs involve similar mechanisms, then the rapid development of isoniazid-induced oral dyskinesia elicited by acute administration of isoniazid offers a tremendous advantage over long-term neuroleptic administration, and may expedite research investigating the pathophysiology and prevention of tardive dyskinesia.

Conclusions

Extensive research has explored the pathophysiology of tardive dyskinesia. Animal models and clinical investigations have developed along parallel paths to produce a rich research base for understanding pathophysiology of TD. However no direct evidence of any pathological process has been identified. Many preclinical models have been developed to understand the underlying pathophysiology of TD, but none has yet produced a valuable explanation. Even though vacuous chewing movements induced by chronic neuroleptic therapy is most frequently employed model, this model suffer from some methodological and phenomenological prolems. As the existing animal models of tardive dyskinesia have several pitfalls, development of new models, having similarities with that of clinical picture and highly predictive of pathophysiology of TD can expedite the tardive dyskinesia research for the better understanding of the pathophysiology of TD and to discover new therapeutic targets for the treatment of tardive dyskinesia.

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