INCREASED NOVELTY SEEKING AND DECREASED HARM AVOIDANCE IN RATS SHOWING TYPE 2-LIKE BEHAVIOUR FOLLOWING BASAL FOREBRAIN NEURONAL LOSS

ÁSA K. JOHANSSON and STEFAN HANSEN*
Department of Psychology, Göteborg University, Box 500, SE-405 30 Göteborg, Sweden

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Abstract — Previous research has shown that excitotoxic lesions of the septum, ventral striatum and adjacent areas increase alcohol intake and defensive aggression in the rat. This behavioural constellation resembles that observed in early-onset Type 2 alcoholism. Due to the fact that the prototypical Type 2 alcoholic scores high on novelty seeking and low on harm avoidance, we studied these temperamental traits in rats with basal forebrain lesions. In comparison with controls, such rats showed more exploration (nose-poking) of a hole-board (indicating increased novelty seeking) and less risk assessment behaviour (stretched attend posturing) in an unfamiliar arena (indicating reduced harm avoidance). In both tests the experimental rats showed signs of motor restlessness. The results obtained indicate that basal forebrain neuronal loss may be associated with an enhanced exploratory responsiveness to novel stimuli together with a relative freedom of anticipatory anxiety.

INTRODUCTION

Since the seminal work of Brady and Nauta (1953), it has become apparent that excessive defensive aggression — also known in the research literature as hyper-reactivity, hyper-emotionality, hyper-defensiveness or hyper-irritability — can be induced in the laboratory rat by lesions to the septal area, the ventral striatum and adjacent structures (Albert and Richmond, 1975; Blanchard et al., 1979; Lee et al., 1983; Albert and Walsh, 1984; Albert et al., 1993). We have repeatedly shown that axon-sparing lesions in this area, in addition to enhancing aggressiveness, also increase voluntary ethanol drinking in a two-bottle choice paradigm (Hansen et al., 1995; Bergvall et al., 1996; Johansson et al., 1999; Johansson and Hansen, 2000). Thus neuronal loss in the basal forebrain increases daily alcohol intake and heightens aggression.

Alcohol abuse coupled with an aggressive life-style figures prominently in the clinical literature on alcoholism. Thus, nearly all typologies of alcoholism identify a subtype in which the drinking problem is linked to enhanced aggressiveness and a history of violence (Babor, 1996). For example, besides their drinking problem, many so-called Type 2 alcoholics (Cloninger et al., 1996) are aggressive, criminal and antisocial (Hallman et al., 1996). Type 2 alcoholism is most likely to occur in individuals with a particular temperamental configuration. Using the nomenclature of Cloninger (Cloninger et al., 1993), their level of novelty seeking (approach to possible rewards) is typically above average. Harm avoidance (avoidance of possible punishment) on the other hand, is generally below normal (Cloninger et al., 1996). This particular organization of personality is considered to pave the way for thrill-seeking, impulsive–aggressive behaviours and outwardly directed anger (von Knorring et al., 1987; Virkkunen et al., 1994). Frontal lobe dysfunction as expressed as childhood hyperactivity and impulsiveness is related to adult alcohol misuse and antisocial behaviour (af Klinteberg et al., 1993).

Because temperamental traits, such as novelty seeking and harm avoidance, have deep phylogenetic roots (e.g. Adamec and Stark-Adamec, 1986; Suomi, 1987; Kagan et al., 1988; Cloninger, 1994), it is possible to investigate whether lesioned rats with high levels of alcohol intake and aggression show a ‘personality profile’ similar to that described in Type 2 alcoholics. The purpose of the present study was therefore to assess novelty seeking and harm avoidance in rats exhibiting Type 2-like behaviour. According to Cloninger (1994), rodents high in novelty seeking show a considerable amount of exploratory behaviour and readily approach novel stimuli. We tapped this temperamental dimension in the rat by use of the hole-board test (File and Wardill, 1975). The key measure in this test is nose-poking, i.e. the frequency with which the animal investigates and explores any of the holes in the floor of the test apparatus. Rodents with low harm avoidance show reduced fearfulness (Cloninger, 1994). The stretched attend (or approach) posture is an important risk assessment behaviour through which the rat gathers information about potential dangers (Blanchard and Blanchard, 1994). We therefore measured the number of stretched attend postures exhibited by rats placed in an unfamiliar, partially unsheilded testing environment capable of eliciting particularly high levels of risk assessment behaviours (Grewal et al., 1997).

MATERIALS AND METHODS

Subjects and housing conditions

Male Wistar rats weighing 200–225 g were purchased from Möllegaard Breeding Laboratories (Denmark). They were housed in an air-conditioned colony room (lights off 10:00–22:00) with free access to food (R70, Labfor) and water. The animals were allowed 2 weeks to adapt to the novel laboratory conditions before the experiment began. The experiment was authorized by the local ethical committee of the Swedish National Board for Laboratory Animals. All tests were conducted blind.

Surgery

Brain lesions were made in nine animals under pentobarbital anaesthesia (30 mg/kg, intraperitoneally) while the animal was fixed in a Kopf stereotaxic instrument. Basal
forebrain excitotoxic lesions were created by infusing ibotenic acid (10 µg/µl; Sigma) in the basal forebrain at the following stereotaxic coordinates (incisor bar: −3.3 mm); 0.7 mm in front of bregma, 0.7 mm lateral to midline, 8.0 mm below the skull. The infusions (5 µg/0.5 µl for 30 s in each hemisphere) were made through a stainless steel cannula (outer diameter: 0.25 mm) using a CMA 100 (Stockholm, Sweden) micro-injection pump. The cannula remained in place for 3.5 min after the end of the infusion. Sham-operated animals (n = 9) were infused with an equal volume of vehicle (0.1 mol/l phosphate buffered saline, pH 7.4).

Reactivity

For the reactivity tests, given 4 and 7 days following surgery, the rat was placed in a Plexiglas cage (60 × 31 × 41 cm high) and allowed to habituate for 30 s. Its reaction to four stimuli was then assessed (modified from Lee et al., 1983). (1) A wooden rod slowly moved to approach and touch the rat’s snout; 0: no response or sniffs at the rod; 1: intermittently bites or attacks the rod and/or adopts a defensive upright posture; 2: continuously bites/attacks the rod. (2) Starle to an air puff (air blow from a 50 ml syringe) at the back; 0: no response or some movement; 1: jumping response; 2: exaggerated jumping response. (3) Poking with a wooden rod at the flanks; 0: no response or sniffing at the rod; 1: defensive upright posture; 2: defensive upright posture together with biting/attack. (4) Capturing with a gloved hand; 0: very easy to capture; 1: easy to capture but some resistance and/or prolonged vocalization; 2: difficult to capture because of escape, attacking or biting; 3: very difficult to capture because of continuous violent attacks/bites. Previous studies (Albert and Richmond, 1975; Albert and Walsh, 1984; Albert et al., 1993; Blanchard et al., 1979; Hansen et al., 1995; Bergvall et al., 1996; Johansson et al., 1999; Johansson and Hansen, 2000) have shown that the moderately-sized lesions studied here do not give rise to the vicious defensive aggression reflected by very high scores in this test battery (maximum total score is 9). Rather, to facilitate animal management, we performed medium-sized lesions which elicit a moderate degree of hyper-reactivity with little outright aggression (Albert and Richmond, 1975; Bergvall et al., 1996; Johansson et al., 1999; Johansson and Hansen, 2000).

Risk assessment

The anxiety test apparatus (Grewal et al., 1997) comprised a circular (104 cm diameter), deep green platform elevated to 73 cm above the ground level. A clear red Perspex circular canopy (70 cm diameter) was supported 10 cm directly above the platform by a central pillar. This divided the apparatus into a covered closed zone, and an outer open zone. Eight white lines were drawn radially from the centre of the platform. The arena was illuminated by normal fluorescence room lighting, yielding a level of illumination of approximately 165 lux in the covered zone and 560 lux in the open zone.

The 10-min test began by placing the animal under the canopy. One observer registered the number of stretched attend postures and the number of lines crossed with all four limbs. Another observer registered the time spent in the outer exposed zone of the arena. A stretched attend posture was defined as flexed hindlimbs and a flattened lower back position with extended forelimbs; usually the response was accompanied by either a lack of movement or a very slow gait.
Risk assessment (number of nose-pokes) were measured in rats with axon-sparing sustained cell loss in the septum (including the medial part of the diagonal band of Broca), and the medial nucleus accumbens. There was also some damage in medial frontal cortex rostrally, in the olfactory tubercle ventrally and bed nucleus of the stria terminalis caudally. An illustration of a typical lesion using exactly the same parameters as in the present study can be found in Johansson et al. (1999) (Fig. 2).

DISCUSSION

A previous research study carried out by our group showed that excitotoxic lesions of the septum, ventral striatum and adjacent areas in rats elicited a syndrome consisting of increased alcohol intake, irritability, diminished responsiveness to aversive stimuli and future rewards, and lowered brain serotonin levels (Hansen et al., 1995; Bergvall et al., 1996; Johansson et al., 1999; Johansson and Hansen, 2000). These signs parallel those observed in early-onset Type 2 alcoholism (Virkkunen and Linnoila, 1990; Cloninger et al., 1996). In the present study we add yet another item to this list of parallels: similar to the prototypical Type 2 alcoholics (Virkkunen and Linnoila, 1990; Cloninger et al., 1996), rats with basal forebrain neuronal loss are characterized not only by low harm avoidance but also by high levels of novelty seeking.

Exploration is an important facet of novelty seeking (Cloninger, 1994) and the nose-poking activity in a hole-board is considered a valid index of exploration in the rat (File and Wardill, 1975; Abel, 1995). Little is known about the neurobiological basis of exploratory behaviour or novelty seeking, and regrettably the present study provides little additional information on this topic. This is due to the fact that the lesions impinged on the three major emotional motor systems located in the basal forebrain: the septal system, the ventral striatopallidal system and the extended amygdala (Alheid and Heimer, 1996), and damage to any of these might conceivably have contributed to the behavioural effect. Nevertheless we suspect that damage to the ventral striatum, particularly the nucleus accumbens, may have played a central role. The activity of neurons intrinsic to the ventral striatum is modulated during ongoing exploratory nose-poking behaviour (Lee et al., 1998). Pharmacological manipulations of ventral striatal mechanisms disrupt novelty-induced activity (Hooks and Kalivas, 1995), as do lesions in the region of the nucleus accumbens (Burns et al., 1996). As the ventral striatum is densely innervated by dopaminergic terminals, the activity of which changes in the presence of novelty and other psychologically significant stimuli (Hansen et al., 1993; Bardo et al., 1996; Schultz, 2000), it is of great interest that novelty seeking has been linked to certain dopamine receptor gene polymorphisms in humans (Benjamin et al., 1996). In view of the evidence suggesting a ventral striatopallidal basis for novelty seeking, it seems likely that the increase in exploration observed in the present study was due to lesion-induced dysfunction in this part of the basal forebrain. However, since portions of the septum were also included in the damaged area, one cannot exclude the possibility that septal injury contributed to the increase in nose-poking. It has, for instance, been reported that septal lesions increase exploration although the effect tends to be short-lived, disappearing within days after surgery (Santacana et al., 1975).

When adopting the stretched attend posture, the rat collects information concerning anticipated or potential dangers. The outcome of this emotional appraisal determines whether the animal will go on to show more specific defensive behaviours (e.g. freezing, flight, attack) or loosen its vigilance (Blanchard and Blanchard, 1994). The stretched attend posture, which is sensitive to a number of anxiolytic agents (Blanchard and Blanchard, 1994; Molewijk et al., 1995; Grewal et al., 1997), thus mirrors a crucial element in the temperamental dimension of harm avoidance: namely, anxiety, worry and apprehension, especially in anticipation of future problems (Cloninger, 1994). The present study shows that basal forebrain neuronal loss reduces this central component of the defensive behaviour repertoire. Taken together with results obtained in previous...
studies, it would appear that neuronal loss in the septum and nucleus accumbens reduces defensiveness to anticipated threats (decreased risk assessment behaviour) and at the same time intensifies defensiveness to actual threats (enhanced defensive aggression, altered propensity for flight and freezing; see Johansson et al., 1999; Johansson and Hansen, 2000). Individuals with a dearth of neurons in this area may thus be relatively free of anticipatory anxiety but prone to show specific defensive actions, such as violent behaviour, in response to actual or perceived threats (cf. Albert et al., 1993).

Excitotoxic or electrolytic lesions of the septum produce anxiolytic effects in the elevated plus-maze (Pesold and Treit, 1992; Treit and Menard, 1997), a test related to the one employed in the present study (see Grewal et al., 1997). Furthermore, the fact that septal rats fail to withhold appetitively motivated responses in the presence of aversive cues (McCleary, 1961; Kaada et al., 1962; Gray, 1982) is consistent with reduced behavioural inhibition and the view that low harm avoidance is associated with poor performance in passive avoidance tasks (Cloninger, 1994). These considerations lead to the suggestion that damage to the septal area might have been instrumental in bringing about the reduction in risk assessment. However, the effects of septal lesions on fear-motivated behaviour are complex (e.g. Sparks and LeDoux, 1995), and, owing to the location of the lesion, it is quite possible that injury to any of the other emotional basal forebrain systems of Alheid and Heimer (1996) has contributed to the behavioural alteration. For example, damage to the nucleus accumbens alters defensiveness and passive avoidance (Johansson and Hansen, 2000).

Moreover, serotonin levels in the ventral striatum are associated with plus-maze behaviour in the rat (Schwarting et al., 1998). Finally, considering the well-established role of the amygdala in fear-motivated behaviour, it is very likely that pathology in the medial-anterior limb of the extended amygdala modifies anxiety-related behaviours (see Alheid and Heimer, 1996).

In both tests for nose-poking and stretched attend postures the experimental animals exhibited an increased motor activity, in comparison to controls. This difference in locomotor activity could have contributed partly to the group differences in nose-poking and stretched attend postures, by potentiating the former and interfering with the latter. Conversely, the lesion-induced temperamental change might be expressed as motor restlessness.

In conclusion, the present work is in line with earlier experimental animal research showing that individual differences in traits related to novelty seeking (Piazza et al., 1989, 1996) or harm avoidance (Spanagel et al., 1995; Möller et al., 1997) are associated with variations in the susceptibility to drugs of abuse. It is also interesting to note that rats with axon-sparing basal forebrain lesions share several behavioural characteristics with Roman high-avoidance rats, selectively bred for their rapid acquisition of two-way active avoidance learning (reviewed by Fernández-Teruel et al., 1997). In comparison to Roman low-avoidance animals, these rats are high on novelty seeking, low on harm avoidance and consume large amounts of alcohol (Fernández-Teruel and Escurihuela, 1997; Fernández-Teruel et al., 1997). It is tempting to speculate that the behavioural profile of Roman high-avoiding rats is due to a genetically determined anomalous development of the basal forebrain, which is partly, but importantly, reproduced by axon-sparing excitotoxic lesions in wild-type animals.

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