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Review

Activation of the hypothalamic-pituitary-adrenal axis in lithium-induced conditioned taste aversion learning

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ABSTRACT

Intraperitoneal injections (ip) of lithium chloride at large doses induce c-Fos expression in the brain regions implicated in conditioned taste aversion (CTA) learning, and also activate the hypothalamic-pituitary-adrenal (HPA) axis and increase the plasma corticosterone levels in rats. A pharmacologic treatment blunting the lithium-induced c-Fos expression in the brain regions, but not the HPA axis activation, induced CTA formation. Synthetic glucocorticoids at conditioning, but not glucocorticoid antagonist, attenuated the lithium-induced CTA acquisition. The CTA acquisition by ip lithium was not affected by adrenalectomy regardless of basal corticosterone supplement, but the extinction was delayed in the absence of basal corticosterone. Glucocorticoids overloading delayed the extinction memory formation of lithium-induced CTA. ip lithium consistently induced the brain c-Fos expression, the HPA activation and CTA formation regardless of the circadian activation of the HPA axis. Intracerebroventricular (icv) injections of lithium at day time also increased the brain c-Fos expression, activated the HPA axis and induced CTA acquisition. However, icv lithium at night, when the HPA axis shows its circadian activation, did not induce CTA acquisition nor activate the HPA axis, although it increased the brain c-Fos expression. These results suggest that the circadian activation of the HPA axis may affect central, but not peripheral, effect of lithium in CTA learning in rats, and the HPA axis activation may be necessary for the central effect of lithium in CTA formation. Also, glucocorticoids may be required for a better extinction; however, increased glucocorticoids hinder both the acquisition and the extinction of lithium-induced CTA.

Contents

1. Introduction

Although lithium has been used clinically for many years and numbers of studies related to its therapeutic effects have been done (Pilcher, 2003), the cellular and molecular bases of the

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therapeutic and toxic effects of lithium still remain poorly understood. Lithium is one of the most effective therapeutic agents prescribed for the treatment of bipolar disorder and depression. Dysfunction of the hypothalamic-pituitary-adrenal (HPA) system is one of the major pathophysiological alterations observed in patients suffering from mood disorders, and the abnormalities of the HPA activity return to normal following successful pharmacotherapy with lithium and other antidepressants (Holsboer and Barden, 1996). It is suggested that interactions of lithium with the HPA system may, at least partly, contribute to its therapeutic effects.

Lithium has been widely used as conventional stimulus to produce conditioned taste aversion (CTA) for its toxic effect. Intraperitoneal (ip) administration of lithium chloride activates the HPA axis in rats; i.e. increases plasma levels of adrenocorticotrophic hormone (ACTH) and corticosterone (Hennessy et al., 1976; Smotherman, 1985; Sugawara et al., 1988). Blockade of the HPA activation with adrenalectomy impaired the acquisition of lithium-induced CTA in mice (Peeters and Broekkamp, 1994), and pharmacological manipulation of the HPA system altered the strength of lithium-induced CTA in rats (Smotherman et al., 1976; Hennessy et al., 1980; Revusky and Martin, 1988). These studies suggest that activation of the HPA axis by lithium may be a part of its effects as unconditioned stimulus in CTA learning. In this review, functional implication of the HPA axis activation in lithium-induced CTA learning will be discussed, which would provide some insights in understanding its therapeutic effects as well.

2. Lithium-induced conditioned taste aversion

CTA is a robust form of associative learning, in which a single pairing of a novel taste with a toxic substance produces a strong and persistent avoidance of substances containing that taste (Garcia et al., 1974). In this learning paradigm, a toxic substance plays a role as unconditioned stimulus (US) and a novel taste becomes conditioned stimulus (CS). Acute ip injection of lithium chloride at large doses (0.15 M, 6–20 ml/kg) induces neuronal activation, referred by c-Fos expression, in the brain regions including the parabrachial nucleus (PBN), the nucleus tractus of solitarius (NTS), the hypothalamic paraventricular nucleus (PVN) and the central nucleus of amygdala (CeA), and the lithium-induced c-Fos expression in those brain regions has been reported to correlate with CTA formation (Houpt et al., 1994; Jahng et al., 2004a; Lamprecht and Dudai, 1995; Sakai and Yamamoto, 1997; Schafe and Bernstein, 1996; Yamamoto et al., 1992).

Also, ip lithium chloride at large doses, as a toxic substance, induces nausea, diarrhea and gastrointestinal distress, and this effect was believed to contribute to formulate CTA (Domjan and Gillan, 1976; Nachman and Ashe, 1973). Nauseogenic effect of ip lithium comprising delayed gastric empting was suggested to be mediated by both magnocellular and parvocellular oxytocin neurons in the PVN (McCann et al., 1989). ip lithium activates oxytocin neurons in the PVN and supraoptic nucleus (SON) (Olszewski et al., 2000) and increases neurohypophyseal secretion of oxytocin (Verbalis et al., 1986). However, it is unclear whether oxytocin is a key facilitator of aversion or merely its marker. Oxytocin receptor blockade at the acquisition of lithium-induced CTA diminished aversion to saccharin, but one at the retrieval of it did not affect aversion (Olszewski et al., 2013). Interestingly, oxytocin receptor blockade blunted the lithium-induced c-Fos expression only on the CeA, but not in the other regions such as the area postrema (AP), NTS, PVN, SON and the basolateral amygdala (Olszewski et al., 2013). Thus, it is suggested that the CeA neurons may mediate the oxytocin effects, if any, in lithium-induced CTA formation. However, a recent study has reported that ventromedial hypothalamic oxytocin suppresses food intake without inducing CTA (Noble et al., 2014). The brainstem AP was also believed to mediate the nauseogenic effects of lithium chloride, and studies have reported that AP lesions not only block the lithium-induced CTA (Curtis et al., 1994) but also attenuate the lithium-induced c-Fos expression in the brain regions, such as the PBN and NTS (Spencer et al., 2011).

3. Nitric oxide in lithium-induced CTA learning

Nitric oxide (NO) has been considered as a neuromodulator in the central nervous system (Moncada et al., 1991; Snyder and Bredt, 1992), and reported to play a role in learning and memory (Haley et al., 1992; O'Dell et al., 1991; Schuman and Madison, 1991). Previous reports regarding the role of NO in CTA learning have been somewhat inconsistent. That is, NO donor, sodium nitroprusside or N-tert-butyl-alpha-phenyl nitrone produced a CTA in rats, which was prevented by pretreatment with a NOS inhibitor, N^{ω}-nitro-L-arginine (Rabin, 1996). On the other hand, NO precursor, L-arginine, was reported to counteract the aversion produced by lithium chloride. Furthermore, NOS inhibitors, such as methylene blue, 7-nitroindazole, and N^{ω}-nitro-L-arginine methyl ester (L-NAME) all produced a CTA (Prendergast et al., 1997; Wegener et al., 2001). However, studies have reported that systemic lithium chloride increases both the synthesis and activity of nitric oxide synthase (NOS) in the brain (Bagetta et al., 1993) and NO modulates lithium-induced CTA learning (Wegener et al., 2001). Indeed, large populations of neuronal nitric oxide synthase (nNOS) containing cells and fibers are distributed in the brain regions implicated in CTA learning such as the PVN (Vincent and Kimura, 1992), PBN, NTS, and various subdivisions of the ventrolateral medulla (Dun et al., 1994; Krukoff and Khalili, 1997; Vincent and Kimura, 1992). These reports together suggested that NO may play a role in lithium-induced CTA learning.

Interestingly, L-NAME pretreatment at the conditioning did not blunt, but rather augmented the acquisition of lithium-induced CTA, although it significantly attenuated the lithium-induced c-Fos expression in brain regions such as the PVN, CeA and NTS (Jahng et al., 2004a). This result suggests that the amount of neuronal activation, referred by the number of c-Fos expressing neurons, in the brain regions at the conditioning may not be strongly correlated with the strength of CTA acquisition, and further, c-Fos expression in the brain regions, at least in the PVN, CeA and NTS, could not always be used as a reliable molecular index of CTA learning. The number of c-Fos expressing neurons in the brain regions may not be directly correlated with the acquisition of an aversive memory. LiCl-like c-Fos patterns of neuronal activation were observed in the absence of behaviorally evident aversive consequences (Benoit et al., 2000).

It was reported that mRNA level of nNOS in the hypothalamic PVN, the center of the HPA axis, is increased in lithium-treated rats (Anai et al., 2001). Studies performed with NOS blockers have demonstrated that NO participates in the regulation of corticotropin-releasing factor (CRF) and arginine vasopressin release from the hypothalamic neurons (Costa et al., 1993; Ota et al., 1993) as well as in the stress-induced release of ACTH and corticosterone (Rivier, 1994) and c-Fos expression in the hypothalamus (Amir et al., 1997). NO has also been reported to stimulate transcription of CRF and its receptor in the hypothalamus of intact rats (Lee et al., 1999). These reports together suggest a possible implication of NO in the formation of lithium-induced CTA, possibly via a modulation of the HPA axis activation. However, nNOS inhibitor L-NAME did not affect the lithium-induced increase of corticosterone (Jahng et al., 2004a), suggesting that NO may not be involved in lithium-induced activation of the HPA axis.