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ARTICLE

Histamine infused into basolateral amygdala enhances memory consolidation of inhibitory avoidance

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Abstract

The role of the basolateral amygdala (BLA) in the consolidation of aversive memory is well established. Here we investigate the involvement of the histaminergic system in BLA on this variable. Rats were chronically implanted with bilateral cannulae in the BLA and after recovery were trained in a one-trial step-down inhibitory avoidance task. Immediately after training histaminergic compounds either alone or in combination were infused through the cannulae. Memory was assessed in test sessions carried out 24 h after the training session. Post-training histamine (1–10 nmol; 0.5 μl/side) enhanced consolidation and the histamine H_3 receptor antagonist thioperamide (50 nmol; 0.5 μl/side) impaired memory consolidation. The effect was shared by the histamine *N*-methyltransferase inhibitor SKF-91844 (50 nmol; 0.5 μl/side) as well as by the H_3 receptor agonist imetit (10 nmol; 0.5 μl/side). The promnesic action of histamine was unaffected by the H_1 receptor antagonist pyrilamine (50 nmol; 0.5 μl/side). The H_1 receptor agonist pyridylethylamine (10 nmol; 0.5 μl/side), the H_2 agonist dimaprit (10 nmol; 0.5 μl/side) and the H_2 antagonist ranitidine (50 nmol; 0.5 μl/side) were ineffective. Histaminergic compounds infused into the BLA had no effect on open-field or elevated plus-maze behaviour. The data show that histamine induces a dose-dependent mnemonic effect in rats and indicate that this reflects a role of endogenous histamine in the BLA mediated by H_3 receptors.

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Introduction

Histamine given post-training in various brain regions modulates memory consolidation of various learning tasks. The first description of memory modulation by histamine was an enhancement of the consolidation of one-trial inhibitory avoidance (IA) with post-training i.c.v. administrations (Almeida and Izquierdo, 1986). In that paper, histamine was effective at low doses (1 or 10 ng/rat) and was blocked by both promethazine and cimetidine but not by either drug alone. Since then, the effects on memory of histamine, histamine releasers, enhancers and antagonists given in various structures of the brain were studied in different forms of memory. Some reports have concluded that histamine facilitates consolidation and others that it depresses it by action on different receptors in different brain sites (Cacabelos and Alvarez, 1991; Frisch et al., 1999; Spieler et al., 1999; Passani et al., 2001; Cangioli et al., 2002; Giovannini et al., 2003; Alvarez and Ruarte, 2004; Baldi et al., 2005; Da Silva et al., 2006; Liu et al., 2007; Alvarez and Banzan, 2008; Foley et al., 2009; Bonini et al., 2011; Charlier and Tirelli, 2011; Benetti et al., 2012a, b) so the overall picture is far from clear. It is possible that at some receptors and in some brain areas, histamine enhances memory consolidation of certain tasks, and at other receptors and in other areas or tasks it may have different effects. For example, memory facilitation of IA has been described both with histamine given i.c.v. (Almeida and Izquierdo, 1986) and with pharmacological inhibition of the tuberomammilary nucleus, the source of brain histamine (Frisch et al., 1999). Many histamine effects on memory have been attributed to histamine H_1, H_2 or H_1 plus H_2 receptors (Almeida and Izquierdo, 1986; Alvarez and Ruarte, 2004; Alvarez and Banzan, 2008; Benetti et al., 2012a) but as will be seen later, clearly other effects in areas critical for memory formation are mediated by H_3 receptors (Benetti et al., 2012a). Interestingly, the H_3 receptor antagonist thioperamide has been reported to enhance consolidation in some tasks or brain regions (Ghi et al., 1998; Molinengo

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et al., 1999; Orsetti et al., 2002; Bernaerts et al., 2004) and as will be seen later, also to antagonize the enhancing action of histamine in others.

The basolateral nuclear complex of the amygdala (BLA) has been repeatedly and convincingly shown to modulate the memory consolidation of one-trial IA in the rat and various other species (McGaugh, 2004; Izquierdo et al., 2006) and has been relatively little explored in connection with histamine effects on this process. Various types of histamine receptors in the BLA have been described and it has been suggested that they may play a role in the consolidation of different tasks (see Alvarez and Ruarte, 2004; Fiorenza et al., 2012). Here we study the effect of histamine, of an enhancer of histamine action, *N*-methyltransferase inhibitor SKF-91488 and of different histamine receptor blockers micro-infused immediately post-training into the BLA on memory consolidation of one-trial IA in rat.

Materials and method

Subjects

Male Wistar rats (aged 2.5–3 months; 290–330 g) purchased from the State Center for Production and Research in the Health Sciences, our regular provider, were housed five to a cage with water and food (Purina lab pellets) *ad libitum*, under a 12-h light/12-h dark cycle (lights on 07:00 hours). The temperature of the animal room was maintained at 22–24 °C. All procedures followed the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Bioethics Committee of the University.

Surgery, handling and habituation to experimenter

At least 5 d after their arrival the animals were implanted with 75 mg/kg ketamine plus 10 mg/kg xylazine anaesthesia with bilateral 22-g guide cannulas aimed 1.0 mm above the BLA (A −2.8, L ±4.7, V −7.5 mm). Coordinates are from the atlas by Paxinos and Watson (1998). After 4–7 d recovery from surgery, the animals were handled by the experimenter gently touching and holding the rat with two hands using gloves, for approximately 5 min, once daily for two consecutive days. After this they were trained in the IA procedure between 08:00 and 11:00 hours.

Training was carried out in a 50 × 25 × 25 cm plexiglass box with 5 cm-high, 7 cm-wide and 25 cm-long Formica platform on the left end of a series of 0.3 cm-calibre bronze bars spaced 1.0 cm apart that made up the floor of the box. The animals were placed on the platform facing the rear left corner of the training box. When they stepped down placing their four paws on the grid they received a 2 s 0.5 mA scrambled foot shock and were then withdrawn from the apparatus. Later (24 h) they were again placed on the platform as described and allowed to move freely without receiving a foot shock when they stepped down. Step-down latency was measured in the training and the test session with a chronometer activated automatically. Drug or vehicle treatments were administered immediately after the training session. Step-down latencies were cut-off at 300 s in the test session (Da Silva et al., 2006; Bonini et al., 2011; Benetti et al., 2012b; Fiorenza et al., 2012).

Drug infusions

Rats were infused intra-BLA bilaterally, first on the right side and 30 s later on the left side, through a 5 μl Hamilton syringe coupled to a pump (EICOM, Japan) at a flow rate of 0.5 μl/min; infusion cannulas were left in place 30 s after each infusion so as to minimize backflow. The doses used were chosen from those described in the literature as being effective, based on pilot experiments.

Open field and plus maze

To analyse their locomotor and exploratory activities, animals were placed in a 50 × 50 × 39 cm open-field arena with the floor divided into 12 equal rectangles. Line crossings and rearings were measured over a 5 min period. To evaluate their anxiety state, rats were exposed to an elevated plus maze as described by Pellow et al. (1985) and more recently by Benetti et al. (2009). The total number of entries into the four arms and the number of entries and time spent into the open arms were recorded over a 5-min session. The animals used for IA training were not reutilized in open-field and plus-maze experiments. Twenty-four hours before exposure to the open field or the plus maze, the animals received 0.5 μl/side bilateral infusions of the treatments as shown in Table 1, in the BLA. All behavioural observations were carried out in the light part of the light/dark cycle (lights on 07.00 hours).

Statistics

Data obtained in IA were expressed as medians and interquartile range and were analysed by a non-parametric analysis of variance (ANOVA) test, the Kruskal–Wallis test, followed by Dunn's multiple comparison tests. We used non-parametric statistics for this measure because the ceiling of 300 s caused the results to be non-Gaussian. Data obtained on the plus maze and open-field test were expressed as by means ± S.E.M. and were analysed by one-way ANOVA for repeated measures followed by *post hoc* Newman–Keuls tests comparing all pairs of columns. Probability $p < 0.05$ was considered significant.

Correct cannula placements are shown in Fig. 1. They were established by measuring the spread of infusions of 0.5 μl 4% Methylene Blue over 30 s into BLA at the coordinates mentioned earlier, 2 d after the final behavioural procedure. The spread of the dye was taken as an estimate of that of the drug infusions in the same animals. Placements were considered correct when the spread was

Table 1. Intra basolateral nuclear complex of the amygdala (BLA) infusion of histamine, agonist or antagonist of histamine receptors did not show effects in the locomotor activity and anxiety in rats

	Saline	Histamine (10 nmol)	SKF 91488 (50 nmol)	Thioperamide (50 nmol)	Imetit (10 nmol)	Histamine + Thioperamide	SKF 91488 + Thioperamide
Plus maze							
Total number entries	11.1 ± 1.1	10.5 ± 0.7	11.2 ± 0.7	10.5 ± 0.6	11.4 ± 0.9	10.1 ± 0.6	10.2 ± 0.8
Entries in open arms	6.2 ± 0.6	5.9 ± 0.7	6.1 ± 0.8	5.2 ± 0.4	5.6 ± 0.7	4.9 ± 0.41	5.0 ± 0.7
% Time in open arms	59.1 ± 6.0	54.6 ± 4.5	50.6 ± 3.6	50.4 ± 4.9	48.2 ± 4.2	51.7 ± 6.0	46.8 ± 4.9
Open field							
Crossings number	57.8 ± 5.5	55.9 ± 5.7	56.3 ± 7.0	59.4 ± 6.3	57.7 ± 5.3	54.0 ± 6.5	61.3 ± 7.5
Rearing number	16.8 ± 1.7	16.0 ± 2.4	15.6 ± 1.9	17.0 ± 2.0	17.5 ± 2.0	16.4 ± 1.8	17.1 ± 2.1

Histamine, *N*-methyltransferase inhibitor SKF 91488, imetit or conjugated drugs SKF 91488 + thioperamide and histamine + thioperamide 50 were infused intra BLA 24 h before the open-field or plus-maze session. Results are expressed as mean ± SE for each behavioural parameter analysed for each animal group ($n = 12$). Probability $p < 0.05$, one-way repeated measures analysis of variance and *post hoc* Newman–Keuls with multiple comparison test.

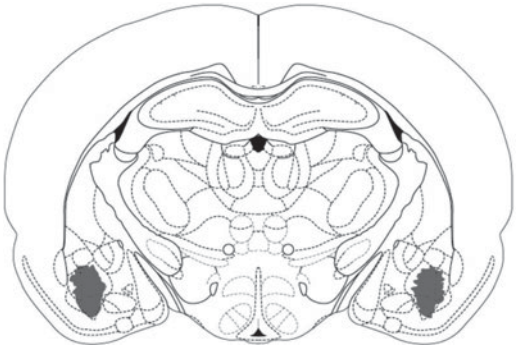

Fig. 1. Schematic drawing taken from the atlas of Paxinos and Watson (1998) showing the correct location of the cannula positions in the basolateral nuclear complex of the amygdala and the area reached by 0.5 μl 4% Methylene Blue infusions.

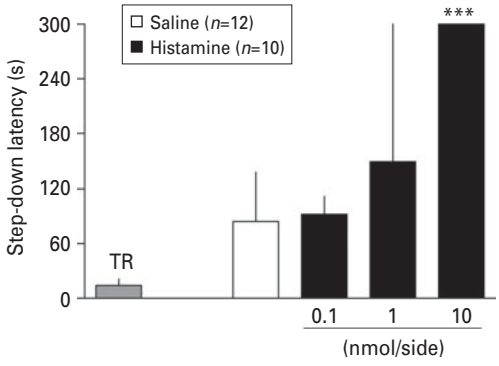

Fig. 2. Infusion of histamine into the basolateral nuclear complex of the amygdala (BLA) enhances aversive memory in rats and in a specific drug concentration. Histamine dose–response curve in three different concentrations (0.1, 1.0 or 10 nmol) per side were bilaterally infused (0.5 μl) into the BLA immediately after inhibitory avoidance training. TR, Training session step-down latency. Bars represent median (± interquartile range) step-down latencies during a memory retention test carried out 24 h after training. n = number of animals per group. *** $p < 0.0001$ (one-way analysis of variance) non-parametric Kruskal–Wallis test followed by Dunn's multiple comparison test.

$\leqslant 1\ mm^3$ from the intended infusion sites; this occurred in 98% of the animals. Although we do not know the diffusion rate of the dye or that of the drugs used, clearly this procedure is an improvement over the mere verification of the cannula tip position.

Results

As shown in Fig. 2, histamine at the dose of 1 or 10 nmol/side enhanced memory consolidation in comparison with saline: $p < 0.0001$ in a one-way Kruskal–Wallis test followed by a Dunn's multiple comparison test. The difference between the effect of both doses was also significant ($p < 0.001$).

The enhancing effect of the histamine potentiator, SKF-91488 was significant at the level of $p < 0.01$ in a Kruskal–Wallis test followed by a Dunn's multiple comparison tests and was therefore similar to that of histamine. However, its effect was fully antagonized by the co-infusion SKF-91488 plus thioperamide; $p < 0.0001$ in a Kruskal–Wallis test followed by a Dunn's multiple comparison test (Fig. 3).

The antagonists of each histaminergic receptor H_1, H_2 or H_3 in comparison with saline had no effect on their own (Fig. 4) at the doses given ($p > 0.05$; one-way ANOVA, non parametric Kruskal–Wallis test followed by Dunn's multiple comparison test). However, interestingly the H_3 antagonist thioperamide co-infused with histamine blocked the enhancing effect of 10 nmol histamine ($p < 0.0001$ in comparison with the other two antagonists pyrilamine and ranitidine co-infused with histamine). Furthermore, histamine at a dose of 10 nmol and histamine plus pyrilamine replicated the enhancement in aversive memory consolidation in comparison with saline ($p < 0.01$ in a Kruskal–Wallis test followed by Dunn's multiple comparison tests; Fig. 5).

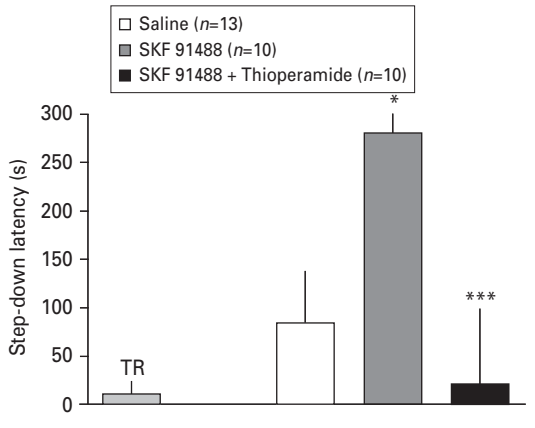

Fig. 3. *N*-methyltransferase inhibitor SKF-91488 mimics the enhancement of consolidation caused by histamine and its effect is antagonized by thioperamide. SKF-91844 (50 nmol), or a solution with thioperamide (50 nmol) plus SKF-91488 (50 nmol) were prepared and were bilaterally infused (0.5 μl) into the basolateral nuclear complex of the amygdala immediately after inhibitory avoidance training. TR, Training session step-down latency. Bars represent median ($\pm$interquartile range) step-down latencies during a memory retention test carried out 24 h after training; n = number of animals per group. * $p < 0.01$ and *** $p < 0.001$ (one-way analysis of variance) non-parametric Kruskal–Wallis test followed by Dunn's multiple comparison test.

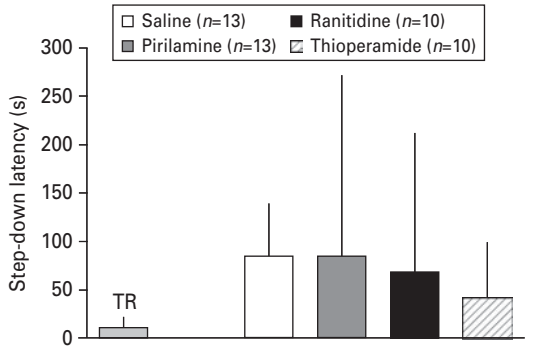

Fig. 4. Effects of antagonists of H_1, H_2, H_3 histamine receptors infused into the basolateral nuclear complex of the amygdala immediately after training in inhibitory avoidance task in rats. H_1 antagonist pyrilamine, the H_2 antagonist ranitidine and the H_3 antagonist thioperamide were bilaterally infused (0.5 μl) into the basolateral nuclear complex of the amygdala after inhibitory avoidance training at 50 nmol/side. Any one histaminergic antagonist receptor showed specific effects in blockage aversive memory. TR, training session step-down latency. Bars represent median ($\pm$interquartile range) step-down latencies during a memory retention test carried out 24 h after training; n = number of animals per group. $p < 0.05$ (one-way analysis of variance) non-parametric Kruskal–Wallis test followed by Dunn's multiple comparison test.

The H_3 agonist, imetit ($p < 0.0001$) unlike the other two histamine receptor agonists tested, enhanced consolidation on its own in a Kruskal–Wallis test followed by Dunn's multiple comparison test (Fig. 6).

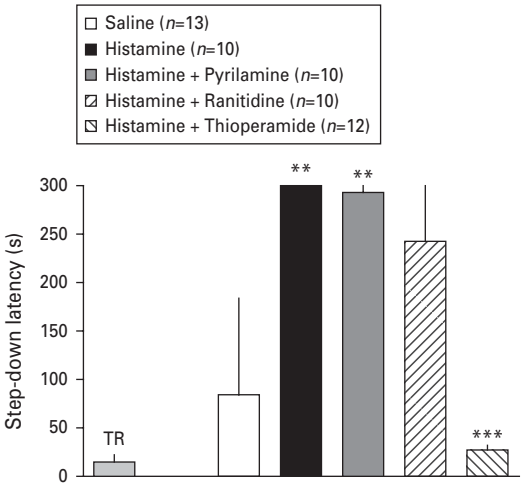

Fig. 5. Aversive memory enhancement induced by the intra basolateral nuclear complex of the amygdala (BLA) infusion of histamine and SKF-91488 was blocked by H_3, but not H_1 and H_2 antagonists of histaminergic receptors. Rats received bilateral infusions intra- BLA (0.5 μl) of saline, histamine (10 nmol/side) or a prepared solution with histamine (10 nmol/side) plus another specific antagonists (50 nmol/side) of type H_1 histaminergic receptors (pyrilamine) or antagonist of type H_2 histaminergic receptor (ranitidine) or type H_3 (thioperamide) immediately after training. TR, Training session step-down latency. Bars represent median ($\pm$interquartile range) of step-down latencies during a memory retention test carried out 24 h after training; n = number of animals per group. ** $p < 0.001$, *** $p < 0.0001$ *vs.* saline *vs.* all groups in Dunn's comparison after Kruskal–Wallis test.

None of the treatments tested had any effect on open-field or plus-maze performance (Table 1), which rules out an influence on hippocampus/BLA independent of memory.

Discussion

Clearly, histamine enhances memory consolidation in the BLA and the effect is attributable to an action upon H_3 receptors, inasmuch as it is mimicked by the H_3 agonist imetit and blocked by the H_3 antagonist, thioperamide. It appears to reflect an influence of endogenous histamine as suggested by the action of the inhibitor of histamine catabolism, SKF-91488 and its reversal by thioperamide. The effect would appear to occur independently of the H_2 receptor-mediated histamine facilitation of consolidation processes for this task in the hippocampus (Da Silva et al., 2006). All types of histamine receptor have been found in the BLA and have been attributed different functions on the basis of pharmacological experiments (Passani et al., 2001; Cangioli et al., 2002; Jiang et al., 2005; Bananej et al., 2012).

The present findings add to the growing evidence for a role of histamine in memory modulation (see references in Introduction). Unlike its role in consolidation of IA in the hippocampus, which as stated is mediated by H_2

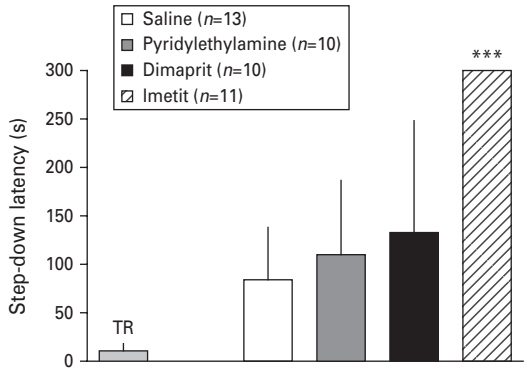

Fig. 6. Consolidation of aversive memory can be enhanced in rats by the infusion of specific histaminergic H_3 agonist imetit into the basolateral nuclear complex of the amygdala. Rats trained in inhibitory avoidance task received bilateral infusion (0.5 μl) of saline, agonist H_1 pyridylethylamine (10 nmol/side), agonist H_2 dimaprit (10 nmol/side) or H_3 agonist imetit (10 nmol/side). H_1 and H_2 agonists had no effect but imetit caused aversive memory enhancement. TR, Training session step-down latency. Bars represent median ($\pm$interquartile range) of step-down latencies during a memory retention test carried out 24 h after training, n = number of animals per group; *** $p < 0.001$ (one-way analysis of variance) non-parametric Kruskal–Wallis test followed by Dunn's multiple comparison test.

receptors, or in the consolidation of extinction, which is also mediated by H_2 receptors but in BLA, hippocampus and ventromedial prefrontal cortex simultaneously (Fiorenza et al., 2012), the facilitatory influence of histamine on IA consolidation in BLA is mediated by H_3 receptors sensitive to imetit and thioperamide. H_3 receptors also mediate the enhancing role of histamine in consolidation of conditioned fear in the nucleus basalis magnocellularis (Benetti et al., 2012a). In other tasks, H_3 receptor blockade has been reported to actually improve memory consolidation (Passani et al., 2001; Orsetti et al., 2002). H_3 receptor agonists increase (Cangioli et al., 2002) and H_3 antagonists decrease the spontaneous release of acetylcholine in the BLA (Passani et al., 2001). Thus, it has been speculated that histamine actions on H_3 receptors may depend at least in part on influences on cholinergic transmission (see Benetti et al., 2012b). Muscarinic cholinergic transmission in BLA is widely regarded as important for memory consolidation in various tasks (Power et al., 2003). Curiously, thioperamide reverses amnesia induced by MK-801 or scopolamine (Bernaerts et al., 2004). Furthermore, histamine H_2 receptor stimulation in the CA1 of dorsal hippocampus has recently been shown to counteract the deleterious effect on the consolidation of one-trial avoidance brought about by the cholinergic dysfunction created by early maternal deprivation in rats (Benetti et al., 2012b).

Although we have no way of knowing if the spread of the dye was identical to that of the infused substances, clearly this procedure gives a better estimate than that provided by the mere localization of the cannula tips.

In addition, the present findings on thioperamide are at odds with others reported in the literature with other H_3 receptor antagonists that have promnesic effects of systemic or intracerebral effects on memory consolidation (Fox et al., 2005; Medhurst et al., 2007; Esbenshade et al., 2008; Giannoni et al., 2010; Passani and Blandina, 2011). This may be due to a number of factors, among which a different amount of acetylcholine modulatory release by H_3 auto-receptors or hetero-receptors in different tasks or situations and different access of the drug(s) to the BLA or other sites of action in the H_3 receptors are known to influence the release of acetylcholine in BLA (Cangioli et al., 2002). Other transmitters with dopamine, noradrenaline and acetylcholine in other brain areas within cingulated cortex (Medhurst et al., 2007; Esbenshade et al., 2008; Giannoni et al., 2010) including histamine itself may mediate their influence on behaviour totally or partially (Cangioli et al., 2002; Köhler et al., 2011; Benetti et al., 2012b).

The outcome of histaminergic effects on memory processes in the BLA or, for that matter, elsewhere, certainly depends on the relative participation of the various histamine receptor types in the function of the brain area being investigated and in the case of H_3 receptors, of the relative involvement of other neurotransmitters released by stimulation of those receptors. In addition, it is very likely that for different tasks the modulatory influences of histaminergic and other synapses (catecholaminergic, etc.) operate differentially, as recently shown for contextual fear conditioning and IA (see Fiorenza et al., 2012).

Finally, the results showed here, together with others that have been published previously are coherent with the hypothesis that the histaminergic system could provide a crucial mechanism to fine tune amygdala for an adequate behavioural response. Therefore, clearly, the H_3 receptor-mediated role of histamine in the BLA in memory consolidation of one-trial avoidance described here is something different from, and parallel to, other histaminergic actions on the modulation of memory.

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Statement of Interest

None.

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