Sigma agonist 1, 3 di-o-tolyl-guanidine (DTG) on Schizophrenia and Immobility responses

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Recently in our laboratory we found that DTG (sigma receptor agonist 1,3-di-o-tolyl-guanidine) sub-chronic administration reduced the hyperlocomotor activity and reversed the neuronal hypotrophy in the prefrontal cortex, amygdala and nucleus accumbens, generated in rats with neonatal ventral hippocampus lesion (nVHL). We also observed that DTG reversed some of the behavioral and neuromorphological effects of nVHL rats, which supports the possibility that DTG has beneficial effects in the management of symptoms of schizophrenia. We also found that DTG had effects on immobility responses, in the unlesioned rats increased the duration of the dorsal immobility but it did not have effect on the duration of immobility elicited by clamping. However, the nVHL increased the duration of immobility elicited by clamping, but did not have effect on the duration of the dorsal immobility. It should be noted that DTG counteracted the increase in the duration of the immobility by clamping produced by nVHL. The increase in the duration of the dorsal immobility produced by DTG was counteracted by nVHL. We suggested that the differential effect on these two immobility responses, is due to they are different varieties of immobility mediated by different mechanisms. Therefore, we believe that this evidence could help us to connect, schizophrenia with immobility reaction, which may be associated or somehow present in catatonic schizophrenia.

Keywords: immobility response; schizophrenia; neonatal ventral hippocampus lesion; sigma agonist

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The sigma receptors are chaperon proteins, originally proposed as a subclass of opioid receptors (σ opioid receptors), because they were involved in delusion and psychosis induced by pentazocine and benzomorphans such as SKF-10047 [1]. Later on, was demonstrated that σ receptors were nonopioid receptors [2, 3]. There are at least two subtypes of sigma receptors: σ-1 and σ-2 [4, 5]. Only sigma-1 receptor has been cloned [6], for this reason, its biological and physiological roles have been better studied; σ-2 receptor has neither been well examined or cloned. The σ-1 receptor gene encodes membrane proteins with no homology to other mammalian protein [6]. The Sigma-1 receptors are intracellular receptors mainly localized in the endoplasmic reticulum, and they can translocate inside cells when they are stimulated by their ligands [7, 8]. They are expressed in several regions of the brain such as layers of the cortex, hippocampus, hypothalamic nuclei, substantia nigra and cerebellum [4, 9]. When sigma-1 receptors translocate to the cell membrane they regulate ion channels and neurotransmitter release [7, 10]. Sigma-1 receptors are involved in cellular differentiation [11, 12], neuroplasticity [13, 14], neuroprotection [15, 16], and cognitive process of the brain [17].
Neuroprotection and neurite outgrowth contribute to the improvement of neuropsychiatric diseases like schizophrenia. Therefore, in previous studies, we assessed the effect of sub-chronic administration of sigma receptor agonist 1,3-di-o-tolyl-guanidine (DTG) on two immobility responses, locomotor activity, as well as the neural morphology in nHVL rats.

At neonatal age, bilateral excitotoxic injury of the ventral hippocampus have been widely endorsed as a neurodevelopmental model of behaviors associated with schizophrenia [18]. These rats exhibit a complex mix of behavioral, neurochemical and neural morphological changes that manifest mainly at early adult age [18]. Interestingly, our results show that at postpubertal age, nVHL rats showed an increase of the dorsal immobility but did not modify the duration of immobility response elicited by clamping (IC). We also found that DTG counteracted the increase in the duration of the IC produced by nVHL. In addition, the increase in the duration of the dorsal immobility (DI) produced by DTG was counteracted by nVHL. The differential effect on these two immobility reactions, suggests that they are mediated by different mechanisms [19]. This raised the question: “are there multiple immobility responses, or there is one system that activates them in multiple ways?” Probably, there are multiple immobility responses; due to some immobility states can be elicited by different kinds of stimuli. In rodents, immobility states can be induced in pups and young rats by clamping, by bandaging the neck and by maternal transport [20]; in mice by pinching the neck [21], in dogs by tail and scruff pinch [22]. In these immobility responses, the neck is the principal region that receives the greatest amount of stimulation. Added to this, the neck region has a somatotopic mapping in the dorsal central gray related to analgesia [23]. Hence, in mouse, analgesia is linked to the immobility by clamping [24]. In our recent report [19], we found that either clamping or bandaging the neck region can trigger immobility in neonate rats, nevertheless in adult rats only clamping can induce it. An immobility state can be triggered in different animal species by various kinds of stimuli and by multiple types of drugs. Morphine and haloperidol may produce in rat two distinct and contrasting immobility states: morphine produces a state characterized by inhibition of the postural support, while haloperidol produces a state where tonic reactions prevail at the expense of phasic-locomotor responses [25]. Morphine induces a type of immobility characterized by inhibition of righting reactions [26]. The endorphinergic system interacts with dopaminergic systems [27]. It has been found that deficiency of dopaminergic neurotransmission is accompanied of catalepsy, which is a kind of immobility, somehow different to opiate-induced catalepsy, which suggests that these two immobility responses might be connected to a change of dopaminergic neurotransmission. Consequently, the destruction of the neo- or palio-striatal dopaminergic system abolished the immobility induced by neuroleptics, nevertheless, potentiated the immobility trigger by morphine [27]. The catatonia in the schizophrenic patients is probably related to hyperactivity in the dopaminergic neurotransmission, due to its high susceptibility to neuroleptic drug treatment.

The D2 antagonist “haloperidol”, is the main sigma-1 receptor antagonist [28], it increases the duration of immobility response elicited by clamping the neck [29]. Haloperidol is the most common neuroleptic used in the treatment of schizophrenia. In a previous study, we found that DTG reverted the increment in duration of IC due to nVHL. These findings suggest IC could be modulated by dopaminergic and sigma receptor pathways. However, DTG treatment produced an increased in dorsal immobility in sham rats and reduced the duration of this immobility response in nVHL rats. Studies about these two kinds of immobility responses have shown that they are modulated in different ways, although they share common characteristics [29]. The previous results exhibited that DTG by itself has an effect on DI, suggesting that this response is more sensitive to sigma receptor agonist. There had not been a study that correlated neither the IC nor DI with sigma receptors. Nevertheless, there are studies that correlate sigma receptors and depression, which have found that sigma receptor agonists reduce the time of immobility in forced swimming test; this suggest that sigma receptors are related to different forms of immobility [30-32].

One of the main psychiatric disorders in the world is “schizophrenia”, which is characterized by positive symptoms (hallucinations and delusions), negative symptoms (affective flattening, alogia, or abolition) and cognitive deficits (deterioration of concentration and memory). It is known that close to 1 % of the population aged 18 years and older develops schizophrenia (DSM-IV classification) [33]. Schizophrenia was described long time ago, however, the pharmaceutical treatment for this disorder began in the 1950s. The first and main drugs used in the schizophrenia treatment are the classical antipsychotics. Unfortunately, they produce severe extrapyramidal side effects that is why, research work has been focused on the development of new drugs with reduced extrapyramidal impairments.

As we mention before, nVHL has been proposed as a neurodevelopmental model of schizophrenia-related behaviors in the rat. At postpuberal age, rats with nVHL show changes in behaviors, which include locomotor hyperresponsiveness to stress and psychostimulant administration [34, 35], reduced social interaction, deficits in
sensory motor gating [36] and working memory [37]. Additionally, at postpuberal age, nVHLs also induce atrophy of dendritic arbor with reduced spinogenesis in the pyramidal neurons of the prefrontal cortex, and medium spiny neurons of the nucleus accumbens [38, 39], disrupted cholinergic and dopaminergic (DA) transmission [40, 41], as observed in schizophrenic patients.

Different reports have implicated sigma receptors (σ receptors) with schizophrenia, based on the psychotomimetic actions of σ receptor agonists [42], the density of σ receptors present in mesencephalic and limbic areas [43-45], and the action of sigma receptor ligands on dopaminergic and glutamatergic neurons [46-48]. It has also found a reduction of sigma-1 receptors in postmortem brains of schizophrenic patients [43, 44, 48], and there is the evidence that haloperidol has a high affinity for sigma-1 receptors [2, 49]. Studies have shown a clear relation between sigma-1 receptors and modulation of NMDA-type glutamate receptors [4, 49, 51], which have been implicated in the pathophysiology of schizophrenia [50, 51]. Moreover, neuroplasticity and cognitive functioning can be enhanced through sigma-1 receptor agonists modulation. For these reasons, σ-1 receptor agonists are being studying as a therapeutic target for schizophrenia and other mental disorders. In a previous study [52], we found that sub-chronic administration of DTG ameliorates the changes on the dopaminergic systems in nVHL rats as previously studies [53, 57-61]. The post-puberal onset of enhanced stress-induced hyperlocomotion and spontaneous exploration in the nVHL rat model could imply a change in mesolimbic and mesostriatal dopamine neurotransmission [58, 62], which can be ameliorated by neuroleptics [53, 55, 63]. The sigma-1 receptor knockout mice show signs of anxiety in the open field test [64]. We showed that DTG reversed the increase in locomotor activity in nVHL rats, probably, due to the modulation of DA through the sigma 1 receptor [52]. Besides, it has been found that fluvoxamine (a sigma-1 agonist) had beneficial effects on hyperkinetic movement disorders such as tardive dyskinesia and tardive akathisia of schizophrenic patients [65]. In addition, a systemic acute administration of DTG enhances DA release in the nucleus accumbens shell [46]. However, DA modulation by DTG administration depends of the administration via [46, 66]. We found in behavioral tests that sub-chronic administration of DTG had the opposite effect to the direct stimulation of the dopaminergic transmission, which can be due to acute and chronic administration of DTG have different effects on DA modulation [52]. In the nHVL rats, there is a hypotrophy in areas such as prefrontal cortex, nucleus accumbens and the basolateral amygdala. Interestingly, we found that sub-chronic administration of DTG ameliorates the hypotrophy derived from this lesion [52].

Immobility states are expressed in an ample variety of circumstances and can be induced in several species by different kinds of stimuli. It may be presented in response to natural stimuli, to diverse drugs or in some diseases of the nervous system. Despite of all the differences, they share some common neural mechanisms. Immobility is a state of complete absence of movements and relative unresponsiveness. It has been known by several names: “animal hypnosis, death feigning, tonic immobility, akinesia, catalepsy, cataplexy, catatonia etc”. Described for centuries “death feigning” is a type of immobility in which the animal remains completely still in the face of a threat. “Playing dead” is one of the oldest defense mechanisms used by diverse species, including our own, and it occurs in practically all the phylogenetic scale. Immobility responses are characterized by restraint and reduced capacity to react to external stimuli, the duration of these responses depend on the species. The animal can fight, escape or opt for passive defense, adopting a motionless posture, which may persist from a few seconds to several hours. These reactions can include some features such as: temporary immobility response [19, 68], defecation, abnormal EEG patterns, changes in heart rate, in breathing, in central temperature, muscle rigidity and tremors of the extremities [28]. This response is also induced by pharmacological means. Morphine produces a type of immobility known as “catatonia”, in this state, the righting reflexes and stiffness are inhibited [28]. Catalepsy is another form of immobility (used as an indicator of some antipsychotic drugs as haloperidol) where righting reflex is preserved [28]. These neuroleptic actions are linked to the capacity of the drug to antagonize DA receptors and they act on the striatum and nucleus accumbens [21]. Also the electrolytic lesion of the caudate-putamen and accumbens reduced haloperidol-induced catalepsy. It has been suggested that the basal nuclei interact through cholinergic routes with cortical regions such as the prefrontal cortex. Immobility responses have been produced by damaging certain regions of the brain that control postural reflexes and locomotion, like the lateral hypothalamus [26]. Additionally, mesencephalic lesioned and nVHL rats have also shown an increase in different ways of immobility [69, 70]. As we mentioned before, catalepsy is a way of immobility related to hyperactivity dopaminergic transmission and it is very susceptible to neuroleptic drugs. A person with catalepsy undergoes physical immobility when in catatonic seizure is unable to respond to external stimuli. Some diseases of the central nervous system provoke certain forms of immobility.
that can disconnect the people from the world.

The above show evidence that could help us to link, immobility responses, neuronal morphology and schizophrenia, which may be related or somehow present in catatonic schizophrenia. It also opens the possibility of using sigma receptor agonists as DTG as a therapeutic target.

References


29. Fregoso-Aguilar T, Urioñstegui T, Zamudio S, De la Cruz F. The


47. Pabba M, Wong AY, Ahlskog N, Hristova E, Biscaro D, Nassrallah W, et al. NMDA receptors are upregulated and transfected to the plasma membrane after sigma-1 receptor activation in the rat hippocampus. J Neurosci 2014; 34:11325-11338.


57. Brake WG, Sullivan RM, Flores G, Srivastava LK, Gratton A. Neonatal ventral hippocampal lesions attenuate the nucleus...


60. Lipska BK, Weinberger DR. To model a psychiatric disorder in animals: schizophrenia as a reality test. Neuropsychopharmacology 2000; 23:223-239.


66. Gudelsky GA. Effects of sigma receptor ligands on the extracellular concentration of dopamine in the striatum and prefrontal cortex of the rat. Eur J Pharmacol 1995; 286:223-228
