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SHORT COMMUNICATION

Ketamine modulates catecholamine transmission in the bed nucleus of stria terminalis: The possible role of this region in the antidepressant effects of ketamine

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Abstract
Since the therapeutic treatment of depression is far from being satisfactory, new therapeutic strategies ought to be pursued. In addition, further investigation on brain areas involved in the action mechanism of antidepressants can shed light on the aetiology of depression. We have previously reported that typical and atypical antidepressants strongly stimulate catecholamine transmission in the bed nucleus of stria terminalis (BNST). In this study, we have built on that work to examine the effect of ketamine, an unusual antidepressant that can produce a fast-acting and long-lasting antidepressant effect after administration of a single sub-anaesthetic dose. Ketamine is an antagonist of the ionotropic N-methyl-D-aspartate (NMDA) receptor but can also act through its metabolite (2R-6R)-hydroxynorketamine. Using the microdialysis technique in freely moving rats, we monitored the acute effect of ketamine on catecholamine release in the BNST to gain clues to its prompt antidepressant effect. Male Sprague-Dawley rats were implanted with a microdialysis probe in the BNST and 48 h later, were injected with ketamine (10, 20, and 40 mg/kg, i.p.). Ketamine increased norepinephrine (127%, 155%, 186%) and dopamine (114%, 156%, 176%) extracellular concentration above basal in a time and dose dependent manner, without significantly modifying motility. Since the effect of ketamine, although lower, was not substantially different from that produced by classical antidepressants, we suggest that catecholamine increase in BNST is not likely to be related to a rapid ketamine antidepressant effect, though it might be related to its performance in predictive tests of antidepressant properties.

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1. Introduction

Depression is a common psychiatric disorder characterised by personal suffering and elevated societal cost (Pincus and Pettit, 2001). The aetiology of depression is uncertain but it is widely accepted that it can be triggered by the interaction of genetic and epigenetic factors (Feder et al., 2009). Among epigenetic factors, stress has a pivotal role because it can alter neurotransmitter release and neuronal circuitry in several brain areas (Caspi et al., 2003). In particular, noradrenergic transmission plays a major role in the physiological response to environmental challenges and stress (Itoi and Sagimoto, 2010). Among brain areas involved in stress control, the bed nucleus of stria terminalis (BNST) is one of the brain areas most innervated by norepinephrine neurons and has a general role in stress-induced hypothalamic-pituitary-adrenal (HPA) activation (Choi et al., 2007). In particular, the relationship between norepinephrine and corticotrophin releasing factor (CRF) neurons in the BNST suggests that the BNST is involved in the adaptive response to stress (Morilak et al., 2005), and possibly in the aetiology of depression (Jennings et al., 2013).

Depression therapy is mostly based on drugs that target monoaminergic neurotransmissions, but the slow onset of the clinical response and the significant number of non-responders, suggest that drugs with alternative mechanism of action ought to be investigated. In particular, the modulation of the ionotropic N-methyl-D-aspartate (NMDA) receptor is considered to be a promising target for the treatment of depression (Gerhard et al., 2016). This view is in agreement with the consideration that glutamate neurotransmission dysfunction may be a feature of stress-related mental illnesses (Musazzi et al., 2013). In addition, an altered glutamate function has been found in animal models of depression (Sanacora et al., 2012). Among NMDA acting drugs, the intravenous infusion of a single sub-anaesthetic dose of ketamine evoked a fast-acting and long-lasting antidepressant effect (Berman et al., 2000). Depressed patients, even those resistant to monoaminergic-acting antidepressants, reported alleviation of core symptoms within 2 h of a single low-dose infusion, with effects lasting up to 2 weeks (Zarate et al., 2006). Interest in the ketamine effect on brain neurotransmission has been greatly enhanced by a recent report that proposes an NMDA independent antidepressant action of ketamine metabolites (Zanos et al., 2016). We have previously reported that the systemic acute administration of various antidepressants, namely desipramine, reboxetine, imipramine, fluoxetine, citalopram and bupropion increased norepinephrine and dopamine extracellular concentration (output) in the BNST, suggesting that catecholamine transmission in the BNST may be part of a common downstream pathway that is involved in the mechanism of action of antidepressants (Cadeddu et al., 2014). Interestingly, it has been reported that the BNST is involved in the behavioural affective effects of systemic ketamine (Louderback et al., 2013).

Hence, considering the potential role of BNST in stress generated depression, and in the mechanism of action of classical antidepressants, as well as of ketamine, we believed it important to investigate the effect of acute administration of ketamine on catecholamine release in the BNST of freely moving rats through the microdialysis technique.

2. Experimental procedures

2.1. Animals

All animal experimentation was conducted in accordance with the guidelines for care and use of experimental animals set by the European Communities Council Directive and approved by the "Ethics Committee" at the University of Cagliari.

Male Sprague-Dawley rats weighing 250–300 g (Harlan, S. Pietro al Natisone, Italy) were group-housed under standard conditions of humidity (60%), temperature (22 °C) and artificial light (light, 8 a.m. to 8 p.m.). Food and water were available *ad libitum*.

2.2. Probes and surgery

Probes were house constructed (as previously described in Cadeddu et al. (2014)) using AN 69 dialysis fibre, (0.310 and 0.220 μm, outer and inner diameter, respectively), cut-off 40.000 Da (Hospal-Dasco, Bologna, Italy), active-membrane length=2 mm. On the day of the surgery rats were anaesthetised with 400 mg/Kg i.p. chloral hydrate and placed in stereotaxic apparatus (Kopf, Germany). A small hole was drilled on the side of the exposed skull and a microdialysis probe was implanted in the BNST (AP −0.4; L ±1.2; V −8.0) from dura mater (coordinates are in mm from Bregma), according to the atlas by Paxinos and Watson (2007). Probes were then fixed to the skull with dental cement (Shofu Cx-Plus, GmbH, Ratingen, Germany) and the skin sutured. The rats were individually housed in transparent plexiglass hemispheric cages, covered with a top hemisphere, with food and water made available.

2.3. Dialysis experiments

Experiments were performed on freely-moving animals 48 h after the probe implantation. On the day of the experiment, artificial cerebrospinal fluid (Ringer's solution, NaCl 147 mM, $CaCl_2$ 2.2 mM, KCl 4 mM, pH 6.5) was pumped through the dialysis probe at a constant rate of 1 μL/min via a microinjection pump. Dialyzed samples (20 μL) were collected every 20 min and immediately injected with no purification into a HPLC system equipped with reversed-phase column (C-18, 15 cm × 4.6 mm, 3.5 μm Supelco, Milan, Italy) and a coulometric detector (ESA Coulochem II, Bedford, MA, USA; oxidation +125 mV, reduction −175 mV). The mobile phase composition was 0.1 M sodium acetate, 0.3 mM Na2EDTA, 1.8 mM octanesulfonic acid, 120 ml/L methanol, and pH 5.4. The sensitivity of the assay allowed for the detection of 5 fmoles of norepinephrine and dopamine. When the basal output of norepinephrine and dopamine reached stable values (mean of three consecutive samples differing less than 10% from the mean of the previous three samples), rats (n=6 per each dose, n=5 for saline) were given a single acute i.p. injection of ketamine (10, 20, and 40 mg/kg) or saline. Stable levels were usually obtained after the first 2-3 h of dialysis. Basal values (as a mean±SE) of norepinephrine and dopamine were 36.25 (±5.2) and 21.89 (±3.8,) fmol/20 μl sample respectively (n=23).

2.4. Motility

For each experimental group, four rats were in turn exposed in a new environment for three 10 min periods, for time intervals of 15–45 min after drug administration. Total and locomotion activity was evaluated through an "Open Field" metre (Columbus Instruments, Columbus OH, USA). Each 10 min period activity and global exposition period (30 min) activity were statistically analysed (ANOVA) for differences in total and locomotion activity between groups in each period and between periods in each experimental group.

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2.5. Histology

At the end of the experiment, rats were anaesthetised with chloral hydrate (450 mg/Kg i.p.). The brain was removed and stored in formaldehyde (10%). Brains were then cut on an oscillating microtome (Campden Instruments, Lafayette, IN, USA) producing consecutive coronal slices containing the regions of interest following the coordinates according to the Paxinos and Watson (2007). Results from rats implanted outside the BNST (5 out of 28 implanted) were discarded. Probes were considered within the BNST when their anteriority ranged from −0.3 to −0.9 and their laterality ranged from 1.1 to 1.9 mm from bregma. A schematic drawing of the traces left by the implanted probes appears in a previous publication (Carboni et al., 2000).

2.6. Drugs

Ketamine hydrochloride (Ketalar®), purchased from Farmaceutici Gellini (Milan, Italy), was dissolved in saline and administered i.p. immediately.

2.7. Statistics

All data are expressed as mean±SEM. Statistical analysis was carried out by STATISTICA (Statsotf, Tulsa, OK, USA). Two-way analysis of variance (ANOVA) for repeated measures was applied to the data expressed as a percentage of basal norepinephrine and dopamine concentration. Results from treatments showing significant overall changes were subjected to post hoc Tukey's tests with significance for $p<0.05$.

3. Results

Figure 1(a) and (b) shows that ketamine increased norepinephrine (127%, 155%, 186%) and dopamine (114%, 156%, 176%) output when administered at 10, 20, and 40 mg/Kg i.p., respectively. Two-way ANOVA of the results obtained showed a significant treatment effect ($F_{3,19}=3.76$, $p<0.02$ and $F_{3,19}=4.63$, $p<0.01$), time effect ($F_{9,171}=31.41$, $p<0.001$ and $F_{9,171}=12.72$, $p<0.001$) and time × dose interaction ($F_{27,171}=6.29$, $p<0.001$ and $F_{27,171}=3.04$, $p<0.001$) for norepinephrine and dopamine, respectively. Post-hoc analysis showed that the increase of norepinephrine and dopamine output obtained at doses of 20 and 40 mg/Kg, were significantly higher than that produced by the dose of 10 mg/kg. The evaluation of total motility (beam interruptions are indicated in brackets as mean± S.E. for each dose, $n=5$) has shown that ketamine at 10 (895±122), 20 (768±152) or 40 (1120±182) mg/kg, i.p. did not significantly modify motility when compared with saline (1172±146). One-way ANOVA of the results obtained showed no significant main effect ($F_{3,16}=1.99$, $p=0.15$).

4. Discussion

This study shows that the acute systemic administration (i.p.) of ketamine increased norepinephrine and dopamine output in the BNST of freely moving rats, in a time and dose dependent manner. The highest increase was observed 40 min after treatment (85% and 75% above basal levels, for norepinephrine

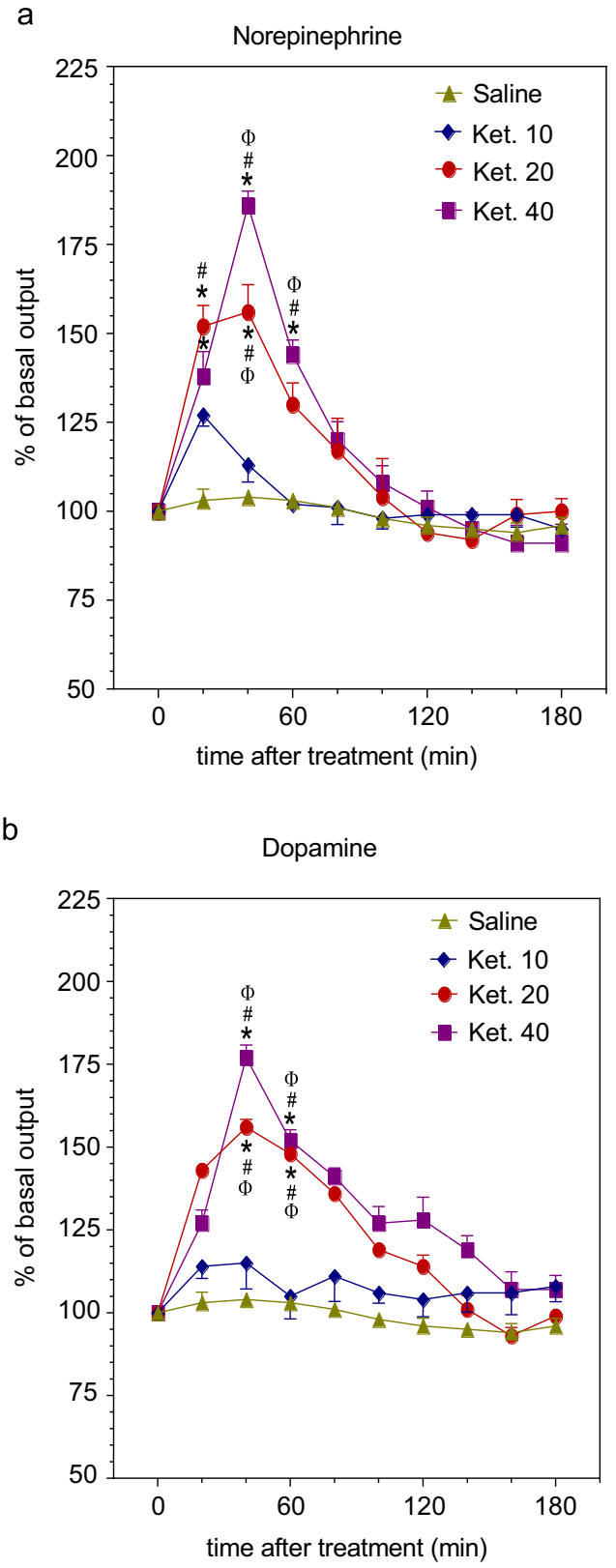

Figure 1 Effect of ketamine (10, 20, 40 mg/Kg i.p.) on BNST dialysate norepinephrine (**a**) or dopamine (b) expressed as a percentage of basal output. Each point is the mean (±SE) of 5 or 6 determinations. $^{*}p<0.05$ from basal values; $^{\#}p<0.05$ versus the corresponding time point after saline; $^{\$}p<0.05$ versus the corresponding time point of 10 mg/Kg.

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and dopamine respectively). Although the effect on dopamine was longer than that on norepinephrine, catecholamine output returned to basal levels within two hours even after 40 mg/kg of ketamine. Since this well sub anaesthetic dose is rather high, we assessed the motor effects of all doses of ketamine. No significant difference was observed in either total or ambulatory activity (total activity data shown in results), between each ketamine dose and saline, and within ketamine doses. In particular, the 10 and 20 mg doses reduced motility by about 25% while 40 mg did not reduce activity, although it did affect behaviour by producing waving ambulation and difficulties in performing the rearing behaviour, which became more intense about 20 min after treatment.

In evaluating the possible mechanisms involved in the results obtained, we would stress that the heterogeneity and the size of BNST nuclei did not allow us to assess dopamine and noradrenaline output in a specific portion of BNST. In this study we used a probe with a 2 mm dialysing length, that allows the recovery of catecholamines from either the ventral or the dorsal part of the BNST, as we have schematically illustrated previously (Carboni et al., 2000). Interestingly, although dopamine innervates the dorsal part of the BNST and norepinephrine mostly the ventral part, both dopamine and norepinephrine innervations form synapses with dendrites of CRF neurons in the dorsolateral and in the ventrolateral BNST respectively (Phelix et al., 1992). Looking at the possible mechanism of action of ketamine on BNST catecholamines, we would first like to consider the possibility that ketamine is acting directly on catecholamine reuptake in the BNST as previously reported by Tso et al. (2004), through the fast cyclic voltammetry (FCV) technique. These authors measured monoamine efflux elicited by electrical stimulation in ventral BNST superfused slices and reported that 100 μM micromolar (+) or (−) ketamine increased release and inhibited norepinephrine uptake. In addition Tso et al. reported that (+) but not (−) 100 μM ketamine increased dopamine efflux in caudate putamen slices. They also observed that both isomers (100 μM) had a similar effect on 5-HT uptake in dorsal raphe slices, and increased stimulated 5-HT efflux, although the (−) isomer had a greater effect. Considering that rat brain concentration of ketamine during anaesthesia has been shown to be around 100 μM (Livingston and Waterman, 1978) and that anaesthesia requires about 100 mg/kg to be induced, it is hard to differentiate the contribution of ketamine effect on reuptake of dopamine and norepinephrine for the doses used in this study.

A second possible mechanism, which may contribute to catecholamine output increase in the BNST, involves the affinity of ketamine for dopamine D2 and serotonin 5-HT2 receptors, which has been found to be similar to that for NMDA receptors (Kapur and Seeman, 2002). However, the fact that haloperidol, even at 0.5 mg/kg (s.c.) did not increase dopamine output in BNST (Carboni et al., 2000) suggests that a ketamine effect on BNST dopamine through D2 receptors, is unlikely. Furthermore, Kapur and Seeman suggested that ketamine could have an agonist action on the D2 receptor, but even the involvement of this action seems unlikely because it should have produced a decrease, rather than an increase of dopamine output in the BNST.

If we exclude a direct interaction of ketamine with dopamine and norepinephrine carriers (i.e. DAT or NET respectively) at BNST level, we can focus attention instead on glutamate receptors to suggest a plausible mechanism of ketamine mediated catecholamine increase in the BNST. Ketamine can produce its rapid antidepressant effect through inhibition of glutamate NMDA receptor as discerningly reviewed by Duman's group (Gerhard et al., 2016). These authors suggested that ketamine has a preferential action on NMDA receptors located on inhibitory GABA neurons in the prefrontal cortex (PFC), which in turn disinhibits pyramidal cells producing glutamate burst, activation of intracellular mechanism, protein synthesis and synaptogenesis. A complementary mechanism has also been recently proposed (Zanos et al., 2016); these authors contend that ketamine would act through its metabolite (2R-6R)-hydroxynorketamine to produce behavioural, electroencephalographic, electrophysiological and cellular antidepressant-related action in mice.

Therefore, PFC pyramidal cell activation could directly stimulate the dopamine and norepinephrine nucleus of origin and increase release in the BNST (El Mansari et al., 2010) but we also have to consider that ketamine could act directly at the BNST level. In fact, glutamate projections from the ventral subiculum (vSub), directed to the PVN, relay in different BNST nuclei, where the excitatory signal from the hippocampus is transformed into inhibitory output to the PVN (Cullinan et al., 1993). In addition, dopamine and norepinephrine afferents to the BNST make synaptic contacts onto CRF-neurons, which in turn influence glutamate release from afferents onto GABA BNST neurons. In turn, these neurons project onto the VTA GABA neurons, providing disinhibition of VTA dopamine neurons (Silberman and Winder, 2013) and thus dopamine release in the BNST. Nevertheless, although a detailed description of the possible mechanisms involved in catecholamine release in the BNST is outside of the scope of this report, we would like to refer to the work of McElligott and Winder (2009) and to our recent paper (Cadeddu et al., 2014) for further considerations.

One of the chief aims of this study was to seek clues on the unique fast antidepressant action of ketamine by comparing its effect on catecholamine transmission in the BNST with that of classical antidepressants. In fact, we have recently observed that, among others, (i) desipramine, a norepinephrine transporter blocker (NET), (ii) citalopram, a selective serotonin transporter blocker (SERT), (iii) imipramine, a SERT and (through its metabolite desipramine) NET blocker, and fourth, bupropion, a dopamine transporter (DAT) and NET blocker, independently of their mechanism of action, strongly increased catecholamine output in the BNST (Cadeddu et al., 2014). On this basis, we proposed that in the long run this effect could contribute to the production of the antidepressant effect of the above listed drugs. Hence, the result of this study adds a new antidepressant to the above list, although the mechanism by which ketamine produces the stimulation of norepinephrine and dopamine transmission in the BNST remains to be clarified.Nevertheless, it appears that the effect observed, being partly similar to that of the above listed antidepressants, does not provide clues to explain the rapid onset of the clinical antidepressant effect of ketamine (Berman et al., 2000; Zarate et al., 2006). On the other hand, we do suggest that the stimulation of catecholamine transmission in the BNST, being a common effect of an antidepressant possessing a different mechanism of action, could be linked to the acute behavioural effects that are observed in the animal

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tests (e.g. forced swim test) used for evaluating the antidepressant potential of drugs.

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Contributors

Roberto Cadeddu, performed the experiments, wrote the protocol, analysed the data and contributed to the preparation of the manuscript. Dragana Jadzic performed the experiments, wrote the protocol, analysed the data and contributed to the preparation of the manuscript. Ezio Carboni, designed the study and had the responsibility in the preparation of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no any actual or potential conflict of interest including any financial, personal or other relationships with other people or organisations within three (3) years of beginning the work submitted that could inappropriately influence, or be perceived to influence, their work.

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