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Nijmegen High and Low Responders to Novelty: A New Tool in the Search After the Neurobiology of Drug Abuse Liability

ALEXANDER R. COOLS AND MIREILLE A. GINGRAS

Department of Psychoneuropharmacology, Nijmegen Institute of Neurosciences, University of Nijmegen, Postbox 9101, 6500 HB Nijmegen, The Netherlands

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COOLS, A. R. AND M. A. GINGRAS. *Nijmegen high and low responders to novelty: A new tool in the search after the neurobiology of drug abuse liability*. PHARMACOL BIOCHEM BEHAV **60**(1) 151–159, 1998.—Knowledge about the differences in structure, function, and reactivity of the brain and body between Nijmegen high responders to novelty and Nijmegen low responders to novelty may help us to understand which factors give rise to the vulnerability and/or susceptibility to drugs of abuse. For that purpose, this contribution provides a short overview of the outcome of the available studies on Nijmegen high responders to novelty and Nijmegen low responders to novelty. These animals can be selected using three major behavioral paradigms: (a) the open-field test (which allows the separation of high and low responders to novelty); (n) the intruder test (which allows the separation of fleeing and nonfleeing rats); (c) the apomorphine test (which allows the separation of apomorphine-susceptible and apomorphine-unsusceptible rats). Data to date suggest that the same traits have been selected by all three paradigms, and point to the hypothesis that the neurochemical state of the nucleus accumbens directs the sensitivity to drugs of abuse. In addition, recent evidence suggests that the sensitivity to the psychostimulant and/or reinforcing effects of dexamphetamine and ethanol is smaller in HR than in LR under certain experimental conditions, whereas the reverse is found when different experimental conditions are chosen. The data all together lay the foundation for the overall hypothesis that there are three factors ultimately determining the individual-specific sensitivity to drug of abuse: (a) the genetic background that predisposes an individual to become a HR or a LR, (b) early postnatal factors that direct the phenotypic expression of a particular genotype at adult age, and (c) the degree of stress during exposure to the drug of abuse. Further testing of this hypothesis may provide important information about the factors that contribute to individual differences in vulnerability to drugs of abuse. © 1998 Elsevier Science Inc.

Nijmegen high and low responders Novelty Drug abuse liability Open-field test Intruder test Apomorphine test

INDIVIDUAL variation in sensitivity to drugs of abuse—being defined as the vulnerability and/or susceptibility to these drugs—is a well-known phenomenon in animals and humans. Still, it is largely unknown to what extent this individual variability is determined by genetic, perinatal factors, and environmental factors that are present during the exposure to the drug of abuse. It is also largely unknown to what extent this individual variation refers to the structure of the brain and the body, and/or to the reactivity of the brain and the body.

As far as concerns the relationship between the sensitivity to drugs of abuse and their effects upon the brain, it is already known that both dopamine in the nucleus accumbens and corticosteroids are important mediators of the behavioral responses to drugs of abuse such as cocaine, dexamphetamine, ethanol, nicotine, and opiates (3,16,21–23,28,33,41,42,52,55,56).

As far as it concerns the relationship between the individual variation in sensitivity to drugs of abuse and individual-specific differences in the reactivity of the brain and the body, it is relevant to mention that the propensity to develop psychostimulant self-administration can be predicted by the behavioral reactivity of an individual to stressful situations such as exposure to a novel environment. In fact, Piazza and his coworkers have reported that the locomotor response to novelty is positively correlated with the amount of dexamphetamine

Requests for reprints should be addressed to Dr. M. A. Gingras, Université de Bordeaux II, INSERM, Unite 259, Psychobiologie Comportements Adapt, rue Camille Saint-Saens, Dommaine de Carreire, 33077 Bordeaux, Cedex, France.

that is self-administered during the first days of testing (14,37–39). Since then, it is quite common to use so-called high responders to novelty and so-called low responders to novelty in the search after mechanisms underlying individual-specific differences in drug abuse liability. Today, there are several studies that have confirmed the presence of a positive correlation between the response to novelty and the sensitivity to drugs of abuse such as cocaine, dexamphetamine, and opiates (1,15,20,29,30).

During the past years we also have focused our attention on high responders to novelty and low responders to novelty. As reviewed below, these two types of rat that are present in the nonselected outbred Nijmegen strain of WISTAR rats, are marked by type-specific differences in structure, function, and reactivity of (a) the limbic–mesolimbic–striatal axis, and (b) the hypothalamic–pituitary–adrenal (HPA) axis. These differences are under control of genetic factors that direct the behavioral, physiological and endocrinological response to stressors that allows the individual to deal with the stressor (coping strategy) assessed during early life: the ultimate structure, function, and reactivity of these two axes in the brain and body of adult individuals have been found to depend on the nature of challenges to which the individual is exposed during early life.

More recently, evidence that the experimental conditions to a large degree direct the sensitivity to drugs of abuse in our high and low responders to novelty has been hypothesized. Thus, the sensitivity to the psychostimulant and/or reinforcing effects of agents such as dexamphetamine (17), ethanol (24), and sucrose or quinine (27) is smaller in Nijmegen high responders to novelty than in Nijmegen low responders to novelty, when these animals self-administer the drugs in their home cage and/or are habituated to the experimental conditions including the injection itself. When the drugs are given to naive and otherwise nonhandled animals, however, the reverse is seen: in that case, the sensitivity to the psychostimulant and/or reinforcing effects of drugs of abuse such as dexamphetamine (12,26), cocaine (unpublished data), and ethanol (25) is greater in Nijmegen high responders to novelty than in Nijmegen low responders.

Knowledge about differences in structure, function, and reactivity of the brain and body between Nijmegen high responders to novelty and Nijmegen low responders to novelty may help us to understand which factors give rise to the reversal of the sensitivity to these drugs in HR and LR. For that purpose, this contribution provides a short overview of the outcome of available studies on Nijmegen high responders to novelty and Nijmegen low responders to novelty.

BIMODAL SHAPE OF VARIATION IN WISTAR RATS

Selection Procedure

The Nijmegen outbred population of Wistar rats has been found to contain at least two distinct types of individual, each of them marked by their own structure, function, and reactivity of the brain and body. There are three validated methods to select these types of rat. First, assessment of the open field test [(6,10); cf. (37)], which allows the separation of high responders to novelty (HR) and low responders to novelty (LR). Both the dimension of our open field—being 160 × 160 cm—and the absence of external cues are important features of this open-field test. HR and LR actually display a different coping strategy in this novel environment: HR are bound to the only available external stimulus, being the edge of the open field, and they continue their exploratory behavior for a very long period of time (>840 s). As in the Intruder test (see below), HR only interrupt their ongoing behavior, when a change in their environment occurs: this is considered to reflect a high degree of context dependency. In contrast, LR start to explore their novel environment and, after about 480 s, stop their exploratory activity in an otherwise undisturbed environment. Thus, like in the intruder test (see below), LR can interrupt their ongoing behavior by themselves: this is considered to reflect a high degree of self-control.

Second, assessment of the so-called intruder test in which "freezing" defined as "sitting motionless >45 s," and "fleeing,"defined as "number of fleeing spells seen during the whole observation period of 6 min," serve as dependent variables (2,6,51). This test allows the separation of rats that primarily flee (FLEE rats) and rats that primarily freeze (NONFLEE rats). Because FLEE rats—being the intruders–primarily flee during the direct confrontation with the resident (coping situation), but freeze as long as the intruder can only see and smell the resident without being able to attack him (noncoping situation), and because NONFLEE rats freeze during the coping situation, but actively explore during the noncoping situation, the nature of the selected coping strategy (active or passive) varies according to the context and is, therefore, not a trait of the individual.

Third, the apomorphine test (6), which allows the separation of apomorphine-susceptible rats (APO-SUS) and apomorphine-unsusceptible rats (APO-UNSUS): APO-SUS display more than 500 gnawing spells/45 min following an injection of 1.5 mg/kg apomorphine (SC), and APO-UNSUS display less than 10 gnawing spells/45 min following such an injection. Since 1985 the latter rats are also bred, using a particular breeding schedule to prevent inbreeding and to maintain the original genotypic heterogeneity, apart from the alleles at the loci (or locus) involved in the determination of the chosen traits. Nevertheless, inbreeding that reduces the genotypic heterogeneity and, ultimately, creates new substrains and strains, cannot be prevented in the long run; given our interest in the individual variability that occurs within a single strain, namely a situation that approaches the human situation as closely as possible, it became necessary to restart the breeding of these lines, once every 5–8 years.

We have been able to show that the bimodal variation in apomorphine susceptibility, the original selection criterion for the breeding, is consistently coupled to a bimodel variation in various neuroanatomical, neurochemical, endocrinological, immunological, and behavioral features. Evidence has been provided that rats marked by a high apomorphine susceptibility (APO-SUS) are high responders to novelty in terms of both their behavioral response and their endocrinological responses, and that rats marked by a low apomorphine susceptibility (APO-UNSUS) are low responders to novelty in terms of their behavioral and endocrinological responses (6,8–10,44–48). This individual consistency in behavior and physiology has revealed that any of the biological or behavioral variables known to differ between these rats can be used as criterion for selecting these two types of rat. For example, APO-SUS and APO-UNSUS rats can be selected from outbred strains of Wistar rats by establishing their response to novelty and labeled high responders to novelty (Nijmegen HR) as long they really fulfill the criterion of the novelty-induced response as defined in APO-SUS; the same holds true for the selection of Nijmegen low responders to novelty (6,9). In sum, the male HR, FLEE rats and APO-SUS are marked by idiosyncratic features of one and the same type of individual; the same holds true for male LR, NONFLEE rats and

APO-UNSUS. In other words, the hypothesis is that there are two distinct types of individuals whose genetic makeup is reflected in the above three responses (6).

HR and LR are not tails of the population, but each group (HR and LR) represents a major part (40–45%) of our outbred strain of Nijmegen Wistar rats; the remaining 10–20% of rats form a heterogeneous group of rats, showing a mixture of HR and LR features, of which no details about the behavioral, neurochemical, and endocrinological features are known. As mentioned below (Role of Early-Life Events section), the ultimate neurochemical and behavioral phenotype of these two types of animal is determined among others by early postnatal factors. Owing to this factor and owing to distinct selection procedures, one has to be aware of the fact that HR and LR that are studied in different research centers are not necessarily fully identical. Nevertheless, it is important to note that both the HR/LR studied by Exner and Clark (20), Piazza's team (37,49) and those studied by Hooks' team (29,30) share at least the following features with the Nijmegen HR/LR: there exists a positive correlation between the locomotor response to novelty and the acute behavioral response to dexamphetamine (12), and environmental or pharmacological stressors produce a greater increase in the extracellular concentration of accumbal dopamine in HR than in LR (50). Furthermore, both Piazza's team (39) and our group (44) has found that HR show a greater release of corticosteroids in response to stressors than LR. Finally, it has been recently found by Wise and colleagues (unpublished data) that Nijmegen HR, like those studied by Piazza's group (37) acquire self-administration of psychostimulants such as cocaine (our rats) and dexamphetamine (Piazza's rats) much faster than LR.

In the present study, we use the labels HR and LR for the Nijmegen HR (APO-SUS) and the Nijmegen LR (APO-UNSUS), respectively, whereas we refer to "high responders to novelty," and respectively, "low responders to novelty" when we refer to studies of other groups.

Type-Specific Features: Global Survey

Adult HR and LR animals are male rats that normally occur in every outbred strain of Wistar rats: these rats are neither mutants nor belonging to different substrains or strains. As mentioned above, these rats are marked by the genotypic heterogeneity that is originally present in every outbred strain of Wistar rats. However, characteristic features remarkably differ between these rats. The most characteristic ones are mentioned below.

1. Stress sensitivity. HR are more stress sensitive in terms of behavioral (locomotor activity) and endocrine (release of ACTH and corticosteroids) responses than LR. In this context stress refers to novelty-induced stress as well as to stress measured in the so-called conditioned emotional test (44–46): the locomotor response to novelty as well as the release of plasma release of ACTH and corticosteroids in response to stress is far greater and longer lasting in HR than LR.
2. Acquisition of radial maze task. HR that are not habituated to the maze, start to learn a simple cued four-arm radial maze task during the 3 initial test days, whereas LR start to acquire that task after a period of about 3 test days: the overall rate of acquisition, however, does not differ between HR and LR (10,11). In line with our hypothesis that is outlined further on, these differences are considered to be the consequence of a HR-LR difference in sensitivity to stress.
3. Retrieval of recently stored information. HR that have had eight acquisition trials on the first test day in the Morris Water Maze, show a poor performance during the first trial on the second test day that is followed by a far better performance during the next trial given 2–4 min later. In contrast, LR show a relatively improved performance during the first trial on the second test day that is followed by a deterioration of performance during the next trial. These differences are also considered to be the consequence of a HR-LR difference in the sensitivity to stress [(11); unpublished data].
4. Context dependency. HR are very dependent on spatial and contextual stimuli, whereas LR are relatively independent of these stimuli (see Selection Procedure and Role of Early-Life Events sections).
5. Self-control. HR have less self-control than LR do (section Selection Procedure and Role of Early-Life Events sections).
6. Predisposition for mental diseases. HR, but not LR, show patterns of behavior in animal models with construct validity for certain cognitive deficits of schizophrenic patients (18): HR show a reduced latent inhibition as well as a reduced prepulse inhibition, whereas LR show normal latent inhibition and prepulse inhibition.
7. Predisposition for somatoform diseases. HR respond negatively in animal models for autoimmune diseases such as experimental allergic encephalomyelitis (EAA-model), whereas LR respond positively in such models (9): thus, HR develop nearly no symptoms, whereas develop the full syndrome of EAE. On the other hand, HR show a vigorous, Th2-dependent IgE response after infection with the nematode *Trichinella spiralisinfection*, whereas LR do not (31).
8. Predisposition for "therapeutic" and unwanted effects of drugs. HR are more sensitive to anti-Parkinson agents than LR, whereas LR are more sensitive to antipsychotics than HR (6,10): systemic administration of dopaminergic agonists such as apomorphine produce a greater and longer lasting behavioral response in HR than in LR, whereas intraaccumbens administration of neuroleptics such as sulpiride produces a behavioral response in HR that is smaller than that seen in LR.
9. Sensitivity to psychostimulant and/or reinforcing effects of orally or otherwise administered agents. HR are less sensitive to psychostimulant and/or reinforcing effects of ethanol, dexamphetamine, sucrose, and quinine than LR, when these animals self-administer the drugs in their home cage or are habituated to the experimental conditions, including the injection (17,24,27), whereas HR are behaviorally more sensitive to ethanol, dexamphetamine, and cocaine, when the drugs are given to naive and otherwise nonhandled and nonhabituated animals [(12,26); unpublished data].
10. Makeup of the brain. There exist numerous differences in number of receptors [e.g., mineralocorticoid and dopamine receptors: (44–48,53)], concentrations of neurotransmitters [e.g., noradrenaline and dynorphin: (8,44)], number of synapses [nucleus paraventricularis hypothalami: (34,35)], etc.
11. Reactivity of the brain. Stress activates the amygdala input of the nucleus accumbens and inhibits the hippocampus input of that nucleus in HR, whereas the reverse is seen in LR [(11,43), unpublished data].
12. Early postnatal development. A rat of the LR genotype that is deprived of its mother for 24 h on the third postna-

tal day develops into an adult animal with characteristic features of the HR, whereas a rat of the HR genotype grown up with an LR foster mother develops into an adult animal with characteristic features of the LR phenotype [(19), unpublished data].

TYPE-SPECIFIC FEATURES: DIFFERENCES IN BRAIN, BODY, AND BEHAVIOR

Given the role of telencephalic dopamine and that of corticosteroids in the neurochemical and behavioral responses to drugs of abuse such as cocaine, dexamphetamine, ethanol, nicotine, and opiates (3,16,22,23,28,33,41,42,52,55,56), the most salient type-specific differences in this respect will be discussed. These data, together with the remainder of the type-specific differences in brain, body, and behavior, are summarized in the Tables 1–4: these features are characteristic for fully habituated (or unchallenged) HR and LR. An overall picture of the neurochemical state of the brain and the body of an unchallenged HR is given in Fig. 1 (the arrows indicate whether the baseline activity of the involved variable is greater (↑) or smaller (↓) than that found in an unchallenged LR).

HR—being identical to APO-SUS—are far more sensitive to the dopaminergic agonist apomorphine than LR—being identical to APO-UNSUS rats (6). Furthermore, unchallenged HR are more sensitive to noradrenergic agonists. In fact, unchallenged HR behave as if they are sensitized by dexamphetamine; Piazza et al. (38) have also found that their "high responders to novelty" show this phenomenon. This phenomenon is illustrated by the response to intraaccumbens injections of the noradrenergic agonist phenylephrine: unchallenged LR rats need to be sensitized by dexamphetamine before phenylephrine elicits a locomotor response, whereas unchallenged HR immediately show this response (17). In contrast, HR are less sensitive to dopaminergic antagonists such as sulpiride than LR (10).

There are also biochemical features that may contribute to these differences in susceptibility for aminergic agents in these rats (6,8,44–46,48). For example, unchallenged HR have a smaller amount of mesolimbic noradrenaline than unchallenged LR (6,48). As discussed elsewhere in detail (4), this explains why unchallenged HR are more sensitive to the accumbal administration of the alpha-adrenergic agonist phenylephrine (17). Furthermore, unchallenged HR have more striatal dopamine D_1 receptor m-RNA and more tyrosine hydroxylase m-RNA in A9 (substantia nigra, pars compacta) and A12 (nucleus arcuatus) than unchallenged LR, whereas there is such a trend in A10 (ventral tegmental area of Tsai) and A6 [locus coeruleus; (48)], implying that the capacity to enhance the formation of dopamine in response to stress is greater in HR than in LR. Indeed, when the rats are challenged by novelty or tested in the conditioned emotional response test, the behavioral and physiological responses that are mediated by dopamine are greater in HR than LR (6,44–46). The following example illustrates this phenomenon. The dopaminergic, tuberoinfundibular system that arises in A12, normally inhibits prolactin. Thus, prolactin can be used as an indicator of the reactivity of this dopaminergic system. Indeed, the release of prolactin is far stronger inhibited in HR than in LR, when the

TABLE 1

DIFFERENCES IN THE MAKE-UP OF THE BRAIN BETWEEN HR AND LR

Brain Hardware	HR vs. LR
Dopamine D_2 receptors in the neostriatum	HR are marked by higher amounts of ^{125}I-iodosulpiride binding than LR
Noradrenaline immunoreactivity in the nucleus accumbens	HR contain lower amounts than LR
Mineralocorticoid receptors in the hippocampus	HR have more receptors than LR
Corticotropin Releasing Hormone mRNA in the paraventricular nucleus of the hypothalamus	HR have more mRNA than LR
Tyrosin-hydroxylase mRNA in A_9 and A_{12}	HR have more mRNA than LR
Dynorphin-B in the hippocampus	HR are marked by a lower level than LR
Synaptic density in the paraventricular nucleus of the hypothelamus	HR have a higher density than LR
Metabolic activity in the hippocampus	HR have increased 2 deoxyglucose levels in CA_1-CA_3 compared to LR
Dopamine D_1 receptor encoding mRNA levels in the lateral caudate putamen	HR have more than LR

Animals were selected with the apomorphine test.

TABLE 2

DIFFERENCES IN NEUROENDOCRINOLOGICAL AND IMMUNOLOGICAL SYSTEMS BETWEEN HR AND LR

Peripheral System	HR vs. LR
Plasma levels of ACTH	HR have higher amounts of ACTH than LR under baseline conditions
Plasma levels of free CORT	HR have lower amounts than LR
Reactivity of the hypothalamic–pituitary axis	HR show a stronger and longer lasting increase in ACTH and CORT level after stress than LR
Brain corticosteroid fedback	HR have a more prolonged feedback resistance compared to LR
Prolactine inhibition	HR show a stronger novelty-induced inhibition of prolactine than LR
Experimental allergic encephalitis	HR are less susceptible than LR
Rheumatoid arthritis	HR have lower susceptibility than LR
Spleen, # Natural Killer cells	HR have less than LR
Blood: # of B cells	HR have more than LR
Blood: # of T cells (total)	HR contain lower amounts than LR
Blood: # of T_{helper} cells	HR have more than LR
Th1 (cytokine IFN-y) and Th2(cykotine II-4) in splenocytes	HR have a much smaller ratio of the mRNA expression for Th1 and Th2 than LR
Spleen, # of $T_{suppressor}$ cells	HR contain more than LR
Level of anti-T. Spiralis IgE	HR develop a higher level of parasite-specific IgE than LR

Animals were selected with either the open-field test or the apomorphine test.

TABLE 3
PHARMACOLOGICAL DIFFERENCES BETWEEN HR AND LR

Pharmacological	HR vs. LR
Apomorphine-induced gnawing	HR shows a stronger gnawing response than LR
Ergometrine induced locomotor activity (in the NAC)	HR have a more stable response to ergometrine than LR
Phenylephrine induced locomotor activity (in the NAC)	HR show an enhanced locomotor response whereas LR do not
Picrotoxin induced explosive motor behavior (in the deep layers of the SC)	HR showed a greater explosive motor behavior than LR
Postural control test (in the SN)	HR show a greater postural control after picrotoxin than LR
β-adrenergic drugs (in the BLA)	HR show a reduced neophobia after the β-antagonist LR show reduction in neophobia after β-agonist
Sulpiride (in the NAC)	HR show a greater reduction in learning than LR

Abbreviations: NAC = nucleus accumbens; VS = ventral striatum; DS = dorsal striatum; SNR = substantia nigra, pars reticulate; SC = superior colliculus.

Animals were selected with either the open-field test or the apomorphine test.

TABLE 4
BEHAVIORAL DIFFERENCES BETWEEN HR AND LR

Behavioral	HR vs. LR
Acoustal startle paradigm	HR show less prepulse inhibition than LR
Two-way active avoidance	HR have a lower conditioned avoidance response than LR
Latent inhibition	HR show less latent inhibition than LR
Locomotor response to novelty (open field)	HR show higher locomotor activity and elevated thigmotaxic behavior compared to LR
Resident–intruder/defeat test	HR show fleeing response, whereas LR show freezing behavior
Radial maze	HR learn faster than LR do

Animals were selected with either the open-field test or the apomorphine test.

rats are exposed to stress (44,46). Thus, there appears to be a dopaminergic hyperreactivity in challenged HR, when compared with LR.

Given the difference in the behavioral response to stress, it was of interest to study the hypothalamic–pituitary–adrenal axis in HR and LR. First, the amount of corticotrophin-releasing hormone (CRH) m-RNA in the nucleus paraventricularis hypothalami (PVN) of HR is greater than that in the PVN of LR (45), implying that these cells in HR have also a greater capacity to generate CRH than LR do. Because CRH that is under the stimulatory control of dopamine (40) stimulates the release of plasma ACTH, especially during exposure to stress, it is logic to expect a HR-LR difference in the ACTH plasma release in response to stressors such as novelty. This is indeed the case: the stress-induced release of ACTH as well as that of plasma corticosteroids of which the release is stimulated by ACTH, are greater and longer lasting in HR than in LR (45), a finding that fits in with those reported by Piazza et al. (39). Apart from these data, we found that plasma levels of ACTH in HR are greater than those in LR under baseline conditions, but that the plasma release of free corticosteroids in HR is lower than those in LR under these condition (45,46).

STRESS AND THE NEUROCHEMICAL STATE OF THE NUCLEUS ACCUMBENS IN HR AND LR

As elaborated elsewhere in detail (7,8,11,43), there is anatomical, electrophysiological, and pharmacobehavioral evidence in favor of the hypothesis that the neurochemical state of the nucleus accumbens of an unchallenged HR is marked by the following features when compared with LR (Fig. 2 (a) the functional activity at the level of beta-adrenergic receptors that can stimulate the release of dopamine at the level of dopamine D_2 receptors is relatively low; (b) the functional activity at the level of these dopamine D_2 receptors being presynaptically localized on glutaminergic hippocampus-accumbens neurons is relatively low; (c) the functional activity at the level of alpha-adrenergic receptors that can inhibit the release of dopamine at the level of so-called inhibitory dopamine receptors (DAi)—being a subtype of dopamine receptors that could not yet be linked to the two more recently discovered families of dopamine D_1 and D_2 receptors (5)—is relatively low; (d) the functional activity at the level of these DAi receptors—being localized on glutaminergic amygdala-accumbens neurons—is relatively high; and (e) the neurochemical state of the nucleus accumbens of an unchallenged HR strongly differs from that of an unchallenged LR: the functional activity of all neurotransmitters that is relatively low in HR is relatively high in LR, whereas the activity of neurotransmitters that is relatively high in HR is relatively low in HR. Very recently biochemical evidence using the microdialysis technique has shown that the noradrenaline–dopamine interaction in the nucleus accumbens indeed differs completely between HR and LR (13,50). Finally, when challenged by a mild physiological, pharmacological, or environmental stressor, the neurochemical state of the nucleus accumbens and, probably, of other parts of the brain and body as well is temporarily reversed (7,11,43). Thus, the state of a challenged HR goes into the direction of that of an unchallenged LR, whereas that of a challenged LR goes into the direction of that of an unchallenged HR.

ROLE OF EARLY-LIFE EVENTS ON THE DEVELOPMENT OF THE ADULT PHENOTYPE

Before summarizing the effects of two early-life manipulations upon the adult phenotype, the characteristic changes that occur during normal development of HR and LR, have to be considered (47). No type-specific differences in the dopaminergic variables (e.g., D_1 receptor m-RNA and TH m-RNA) and in the variables of the HPA-axis (e.g., ACTH and corticosteroids) are present in 10-day-old rats. But, in 18-day-old rats, the variables of the HPA axis already show some type-specific differences known to occur in 60-day-old adult rats. For instance, the ACTH plasma level under baseline conditions is greater in HR than in LR, and a trend towards lower free corticosterone plasma levels is present in HR; in contrast,

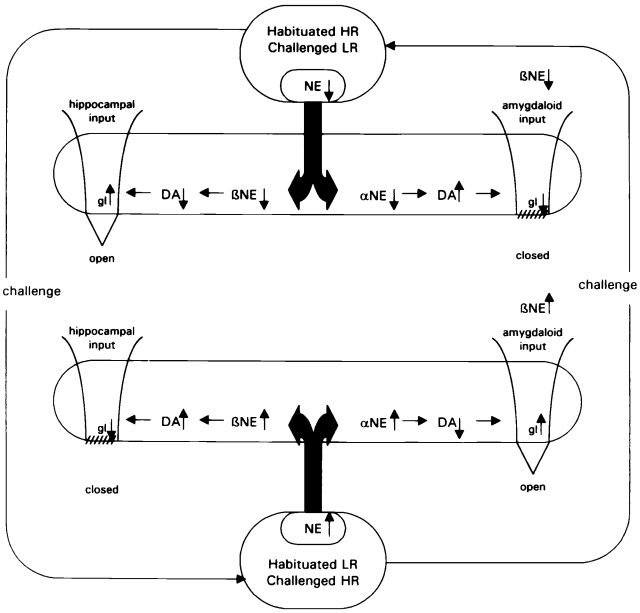

FIG. 1. Illustration of the overall hypothesis about the distinct neurochemical states in the nucleus accumbens of unchallenged and challenged HR and LR (for references: see text). gl = glutamate; DA = dopamine; βNE = adrenergic activity at the level of beta-adrenoceptors; αNE = adrenergic activity at the level; of alpha-adrenoceptors; NE = noradrenaline; HR = Nijmegen high responder to novelty; LR = Nijmegen low responder to novelty.

there are still no type-specific differences in the dopaminergic variables in 18-day-old rats (44,47). Thus, the divergence in the dopamine phenotype of HR and LR develops subsequent to distinct differences in the HPA axis.

To investigate to what extent early experiences direct the development of the adult phenotype, two paradigms were used: crossfostering and maternal deprivation on day 3. Remarkably, crossfostering influences only the adult phenotype of HR, but not LR (19), whereas the maternal deprivation only influences the adult phenotype of LR (unpublished data). In fact, crossfostering reverses HR into LR, whereas maternal deprivation reverses LR into HR, as far as it concerns their apomorphine susceptibility. In addition, we found that maternal deprivation affects various characteristics of the biochemical phenotype: adult rats that are deprived show a higher ACTH plasma level under baseline conditions and a greater amount of TH m-RNA in A9 cells than their controls (44,47). These data together suggest that this early-life experience reverses both the biochemical and the behavioral phenotype of LR into that of HR.

CHALLENGED VS. UNCHALLENGED HR AND LR

As mentioned in the introductory paragraphs, HR are less sensitive to drugs of abuse such as ethanol and the psychostimulant dexamphetamine than LR, when these animals self-administer the drugs in their home cage or are fully habituated to the experimental conditions, including the injection itself. When the drugs are given to naive and otherwise nonhandled and nonhabituated animals, HR are more sensitive to these drugs of abuse than LR. In other words, both HR and LR can develop a relatively high sensitivity to drugs of abuse, depending on the experimental condition that is present during exposure to the drug of abuse.

A post hoc analysis of the experimental conditions that reverse the sensitivity to dexamphetamine and ethanol in HR and LR may help to elucidate the factors that direct this shift in sensitivity. First, HR exhibit a lower locomotor response to dexamphetamine than LR in one study (17), but a higher behavioral response in at least one other study (12). In the first study, the rats were fully habituated to the cage, experimental procedure and intraaccumbens injections: following 3 days of habituation to the test cage that was marked by dimensions that were more or less identical to those of the home cage, for

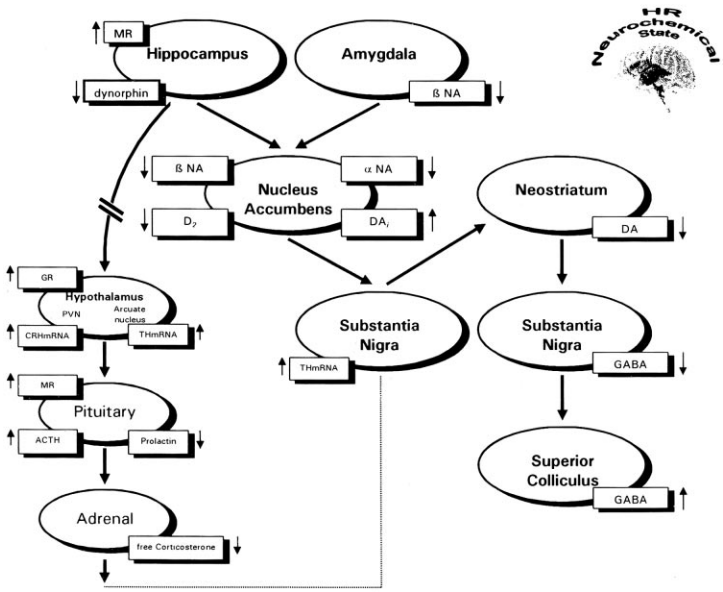

FIG. 2. This figure illustrates the neurochemical state characteristic of an unchallenged HR.

a period of 3 h/day, the rat received an accumbal injection of the solvens of dexamphetamine 24 h prior to the accumbal injection of dexamphetamine: following an additional period of 1-h habituation on the test day, the rat received the test dose of dexamphetamine and the locomotor response was recorded: HR showed a smaller response than LR in this setup. In the second study, naive rats were placed for 30 min in a fully unfamilar environment—being an open field (160 × 160 cm) placed in a room with white walls and then received their test dose of dexamphetamine via an SC injection and the behavioral changes were recorded: HR showed a greater response than LR; this effect was especially evident after intermediate doses of dexamphetamine (0.5–1.0 mg/kg). Although it cannot be excluded that differences in the route of administration have contributed to the distinct responses seen, the hypothesis is that it is primarily a difference in the degree of stress that has caused the reversal of the sensitivity to dexamphetamine in HR and LR in these two studies. Second, HR exhibit a lower response to ethanol than LR in one study (24), but a higher response to ethanol in one other study (25). In the first study, the rats were fully habituated to their test cage and experimental procedure: the rats were habituated for a period of 7 days and, in addition, habituated to the two drinking tubes for a period of 5 days: on the first test day, the rats were offered a 2% ethanol solution in one tube and normal drinking water in the other tube: HR had no preference for ethanol, whereas LR preferred ethanol over water. In the second study on ethanol, rats were just placed in their test cage and, 15 min later, received their test dose of ethanol (0.5 g/kg) via an IP injection: the locomotor response of HR shown after this first injection was greater than that shown by LR [see Fig. 1 in (25)]. Although, in this case also it cannot be excluded that differences in the route of administration and/or chosen variables have contributed to the distinct responses seen, the hypothesis is that it is primarily a difference in the degree of stress that has caused the reversal of the sensitivity to ethanol in HR and LR in these two studies. The latter hypothesis is strengthened by the fact that the experiment in which the effect of habituation on the locomotor response to 0.5 g/kg (IP) was studied in HR, the absence of habituation (or presence of novelty-induced stress) significantly increase the response in HR [(25); Fig. 2, this experiment was not performed with LR, because the latter animals did not increase their locomotor activity after 0.5 g/kg in the initial experiments].

THE HYPOTHESIS

Given these present data, it becomes possible to hypothesize which factors direct the sensitivity to dexamphetamine and ethanol in HR and LR. For both challenged HR and unchallenged LR not only share a relatively high sensitivity to drugs of abuse, but also a more or less identical, neurochemical state of the nucleus accumbens (Fig. 2; Stress and the Neurochemical section), and unchallenged HR not only share a relatively low sensitivity to drugs of abuse, but also a more or less identical, neurochemical state of the nucleus accumbens that fully differs from that seen in challenged HR and unchallenged LR. Thus, it is the neurochemical state of the nucleus accumbens that directs the sensitivity to drugs of abuse such as dexamphetamine and ethanol. Given the psychostimulant theory that psychomotor and reinforcing effects of drugs are related and vary in parallel [review: (55)], it noteworthy to mention that the reinforcing effects of 0.5–7% sucrose solutions [e.g., (36)] and those of 0.001% quinine solutions (27) are far smaller in HR than LR, when these drinking experiments are performed with fully habituated rats and, in addition, the intake is corrected for the effect of (a) the 24 h water deprivation period that preceded the intake test, and (b) the confrontation with an unfamiliar taste by including the intake of saccharin as control solution (27). These data nicely fit in with the above-mentioned hypothesis that it is the neurochemical state of the nucleus accumbens that directs the sensitivity to drugs that have reinforcing effects. In addition, the dopamine activity at the level of the dopamine D_2 receptors in the nucleus accumbens that is known to be related to the reinforcing effects of drugs (16,32,54,55) is far lower in unchallenged HR than in unchallenged LR (Stress and the Neurochemical State section).

The hypothesis that stressors/challenges play such a crucial role in determining whether HR have a greater or smaller sensitivity to drugs of abuse such as dexamphetamine and ethanol, needs to be validated in future experiments. Moreover, it requires a more precise definition of stress. Until now, a retrospective analysis of our experiments has suggested that stressors such as (a) novel environment with features and dimensions that are fully unfamiliar (45), (b) a single injection (see above), and (c) the shock offered in the conditioned emotional response test (46) are strong enough to alter the neurochemical and/or endocrinological state of the animals. Future research is required to delineate the precise nature of stressors that have this effect.

SUMMARY

To summarize the previous sections (a) genetic background, (b) early postnatal environmental conditions, and (c) the degree of stress during exposure to environmental, physiological, or pharmacological challenges have been found to determine among others the nature of the neurochemical state of the nucleus accumbens. This hypothesis implies that three factors ultimately determine the individual specific sensitivity to drugs of abuse: 1) genetic background that predisposes an individual to become a HR or LR; 2) early postnatal factors that direct the phenotypic expression of a particular genotype at adult age; 3) degree of stress during exposure to the drug of abuse. The HR and LR appear to be excellent tools in the search after factors that direct the development of individual specific sensitivity to drugs of abuse.

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