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Corticosterone in the range of stress-induced levels possesses reinforcing properties: Implications for sensation-seeking behaviors

(individual differences/glucocorticoids/stress/hypothalamo–pituitary–adrenal axis/drug abuse)

PIER VINCENZO PIAZZA*, VÉRONIQUE DEROCHE, JEAN-MARIE DEMINIÈRE, STEFANIA MACCARI, MICHEL LE MOAL, AND HERVÉ SIMON

Psychobiologie des Comportements Adaptatifs, Institute National de la Santé et de la Recherche Médicale (INSERM) Unité 259, Université de Bordeaux II, Domaine de Carreire–Rue Camille Saint-Saëns, 33077 Bordeaux Cédex, France

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ABSTRACT **In both humans and animals certain individuals seek stimuli or situations that are considered stressful and consequently avoided by others. A common feature of such situations is an activation of the hypothalamo–pituitary–adrenal axis leading to secretion of glucocorticoids. Since glucocorticoids have euphoric effects in some individuals and have been shown to potentiate the reinforcing properties of drugs of abuse in animals, we hypothesized that corticosterone secretion during stress-like situations may have reinforcing effects and that a higher sensitivity to the reinforcing effects of glucocorticoids might be a biological basis of sensation seeking. In this report we show that (*i*) corticosterone has reinforcing properties, as evidenced by the development of intravenous self-administration, (*ii*) self-administration of corticosterone is observed at plasma levels that are comparable to those induced by stress, and (*iii*) there are individual differences in corticosterone self-administration, which are related to individual reactivity to novelty and sensitivity to drugs of abuse, behavioral features akin to certain traits of high-sensation seekers. These findings provide insight into the physiological role of glucocorticoids and the biology of sensation seeking and may have clinical implications.**

Avoidance is the usual response to stressful situations. However, certain individuals appear to seek situations involving a strong activation accompanied by a degree of stress that are generally avoided by others. "Stress-seeking" behavior has been described in various animal species. For example, in the monkey, Barrett and Spealman (1) have shown that high and constant rates of responding may be maintained on a lever that delivers electric shocks. In rats, it has been reported that a mild stress such as intense handling can induce place preference (2), a behavioral response commonly seen with drugs of abuse, and that certain subjects electrically self-stimulate aversive brain regions, inducing behavioral and autonomic disturbances similar to those of physiological stress (3). Seeking activating or stressful situations, like exposure to novelty in the rodent, has interesting adaptive correlates. Some rats exhibit a high locomotor reactivity when forced to a novel environment (4) or a high preference for novelty when given the choice between a familiar and a novel environment (5). These animals, defined as high responders (HRs) as opposed to low responders (LRs), also show a higher sensitivity to the behavioral and neurochemical effects of psychostimulants (4, 6) and a higher predisposition to self-administer this class of drugs intravenously (4, 7, 8).

To account for the appetitive properties of stressful and stimulating experience, it may be postulated that some of the biological responses to stressful and activating situations have reinforcing effects. Glucocorticoids, the final product of activation of the hypothalamo–pituitary–adrenal (HPA) axis, are good candidates since (*i*) the HPA axis is activated by environmental stimuli and in particular by stress (9–11), and (*ii*) in humans, administration of glucocorticoids has been reported to produce euphoric effects in some individuals (12–14). Furthermore, chronic treatment with glucocorticoids can induce either physical or psychological dependence, in the absence of any abnormality in HPA function or reappearance of the disease for which glucocorticoids were administered (15). (*iii*) HR rats show a longer stress-induced secretion of corticosterone (7, 8), the main glucocorticoid in the rat, and corticosterone potentiates the reinforcing properties of drugs of abuse in animals (8).

To examine the involvement of corticosterone in the appetitive properties of stress in some individuals, we addressed two specific questions: (*i*) does corticosterone, in the range of stress-induced levels, possess reinforcing properties, and if so, (*ii*) are there individual differences in sensitivity to its reinforcing properties? To explore these questions, we tested the ability of corticosterone to support intravenous self-administration (SA), a widely used method for assessment of the reinforcing properties of drugs of abuse. We also measured plasma levels of corticosterone during corticosterone SA and compared them to levels observed during stress. Last, we determined possible differences in corticosterone SA between HRs and LRs.

MATERIALS AND METHODS

General Methods. Male Sprague–Dawley rats (Iffa Credo; 280–300 g at the start of the experiment) were used. The animals were housed individually with ad libitum access to food and water. A constant light/dark cycle (on at 0800 h, off at 2000 h) was maintained in the animal house, and temperature (22°C) and humidity were kept constant. Corticosterone 21-hemisuccinate (AGRAR, Rome) was dissolved in 0.9% NaCl solution, and the pH was adjusted to 7.4 with HCl (6 M) before the infusion. Plasma corticosterone levels were measured by radiocompetitive binding (16). The sensitivity of the assay was 0.4 ng per tube, and the inter- and intra-assay variations were, respectively, 7.1% and 4.2% at a mean value of 1.2 ng per tube and 10.3% and 5.9% at a mean value of 4.8 ng per tube.

Corticosterone SA. Four groups of animals were tested for corticosterone intravenous SA at different doses (per injection): 0 μg (n = 12), 12.5 μg (n = 8), 25 μg (n = 9), and 50 μg (n = 8). Each group was tested at only one dose. For SA, a Silastic catheter (70-μl dead volume) was inserted, under

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Abbreviations: HPA, hypothalamo–pituitary–adrenal axis; SA, self-administration; HR, high responder; LR, low responder.

*To whom reprint requests should be addressed.

chloral hydrate anesthesia (150 mg/kg intraperitoneally), in the right auricle through the external jugular vein. The catheter was then passed under the skin and fixed in the midscapular region and filled with heparin solution (100 units/ml) between SA sessions. SA sessions (one per day, 30 min each, for 6 days) started 1 week later and were carried out in the dark (2100 h), because during this period acquisition of operant tasks is more readily observed. Before the start of each session, the catheter was filled with the corticosterone solution, and its external end was connected to a syringe-driven pump. The SA administration cage (35 × 75 cm floor area, 50 cm high) had one hole in each of the short sides. By introducing their nose (nose poke) into one of the holes, defined as active, rats received an intravenous injection of 20 μl of corticosterone 21-hemisuccinate in 0.9% saline for 2 sec. Subsequent nose pokes during this period had no effect, and so the number of nose pokes in the active hole was generally higher than the actual number of injections received. A nose poke in the other hole (defined as inactive) had no effect. The number of injections and the number of nose pokes in both holes were recorded.

Plasma Corticosterone Levels During Corticosterone SA. Four groups of animals were used. Rats in the first two groups were tested, as described for experiment 1, either for saline SA ($n = 8$) or for corticosterone SA ($n = 12$) at a dose of 37.5 μg. This dose was chosen because it is midway between the doses (50 μg and 25 μg) that induced SA in the previous experiment. The temporal pattern of injection during the first corticosterone SA session was recorded and imposed on the other two groups of animals that had no control over the injection pump. Animals in these two groups ($n = 6$ each) had been previously implanted with two intracardiac catheters, one in each jugular vein. Animals in these two groups received either corticosterone (37.5 μg per injection) or 0.9% saline as coupled injections. On the day of testing, one catheter was connected to the injection pump, while the other was connected to a polyethylene tube (40 cm long) in order to sample blood without disturbing the animal. Four 300-μl blood samples were withdrawn every 10 min, with the first taken at the start of the session. At least 1 min was allowed between sampling and the last injection. Since the dead volumes of the catheter and sampling tube were 70 μl and 30 μl, respectively, the first 100 μl was discarded.

A further group of animals ($n = 6$) was used to determine corticosterone levels induced by stress. Restraint was chosen as a stressor, because it has been found to lead to a marked increase in plasma corticosterone levels. The animals were placed in a plastic cylinder (7 cm in diameter, 25 cm long). After 30 min, a 300-μl blood sample was withdrawn from the tail vein.

Individual Differences in Corticosterone SA. Animals were divided into two groups, HRs and LRs, on the basis of their locomotor response over a 2-h exposure to a novel environment. The novel environment was a circular corridor (170 cm long and 10 cm wide). Four photoelectric cells placed at the perpendicular axes recorded locomotor activity every 10 min. As previously described (4, 6–8, 17, 18), HRs were those animals with an activity score above the median for the whole group. The remainder constituted the LRs. These animals were tested, as described for experiment 1, for corticosterone SA at four different doses: 12.5 μg (seven HRs and seven LRs), 25 μg (eight HRs and eight LRs), 100 μg (seven HRs and seven LRs), 200 μg (five HRs and five LRs). Each dose was tested for at least 5 days, and each animal was tested with no more than two doses.

In another experiment, HRs and LRs ($n = 5$ per group) were injected intravenously with either 0.9% saline solution or 0.75 mg of corticosterone per kg in the SA cage and were handled in the same way as for a SA session. Surgical preparation of the animals and the sampling procedure were identical to those used in experiment 2.

Statistics. ANOVA for repeated measures was carried out using CRUNCH statistical software. A logarithmic transformation was applied to the corticosterone and SA data in order to normalize the distributions. Results were expressed as the mean ± SE.

Experiment 1. The first analysis had one between factor, the dose of corticosterone administered per injection (four levels), and two within factors, the holes from which the nose pokes were counted (two levels) and the day of testing (six levels). We also used an ANOVA having the dose as the between factor (four levels) and the mean number of injection over the last 3 days of testing as the dependent variable. Post hoc comparisons of the number of injections at the different doses were automatically computed as an extension of the ANOVA. Student's *t* test was used for post hoc comparisons.

Experiment 2. The first analysis compared the total number of injections accumulated over the session (30 min) of animals having access either to saline or to corticosterone (one between factor, two levels, saline versus corticosterone). The second analysis compared the total number of nose pokes in the active and inactive hole accumulated over the session (30 min) of the animals having access to corticosterone, the hole (active or inactive) was the within factor (two levels). ANOVA was also used to examine the influence of corticosterone and saline injections on plasma corticosterone levels, with treatment as the between factor (two levels, saline versus corticosterone) and time of sampling as the within factor (four levels).

Experiment 3. We used an ANOVA that had the group as the between factor (two levels, HR versus LR) and the dose as the within factor (four levels). The mean number of injections during the last 3 days of testing was used as the dependent variable.

RESULTS

Experiment 1: Corticosterone SA. Corticosterone induced SA in a dose-dependent manner [hole × dose interaction $F(3,33) = 6.31$, $P < 0.01$] (Fig. 1). Animals tested at the lowest dose, 12.5 μg, like controls (0 μg), did not develop SA. Thus, the number of nose pokes in the active and inactive holes at these doses did not differ. SA appeared at the 25- and 50-μg doses (Fig. 1). At both doses, animals made significantly more nose pokes in the active than in the inactive hole [25 μg, $F(1,8) = 9.42$, $P < 0.01$; 50 μg, $F(1,7) = 11.63$, $P < 0.01$]. A similar dose effect was found on analysis of the mean number of injections over the last 3 days of testing [$F(3,33) = 7.46$, $P < 0.001$] (Table 1). At a 12.5-μg dose, the number of injections did not differ from those of the control group (0 μg). However, significantly more injections were made at the 25-μg ($P < 0.05$) and 50-μg doses ($P < 0.05$). The dose–response curve resembled that of other reinforcing drugs (Table 1)—namely, a decreasing number of injections per session with an increasing dose per injection (19). This is assumed to be the animal's attempt to obtain an optimal level of drug reinforcement. From Table 1 it can be seen that the number of injections at a dose of 50 μg was almost half that at a dose of 25 μg ($P < 0.05$), whereas the corticosterone intake did not differ between the two doses.

Experiment 2: Plasma Corticosterone Levels During Corticosterone SA. Animals developed corticosterone SA from the first day of testing at a dose of 37.5 μg. They showed a higher number of self-injections with respect to rats receiving saline (Fig. 2 *Upper*) [$F(1,18) = 23.9$, $P < 0.001$] and a higher number of nose pokes in the active than in the inactive hole [$F(1,13) = 10.49$, $P < 0.01$]. Corticosterone levels were higher in the rats receiving corticosterone injections [$F(3,30) = 5.83$, $P < 0.01$] than in animals receiving saline injections

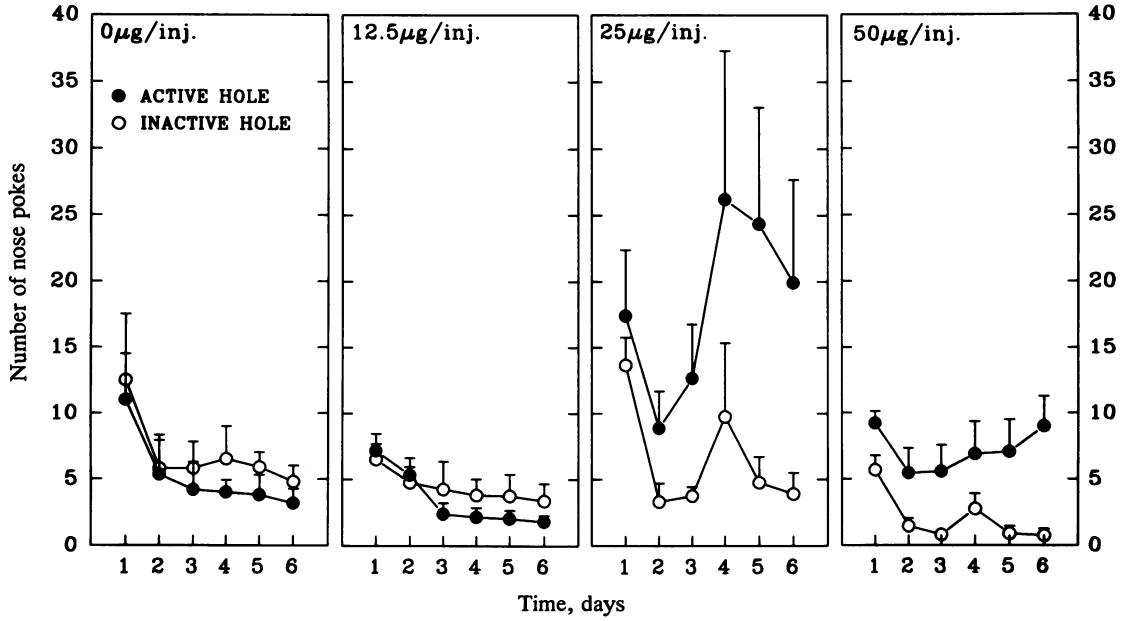

FIG. 1. Number of nose pokes in the active and inactive holes during the 6 days of testing for corticosterone SA. Corticosterone-induced SA at doses of 25 and 50 μg is indicated by the higher number of nose pokes in the hole eliciting corticosterone injections (Active) than in the control hole (Inactive) [ANOVA hole effect: 25 μg, $F(1,8) = 9.42$, $P < 0.01$; 50 μg, $F(1,7) = 11.63$, $P < 0.01$].

(Fig. 2 *Lower*). Corticosterone levels of the saline-coupled animals were higher (≈20 μg/100 ml) than basal physiological levels (≈3 μg/100 ml). This is not altogether unexpected since corticosterone secretion is increased to this extent by exposure to novelty (20), and the SA cage represents a novel environment for these animals. Plasma corticosterone levels in the corticosterone-coupled animals were not statistically different from those induced by the 30-min restraint stress [10 min, $F(1,11) = 0.35$, $P > 0.5$; 20 min, $F(1,11) = 0.19$, $P > 0.5$; 30 min, $F(1,11) = 1.8$, $P > 0.2$]. The mean amount of corticosterone needed to reach stress levels ranged from 180 μg (at 10 min) to 300 μg (at 20 min). In animals receiving saline injections, plasma corticosterone levels were significantly lower than those induced by restraint stress [10 min, $F(1,11) = 5.4$, $P < 0.02$; 20 min, $F(1,11) = 4.2$, $P < 0.05$; 30 min, $F(1,11) = 3.9$, $P < 0.05$].

Experiment 3: Individual Differences in Corticosterone SA. HRs and LRs differed in locomotor response to novelty [HR, 1027 ± 41; LR, 567 ± 21; $F(1,34) = 91.64$, $P < 0.001$]. The mean activity of the whole group of animals was 801 with a median at 804 and a standard deviation of 286. HRs and LRs had different dose–response curves for corticosterone SA (Fig. 3). It was shifted to the left in the HR rats [group × dose interaction $F(3,43) = 6.46$, $P < 0.001$]. Neither HRs nor LRs developed SA at the 12.5-μg dose and did not differ in the number of injections made at this dose [$F(1,12) = 0.01$, $P > 0.5$] or in nose pokes in the inactive hole [$F(1,12) = 1.0$, $P > 0.3$]. HRs had the highest rate of SA at the 25-μg dose, whereas LRs only exhibited a comparable rate at a dose of 100 μg. A significant dose effect was found for both HRs [$F(3,23) = 6.5$, $P < 0.01$] and LRs [$F(3,23) = 5.9$, $P < 0.01$]. The shape of the SA dose–response function was identical in the two groups and similar to that observed in the first experiment. Both groups reduced the number of injections at doses higher than the ones that induced the highest rate of SA (>25 μg for HRs and >100 μg for LRs). It is noteworthy that the amount of corticosterone required by HR animals (201 ± 40 μg) for the maximum rate of responding during SA (at the 25-μg dose) was comparable to the doses (180–300 μg) in the previous experiment, which raised plasma corticosterone to stress-induced levels. In comparison, LR animals required a 3-fold higher intake of corticosterone (650 ± 40 μg) to show a similar rate of SA (100-μg dose).

HRs and LRs did not differ in endogenous corticosterone levels at the beginning of the SA session [HR, 18.5 ± 1.5 μg/100 ml; LR, 19.09 ± 2 μg/100 ml; $F(1,16) = 0.21$, $P > 0.6$] or 20 min after intravenous administration of 0.75 mg of corticosterone per kg [HR, 29.6 ± 3 μg/100 ml; LR, 31 ± 2.3 μg/100 ml; $F(1,8) = 0.49$, $P > 0.5$] or 0.9% saline [HR, 22.1 ± 0.9 μg/100 ml; LR, 21.31 ± 2 μg/100 ml; $F(1,8) = 0.31$, $P > 0.7$]. Plasma corticosterone levels were higher in all corticosterone-injected animals (30.31 ± 2.8 μg/100 ml) than in those receiving saline (21.7 ± 1.9 μg/100 ml) [$F(1,16) = 5.41$, $P < 0.03$].

DISCUSSION

Our results show that (*i*) corticosterone is self-administered by rats and thus has reinforcing properties, (*ii*) corticosterone SA occurs at corticosterone levels within the range of those induced by stress, and (*iii*) animals with different reactivities to novelty and propensities to self-administer drugs of abuse (HRs and LRs) also differ in corticosterone SA.

The reinforcing effects of corticosterone may be mediated by the dopaminergic mesocorticolimbic system since these neurons contain corticosteroid receptors (21) and are con-

Table 1. Number of injections and corticosterone intake during intravenous SA

Parameter	Corticosterone dose, μg			
	0	12.5	25	50
Number of injections	1.22 ± 0.46	1 ± 0.28	7.44 ± 1.83	3.25 ± 0.9
Corticosterone intake, μg	0	15.27 ± 3.5	186.11 ± 45.9	162.5 ± 45.39

The results are expressed as the mean ± SE of the last 3 days of testing. Concentrations are expressed in terms of corticosterone base.

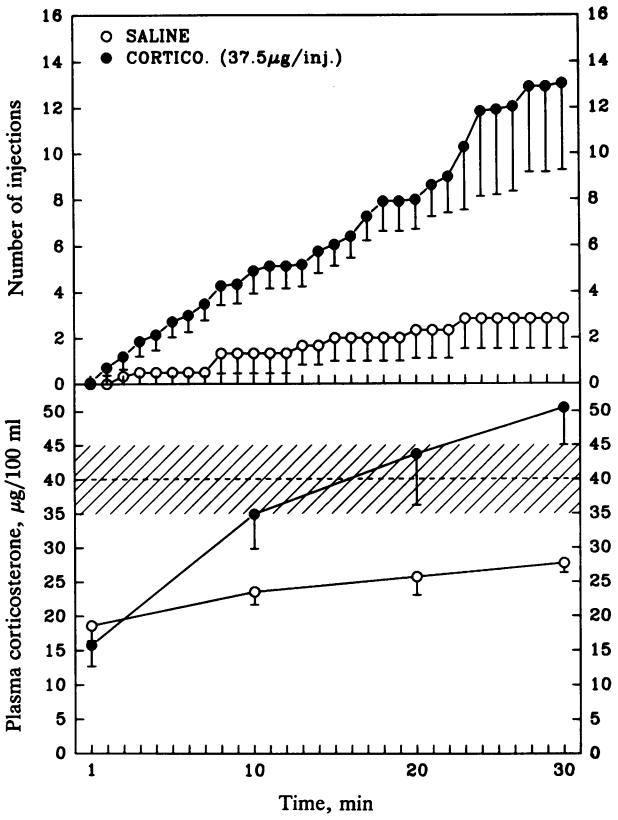

FIG. 2. Number of injections (cumulated over time) during the first session of corticosterone (Cortico.) SA (37.5 μg per injection; *Upper*) and corresponding plasma corticosterone levels in coupled animals (*Lower*). Animals made more injections when receiving corticosterone (n = 12) than saline (n = 8) [$F(1,18) = 12.32$, $P < 0.01$]. Rats coupled to the group self-administering corticosterone had different plasma levels of corticosterone [$F(3,30) = 5.83$; $P < 0.01$], whether they received coupled injections of corticosterone (n = 6) or saline (n = 6). Levels in the corticosterone-injected group were higher and not significantly different from those observed after restraint stress (shaded area).

sidered to be a substrate for the reinforcing effects of various drugs of abuse (22–24). Furthermore, synthetic glucocorticoids, such as dexamethasone, and corticosterone have been shown to induce dopamine release within this system (25, 26). The time course of the corticosterone effect is compatible with our behavioral data. Thus, the corticosterone-induced increase in dopamine is observed within half an hour after an intraperitoneal injection. In line with the notion that a corticosterone–dopamine interaction underlies the putative appetitive properties of stress, we have also recently found (P.V.P., F. Rouge-Pont, V.D., M.L.M., and H.S., unpublished results) that stress-induced dopamine release is reduced in animals in which corticosterone secretion is blocked. However, other neuronal substrates may contribute to the reinforcing properties of corticosterone. For example, it has been shown that corticosterone potentiates opiate (27–29) and glutamatergic transmission (30, 31), which modulates the reinforcing actions of drugs (32).

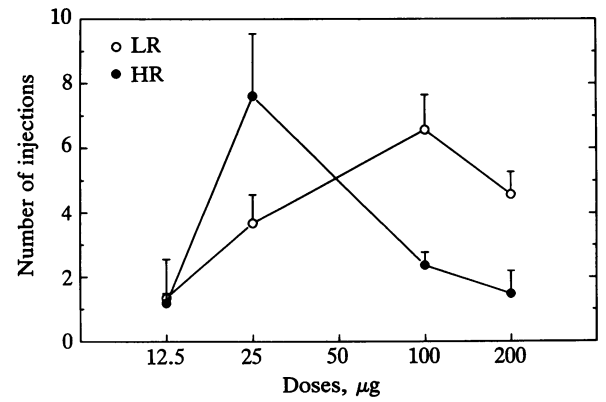

FIG. 3. Number of injections during corticosterone SA in HR (n = 5–8 per dose) and LR animals (n = 5–8 per dose). The results are expressed as mean of the last 3 days of testing. LR animals showed a shift to the right in the dose–response function with respect to that of the HR rats [$F(3,43) = 6.46$, $P < 0.001$].

The difference in corticosterone SA between HR and LR animals suggests that HRs are more sensitive to the reinforcing effect of corticosterone. Thus, maximal responding for corticosterone was observed at a 4-fold lower dose of corticosterone in the HR animals. Furthermore, the shift to the right of the dose–response function for corticosterone SA observed in LRs is considered in SA studies to indicate a reduced sensitivity to the self-administered drug (19). A similar shift to the right in the SA dose–response function is also observed for psychostimulant and opioid SA after injection of the corresponding antagonists (19).

Differences in activity or exploratory behavior cannot account for differences in SA between HRs and LRs. We have shown in previous studies that HRs and LRs do not differ in the number of nose pokes when no drug is available (7) or in the number of nose pokes in the inactive hole during amphetamine SA (4, 8). Similarly, in the present experiments, the two groups did not differ in the number of injections at the 12.5-μg dose or in the number of nose pokes in the inactive hole. Furthermore, differences in endogenous corticosterone secretion or distribution between HR and LR animals cannot account for differences in corticosterone SA between these two groups of animals. Although HRs have higher corticosterone levels than LRs after a 2-hr exposure to novelty (13, 15), the two groups did not differ in corticosterone levels after exposure to the SA cage or the injection of the same dose of corticosterone (0.75 mg/kg).

Differences in dopaminergic activity and in dopamine response to corticosterone between the two groups could underlie the differences in sensitivity to corticosterone. We and other workers (6, 17, 18, 33) have found that HRs have a higher dopaminergic activity in the nucleus accumbens. Furthermore, we have recently found that in response to corticosterone administration, the rise in extracellular dopamine concentration in the nucleus accumbens of HRs was twice that observed in the same brain region of the LRs.†

The higher sensitivity to the reinforcing effects of corticosterone exhibited by the HRs suggests that this hormone may underlie individual differences in the search for strongly activating situations. HRs are not only more reactive when exposed to a novel environment but also choose novel and apparently aversive situations to a higher extent than do LRs (5). When given the choice between a familiar and a novel environment, HRs show a higher preference for the novel environment. Furthermore, when the two groups of animals are placed in a novel environment containing two compartments, a closed, dark one and a white, open, illuminated one, HRs explore the illuminated compartment sooner and more extensively than do the LRs. For rodents, the light compartment is considered to be the more stressful situation. The behavioral features of the HRs resemble the sensation-seeking traits observed in humans (34) and defined as ". . . the need for varied novel, and complex sensations and experiences and the willingness to take physical and social

†Piazza, P. V., Dezoche, V., Rouge-Pont, F., Deminiére, J. M., Maccazi, S., LeMoal, M. & Simon, H., 22nd Annual Meeting of the Society for Neuroscience, October 25–30, 1992, Anaheim, CA, p. 1076 (449.13).

risks for the sake of such experiences. . ." (see ref. 35, p. 434). It is noteworthy that HRs are also more prone than LRs to drug SA, and a positive correlation has been found between scores on sensation-seeking rating scales and drug abuse (36, 37). Higher sensitivity to corticosterone may thus underlie the propensity to seek novel and intense experiences, as well as the higher predisposition to addiction shown by individuals with sensation-seeking personality traits. Indeed, we have previously shown that corticosterone injections facilitate drug-seeking (8) and that HR animals have a longer corticosterone secretion in response to stress (7, 8).

In conclusion, these findings provide insight into the physiology of glucocorticoids and indicate a possible biological basis for individual differences associated with sensation seeking. Since glucocorticoids influence drug SA and are also thought to be involved in certain psychiatric disorders, these findings may be relevant to clinical practice.

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