

Dopaminergic Receptor Type 1 Antagonists and its Possible Role as Preventive Treatment of Post-Traumatic Stress Disorder: A Short Review

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ABSTRACT

Posttraumatic stress disorder (PTSD) is an overreaction to aversive memories and can cause severe health issue. The prevention or treatment memory of PTSD through pharmacological approaches is a rising field, but still with inconclusive results. In this study, the literatures of dopaminergic D1 antagonist were reviewed and author propose that it can be applied to achieve this goal, mainly due to effects on memory persistence. Moreover, administration of D1 antagonists would be simple with few side effects, making this treatment reasonably practical for human use.

INTRODUCTION

Unfortunately, traumatic events are fairly common. Studies report that a range from 40% to 60% of the general population have been exposed to some aversive incident during their life (Creamer *et al.*, 2001; Kessler *et al.*, 1995), while some studies enlarge this rate to around 90% in U.S. (Breslau *et al.*, 1998; Breslau, 2009). These experiences are capable of producing health issues as posttraumatic stress disorder and other forms of psychological impairment. Although exposure rate differs across studies, the lifetime prevalence of PTSD varied within a narrow range: 5-6% in men and 10- 14% in women (Breslau *et al.*, 1998; Breslau, 2009); and 7% in a general estimative (Kessler *et al.*, 2007). Despite not well explored in literature, prevention of PTSD through pharmacological treatment is a rising field with some promising studies (Pitman *et al.*, 2005; Fletcher *et al.*, 2010). Investigated drugs, as

hydrocortisone (Schelling *et al.*, 2001; Schelling *et al.*, 2004), benzodiazepines (Gelpin *et al.*, 1996; Mellman *et al.*, 1998), escitalopram (Suliman *et al.*, 2015), propranolol (Vaiva *et al.*, 2003; Stein *et al.*, 2007; Pitman *et al.*, 2002), antiepileptics (Stein *et al.*, 2007) and morphine (Bryant *et al.*, 2009; Holbrook *et al.*, 2010) focus primarily on modulating the anxiety-related factors of memory consolidation, diminishing the averseness of threatening experiences.

However, these approaches provide some inconclusive results and no clear evidences of PTSD prevention. A Cochrane review in 2014 concluded that in general, there is and no evidence for the efficacy propranolol, escitalopram, temazepam, and gabapentin (Amos *et al.*, 2014). This lack of effects could be due that not every symptom is associated with fear circuitries (Fletcher *et al.*, 2010; Holbrook *et al.*, 2010). Moreover, there is a limited time of fear memory consolidation (Izquierdo *et al.*, 2016), so this small window of opportunity for administration of prophylactic drugs after a traumatic event increases the necessity for more specific and efficient interventions.

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On other hand, dopamine is a vastly studied neurotransmitter, implicated to have roles in several mental impairments, such as anorexia nervosa (Kontis and Theochari, 2012), depression (Höflich *et al.*, 2012), addiction (Taber *et al.*, 2012) and schizophrenia (Pillai *et al.*, 2012; Seeman, 2010), in which D2 dopaminergic receptor antagonists are broadly used for treatment (Pillai *et al.*, 2012; Miyake *et al.*, 2012). Additionally, several studies correlate mutations in dopamine transporters D2 and D3 with susceptibility to PTSD development (Comings *et al.*, 1996; Lawford *et al.*, 2006; Segman *et al.*, 2002; Wolf *et al.*, 2014). Nevertheless this wide range of influence on brain diseases and the direct impact on PTSD manifestation, no research has up to this date directly tested using dopaminergic modulators to PTSD treatment.

In this review, I suggest that due to the known role of dopamine on memory formation and persistence (Jay, 2003; O'Carroll *et al.*, 2006), dopaminergic receptor antagonists could contribute to prevent PTSD and other psychological impairments related to traumatic incidents.

Dopaminergic control of memory persistence

Memory traces can be stored for different amounts of time. Biologically significant events tend to generate memories that last longer than every day scenarios, and the capability of storage particular traces through time is called persistence. The hippocampus encodes memory processes and receives neuromodulatory signals from several cortical and subcortical structures. Among these, one of great importance is the ventral tegmental area (VTA), a mesolimbic structure that has dopaminergic projections to hippocampus (Scatton *et al.*, 2005; Swanson, 1982; Kahn and Shohamy, 2013). When the hippocampus detects novel information, a neural signal is thought to pass first via the subiculum to the nucleus accumbens (NAcc), and then, NAcc neurons stimulate the firing of the VTA. In fact, the dopaminergic loop VTA-hippocampus is assumed to influence processing of information on long-term memory formation and persistence (Jay, 2003; O'Carroll *et al.*, 2006; Lemon *et al.*, 2006; Rossato *et al.*, 2009).

Additionally, the basolateral amygdala (BLA), an area connected to hippocampus and well known for its involvement in fear conditioning, also receives projections from VTA and show D1/D5 receptor expression (Muller *et al.*, 2009). Also, it was shown that a selective dopaminergic D1/D5 receptor antagonist (SCH23390), suppresses long-term potentiation and modulates the acquisition of contextual fear conditioning in both hippocampus and BLA (Huang *et al.*, 1995; Huang *et al.*, 2007; Heath *et al.*, 2015), indicating that D1-like receptor signaling in these regions are necessary to process fear memory. Thus, this modulatory effect of dopamine on plasticity could give rise to a selective strengthening or weakening of memory traces from hippocampus and amygdala.

Exploring these mechanisms, Bethus *et al.* demonstrated that intrahippocampal infusions of SCH23390, modulated the persistence of new memories over time, but not in new paired-

associations in an episodic-like memory task, not affecting encoding per se. Furthermore, investigating specific influence in fear memory persistence, Rossato and collaborators showed that intrahippocampal administration of SCH23390 12hrs after an aversive stimulus is capable of induce fear memory persistence depletion by inhibiting the VTA modulatory inputs on hippocampus. In agreement with this, it is shown at synaptic level that hippocampal dopaminergic receptors D1 are necessary for persistence of memory traces, since its activation lowers the threshold for the induction of both synaptic long term potentiation and long term depression (Huang *et al.*, 1995; Frey and Schroeder, 1990).

Several other factors mediate the memory persistence mechanism, as brain derived neurotrophic factor (BDNF) expression and protein synthesis (Bekinschtein *et al.*, 2007), and alterations in their influence reach similar results. However, differently from dopamine modulators, the drugs used to manipulate these factors are usually not efficient or too harmful to human administration.

Treatment, receptor specificity and optimal administration approach

Supported by the evidences shown so far, our proposal is that dopamine receptor antagonists have the capability of impairing persistence of long term memory and therefore can be applied to prevent aversive memory that could lead to psychological impairments like PTSD. But which are the best pharmacological solutions for this goal?

The most highlighted target is the D1 receptor, because as said, several studies clearly indicate its influence on memory persistence (Jay, 2003; O'Carroll *et al.*, 2006; Lemon *et al.*, 2006; Rossato *et al.*, 2009). Some selective antagonists for this receptor exists, among them the drug SCH-39166 (or ecopipam) that was several times tested for human use in disorders such as drug abuse and compulsive eating, although never approved for medical prescription (Chipkin *et al.*, 1988; Zhang *et al.*, 2009). This scenario is mainly because of side effects such as depression and anxiety, even though these symptoms appear just after chronic intake (Astrup *et al.*, 2007).

Moreover, a main point in the proposed PTSD preventive treatment is the administration time. Since the objective is to control the maintenance and persistence of memory, medicaments should be given preferentially hours, not days, after the traumatic event, in order to impair the necessary VTA modulation and consequent BDNF expression in hippocampus (Bethus *et al.*, 2010; Bekinschtein *et al.*, 2007). To act on this time window, just an acute single dose of the antagonist would be necessary, avoiding these unwanted psychiatric adverse effects.

Another advantage of this proposal is the fact that it does not alter the encoding or retrieval of the memory trace, but the mechanisms that determine its relevance and persistence (Bethus *et al.*, 2010; Rossato *et al.*, 2009). It is an important point, because however memory-modulatory approaches are being considered

promising, these drugs can raise relevant ethical issues, such as the possibility of invalidating testimonials of an event (Parsons and Ressler, 2013; Kolber, 2011).

CONCLUSION

Presented here is a new alternative to preventing trauma-related mental impairments by acute administration of dopamine D1 antagonists in a specific time-window, known to impair aversive memory persistence. This hypothetical treatment can offer several advantages over the current ones, granted that there is a lack of undesired effects, simplicity in application and unquestionable action over fear persistence. However, the limitation of this treatment is the administration time-window, since optimal administrations should be within a few hours after the traumatic event, requiring to the emergency handling unit to especially pay attention to this procedure.

Supporting this hypothesis, D1 receptor antagonists are already used in human trials for other purposes and the literature indicates that its collateral effects are dependent of chronic administration. Therefore, D1 receptor antagonist administration may be reasonably practical for treatment in humans. Furthermore, this treatment would not alter the perception of the traumatic event, but change the fear processing associated to it, by modulation of a specific dopaminergic mechanism.

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