The Pharmacology of Sexual Function and Dysfunction
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The neurochemistry of sexual satiety. An experimental model of inhibited desire

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Significance

The loss of sexual interest, alone or combined with other problems, is now acknowledged as a prevalent sexual dysfunction [1- 4]. Yet, probably because of its relatively new recognition as a distinct diagnostic entity, the difficulties for an operational definition and objective assessment, and the diversity of potential causes, there is a dearth of information about the psychobiological processes underlying this disorder. In some cases it is possible to identify organic etiologies such as hypogonadism, disease states, depression or drugs. However, hypoactive sexual desire frequently occurs in people who are seemingly in good health, and nothing is known about its neural mechanisms.

An animal model that could help to understand the physiological processes leading to the inhibition of sex drive in healthy subjects is the sexually sated rat. This phenomenon was described in detail by Beach and Jordan [5] and further assessed by other laboratories [e. g. 6 - 8]. According to these descriptions, when sexually experienced male rats are allowed unlimited access to receptive females they display a succession of copulatory series until attaining about 7 ejaculations. They then become virtually irresponsive to sexual stimuli for 2-3 days, with a gradual resumption of mating behavior afterwards. Figure 1 summarizes the behavioral pattern characterizing this state of sexual satiety, outlining the criteria used in our laboratory. It should be noted that the sated subjects (i.e. during days 2-3) are not particularly sleepy or inactive. They approach and explore novel receptive females as in normal circumstances. The only apparent difference in their behavior is the absence of copulation.

This state of transient sexual refractoriness presents considerable potential interest as a means of studying the biological mechanisms of sexual motivation and satiety. There are few experimental studies, however, using this paradigm, probably because of methodological limitations such as the long observation periods required for a thorough assessment. They have provided valuable, if limited, information about various neurobiological aspects of these phenomena. Thus, electroencephalographic recordings have shown an increase in sleep in rats approaching sexual satiety, more than after forced wheel running [9]. Brain lesions, namely of the paragigantocellular reticular nucleus in the ventral medula, have been found to prolong the mating time and number of ejaculations prior to exhaustion [10]. Sexual exhaustion has also been documented to inhibit the display of penile erections ex copula, which are usually facilitated after a few ejaculations [11]. At variance with their effects on sexually rested animals, neither spinal block [12] nor apomorphine treatment [13] increased erectile reflexes in sated rats.

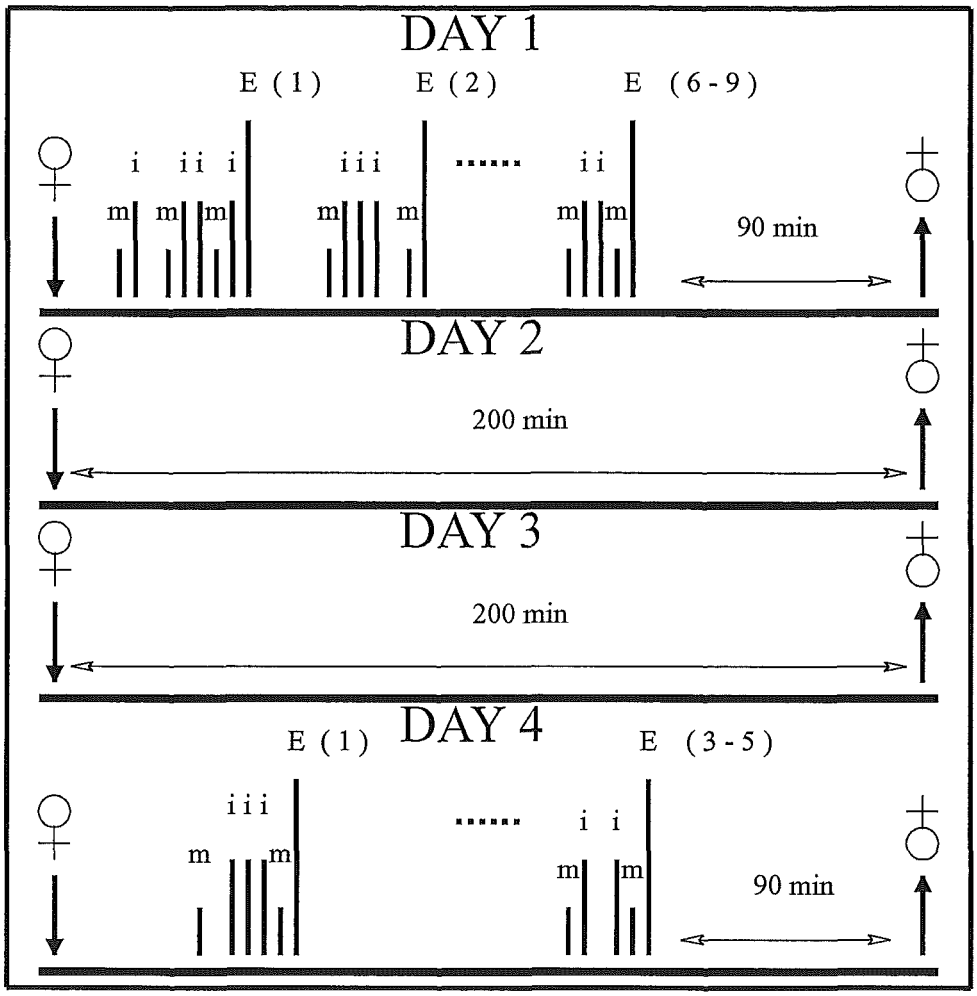

Figure 1. Behavioral characterization of sexual satiety in male rats. On Day 1 the subjects are allowed to copulate until reaching a criterion of 90 min without further mating; it usually takes 6 to 9 ejaculations. The following days they are placed with receptive females for up to 200 min if no copulation occur. On resumption of mating, often in day 4, they attain exhaustion after a smaller number of ejaculations (3-5). The stimulus females are replaced every 30 min. E: ejaculation; m: mount, i: intromission.

There are few reports assessing brain neurochemicals in connection with sexual satiety. Thus, the levels of endogenous opioids (measured by a global radioreceptor assay) in male rats killed when they were nearing sexual exhaustion after mating for 2 hours were decreased in the midbrain and unchanged in the

hypothalamus and the dorsal striatum [14]. Another study found an increase in the dopamine (DA) and serotonin (5-HT) content in medial preoptic area (MPOA) homogenates taken from sexually exhausted males [15].

All the above data were obtained in animals either approaching sexual exhaustion or immediately after reaching that criterion, but do not give information about the ensuing subchronic state of sexual refractoriness (days 2-3 in Figure 1). Regarding the neurochemical data, they were based on one time point only. Furthermore, the physiological relevance of post-mortem findings in neurotransmitter indices is difficult to ascertain since there are dramatical fluctuations in their release and metabolism immediately after death [16]. Presently, the behavior-related changes in endogenous neurochemicals can be better studied by in vivo methods which also allow a more dynamic assessment

Methodological background

In recent years, two methodologies have been developed for the monitoring of neurotransmitter release and metabolism in small brain regions of living, even behaving, animals: voltammetry and microdialysis. They both aim to measuring substances present in the extracellular fluid surrounding probes implanted stereotaxically in the brain. The extremely low concentrations of informational molecules in the extracellular space, several orders of magnitude lower than the levels found in tissue homogenates constitutes an important limiting factor. That has led the investigators using these methodologies to focus on areas having high levels of neurotransmitters, such as DA in the dorsal striatum and the nucleus accumbens (ACB). In regions in which these levels are smaller it is possible to infer the release of transmitters from the extracellular concentration of their main metabolites, the latter being generally much higher than those of the parent neurotransmitters. Thus, in the absence of pharmacological manipulations, the extracellular levels in the living brain of the acidic catechol derivatives dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) provide a suitable index of DA turnover, whereas those of 5-hydroxyindoleacetic acid (5-HIAA) reflect 5-HT utilization.

In vivo voltammetry is based on the oxidation of electroactive species at the tip of carbon-based microelectrodes placed in the desired brain region when a given voltage, characteristic of each neurochemical (its oxidation potential) is applied. This results in a current that can be amplified and recorded. The advantages of voltammetry include the small size of the probes (some microns) and good time resolution (seconds). Its main limitations derive from the precise identification of the compounds being detected and the short life span of the electrodes giving better sensitivity and resolution (electrochemically pretreated carbon microfibers). Microdialysis involves the passage of an artificial cerebrospinal fluid throughout probes having a semipermeable membrane which allows the difussion of relevant substances into the effluent being collected. They can be analyzed, usually by chromatographic techniques. Figure 2 summarizes the general set-up of the microdialysis system for freely moving animals used in our laboratory. An advantage of microdialysis over voltammetry is the clearer identification of the substances assessed. The microdialysis probes are also operative for longer periods and, with the appropriate corrections for recovery, is easier to compare the levels of neurochemicals measured in the same animal at different sessions.

Likewise, lower levels of endogenous substances can usually be detected, provided that a sufficient interval for collecting the dialysates is allowed. This limits the

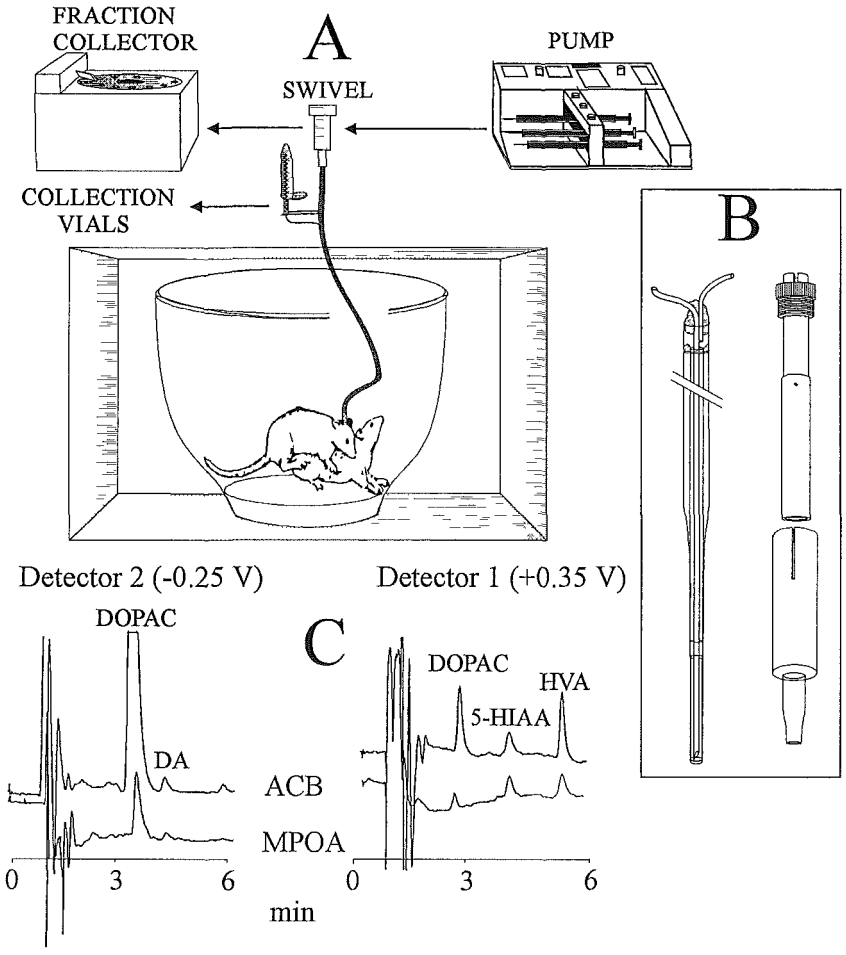

Figure 2. **A**: General set-up for microdialysis collection in sexually behaving animals. **B**: Microdialysis probe (left) and guide-cannula assembly allowing the painless periodic replacement of the probe (right). The lower part is cemented to the skull. The upper part carries the dialysis probe; the protective telescopic cylinder slides back during insertion. **C**: Representative chromatograms of dialysates collected from the ACB and the MPOA recorded with a highly sensitive dual coulometric detector. Note that DA levels in the MPOA are under detection limits.

temporal resolution of microdialysis to several minutes with the analytical techniques currently available. Given their relative merits and limitations, the in vivo voltammetry and microdialysis methodologies should be regarded as complementary. Ideally, they should be used either in combination or individually to address the biological questions for which each of them is better suited. In order to optimize the assessment of neurochemical correlates of sexual behavior, we use both.

Neurotransmitter release during mating

Using voltammetry, we first documented the on-line monitoring of the release of a neurotransmitter (DA) in a brain area (the ACB) concomitantly with the display of mating behavior [17]. These electrochemical findings have been corroborated by several studies using microdialysis in our and and other laboratories [17-22]. All those reports show robust increases in the extracellular levels of DA and its main metabolites in the ACB of male rats during mating. These data have been related to the well-accepted role of this structure as a functional interface between the limbic and motor systems, mediating the translation of motivational phenomena into behavioral acts, a process modulated by the mesoaccumbens dopaminergic innervation [23].

Data on other brain areas or neurotransmitters are scanty at present. A main reason is the above pointed difficulty in measuring the low extracellular concentrations of neuromediators in the brain extracellular fluid. Nevertheless, some other relevant regions, such as the MPOA, have also been explored with microdialysis in mating male rats [22, 24]. Because of the low interstitial concentration of the monoamines, the studies reported so far have focused on the metabolite levels. As shown consistently by the already abundant literature on the ACB, the mating related changes in DOPAC follow closely those in DA release [17-22]. A similar relationship between the changes in metabolite levels and those of the parent transmitters can be reasonably assumed for the brain areas where the low concentration of the amines make them undetectable.

Whereas most of the existing reports about in vivo release or metabolism have dealt with a single transmitter system (usually DA) we also assessed 5-HIAA levels. Interestingly, the rise in 5-HIAA in the brain regions studied was delayed with respect to that of the DA metabolite. Thus, DOPAC levels were elevated since the beginning of mating, whereas those of 5-HIAA were not significantly increased until the animals had ejaculated [22].

These findings were quite consistent with our previous ex vivo data [25]. They suggested that such a temporal dissociation between the utilization of DA and 5-HT during mating could reflect the involvement of the dopaminergic innervation of the forebrain in the motivational aspects of sexual behavior whereas the serotonergic activity would be mostly related with the consummatory aspects and, possibly, the satiety phenomena. This interpretation would be in agreement with a wealth of pharmacological evidence showing that dopaminergic agents usually stimulate sexual activity whereas increasing the serotonergic transmission has mainly inhibitory effects [26-27].

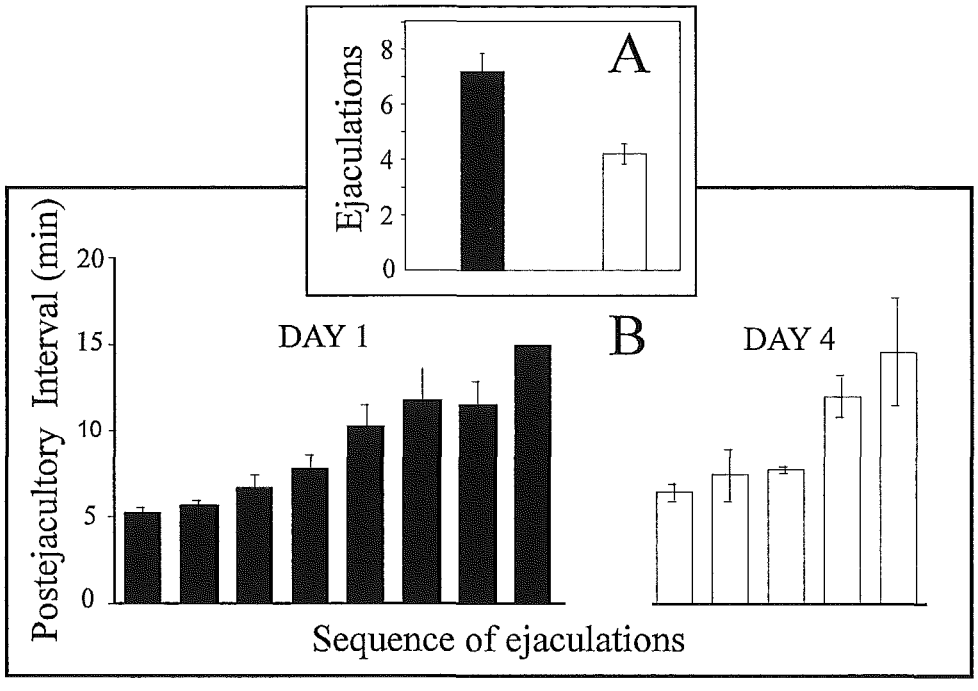

Figure 3. Behavioral parameters in animals mating to sexual exhaustion during microdialysis sessions. **A:** Total number of ejaculations to exhaustion. **B:** Changes in the postejaculatory intervals. Mean ± s.e.m.; n=5.

Neurochemical data on sexual satiety

This theoretical background and availability of suitable methodologies led us to explore the possible changes in neurotransmitter utilization, as assessed in vivo, associated with the state of sexual refractoriness ensuing unrestricted mating. We focused on the MPOA because of its well recognized crucial role in the expression of masculine sexual behavior [see 26]. Such a study, at variance with the preceding short-term experiments, involves neurochemical monitoring for several consecutive days. A limiting factor for long-term microdialysis sampling is the tissue reaction to permanently implanted probes, severely hampering within a few days the diffusion of neurochemicals through the exchange membrane [21]. To circumvent this problem, we adopted a removable probe system (derived from a voltammetric electrode carrier assembly) allowing the painless replacement of the dialysis probes in awake, non-restrained animals (sketched in Figure 2). We have shown that removing the dialysis probe until the next daily collection session minimizes this gliotic reaction, making it possible to obtain fairly stable levels of brain monoamine metabolites in studies lasting several days post-surgery [21]. Using this system, we also observed a remarkably consistent release of DA in the ACB throughout several mating sessions in successive days [21].

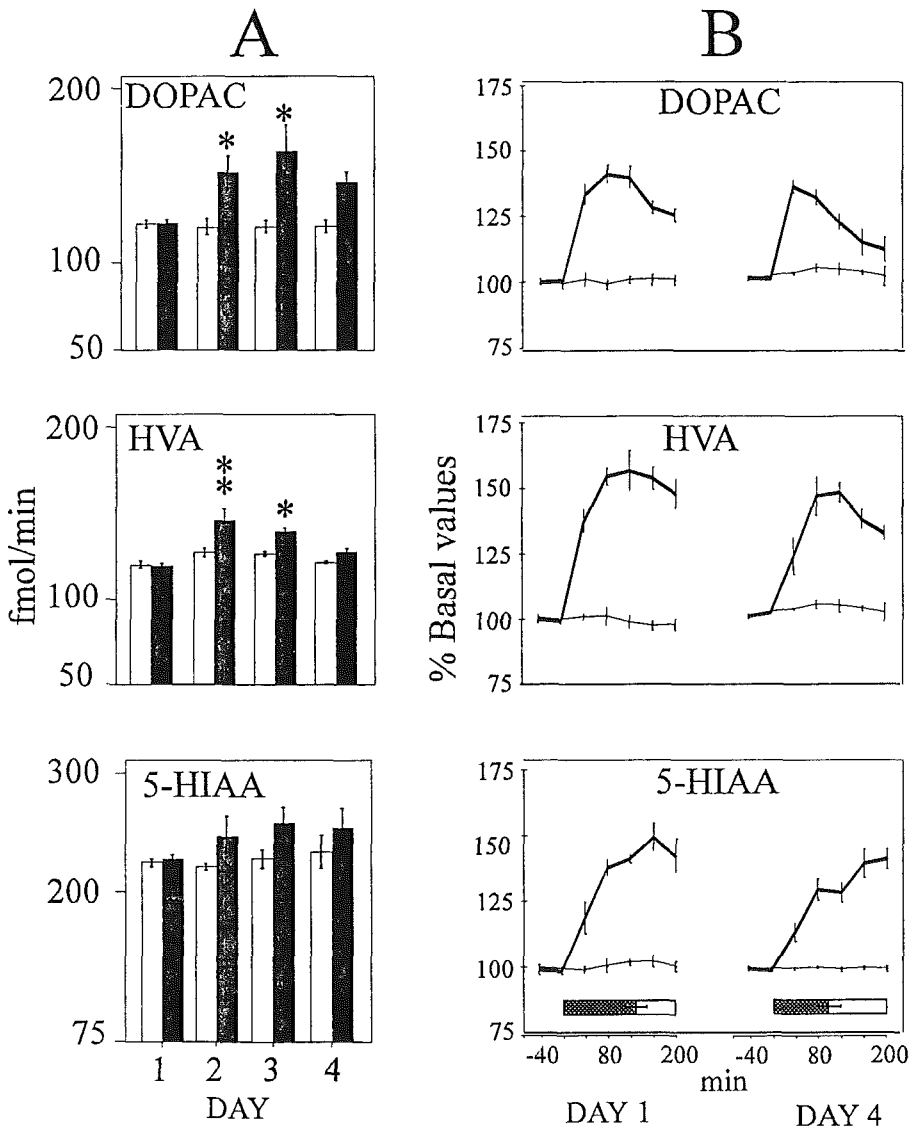

Figure 4. DA and 5-HT metabolites in MPOA dialysates of male rats. **A**: Basal males (open bars, control group). In days 1 and 4, the animals in the experimental group mated to exhaustion, remaining sexually inactive in days 2 and 3. **B**: Relative changes in metabolites during mating. The stippled bar at the bottom indicates the total mating time; the longer open bars indicate the time of dialysate collection. Thick lines: mating animals, thin lines: control group. Mean±s.e.m; n=5; ** $p<0.01$ vs day 1; * $p< 0.05$ vs day 1.

Thus, sexually experienced male rats were implanted with removable microdialysis probe assemblies aiming to the MPOA. After recovering from surgery, the subjects were placed with receptive females until reaching the sexual exhaustion criterion (90 min without further mating). They were exposed again to receptive females for 200 min during the following 3 days. No mating activity was displayed until the third day post-exhaustion (day 4, Figure 2). MPOA dialysates were collected throughout these successive sessions to measure the main metabolites of DA (DOPAC and HVA) and 5-HT (5-HIAA). A control group, consisting of animals exposed to intact males was run in parallel. Figure 3 summarizes some of the behavioral characteristics of the development of sexual satiety. It shows how the subjects had about 7 ejaculations in the first session and a smaller number in the next one (day 4), as well as the steady increase in the postejaculatory interval as the animals approached exhaustion in both sessions. These data are fairly similar to previous descriptions of this phenomenon in intact animals [5-7] and with normative studies in our laboratory. They indicate that the ongoing microdialysis sampling does not interfer with the display of the normal behavioral pattern. During the 2-day interval of sexual refractoriness, the basal levels of both DOPAC and HVA remained elevated whereas those of 5-HIAA were as low as in the dialysates preceding the first mating session. By the third day post-exhaustion, however, just before the animals resumed mating, the basal levels of both dopamine metabolites had decreased to values not significantly different from the pre-exhaustion values (Figure 4). There was a mating-associated increase in the three monoamine metabolites in both sessions, with the 5-HIAA rise being slower. This finding is consistent with our previous shorter-term studies, both ex vivo [25] and in vivo [22], comparing the time-course of the copulation related changes in monoamine metabolites in the MPOA and other brain regions.

The above data suggest a specific enhancement of DA turnover concomitant with the state of sexual satiety. They could reflect increased dopaminergic transmission, as similar increases have been found in the ACB, associated with elevated extracellular DA, characteristically during the appetitive phases of both sexual [17-22] and non-sexual [28-29] behaviors. Yet, this interpetation is difficult to reconcile with a state of exhaustion/satiety. An alternative, more likely, explanation comes from the similarity of these neurochemical changes with the effects of DA receptor blockers. Thus, treatments with DA antagonists have consistently been found to increase the extracellular levels of DA and its metabolites [30-31]. These drugs also have well-recognized inhibitory effects on mating behavior [26-27]. It is, therefore, possible that some endogenous inhibitor of DA transmission could operate during the state of sexual refractoriness.

Interpretation and further work

To test the hypothesis that an inhibition of dopaminergic activity is involved in sexual exhaustion we studied the effects of the DA agonist apomorphine given in a wide range of doses to sexually sated rats. Thus, experienced animals were allowed to copulate until reaching the satiety criteria defined in Figure 1. The next day, after verifying that they remained sexually inactive, the subjects were treated with apomorphine or vehicle and exposed to receptive females for the ensuing 90 minutes. Although the dose-response curve was bell-shaped due to the interfering stereotyped behavior, apomorphine treatment clearly induced mating activity in

these animals. These findings support the notion of a decreased dopaminergic transmission contributing to the state of sexual refractoriness which follows unrestricted mating. Recently, it has been reported that systemic treatments with either the α2 antagonist yohimbine or the 5-HT 1A agonist 8OH DPAT stimulated mating behavior in sexually sated rats [32]. Whereas it is certainly possible the involvement of noradrenergic and serotonergic mechanisms in sexual satiety, it should be noted that both yohimbine and 8OH DPAT have been found to interact with DA transmission [33 - 35]. It is, thus, feasible that a common dopaminergic mechanism could account for the recovery from sexual exhaustion induced by all these drugs.

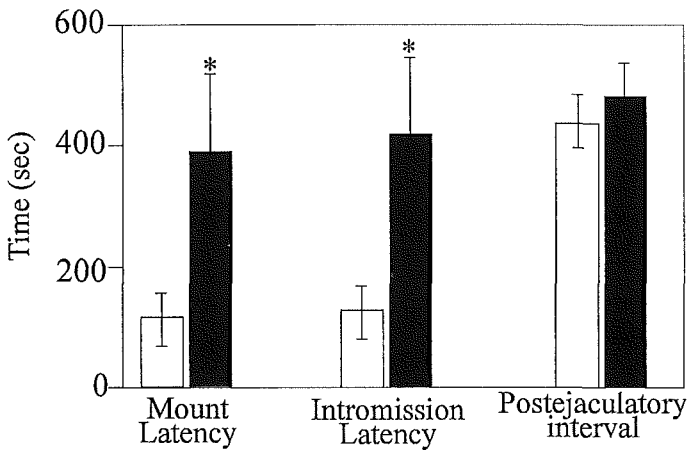

Figure 5. Effects of oPRL (4 mg/Kg sc, 60 min before the test; closed bars) or vehicle (open bars) on measures of sexual behavior of male rats. Mean±s.e.m.; n=12; * $p < 0.05$ vs vehicle.

The identity of the hypothetical "neuroleptic-like" endogenous signal mediating the inhibition of mating behavior in the sexually sated animal remains to be clarified. A potential candidate is the pituitary hormone prolactin (PRL). We have previously shown that several behavioral and neurochemical effects of systemic injections of ovine PRL (oPRL) are similar to those of DA receptor blockers (i.e. hypomotility, increased extracellular levels of DA and DOPAC, and decreased ascorbate) [36]. On the other hand, chronic hyperprolactinemia has long been known to inhibit sexual behavior [e.g. 37]. PRL secretion in male rodents is also known to increase during mating, especially after the ejaculation [e.g. 38-39]. Therefore, we thought it possible that this ejaculation- related PRL release could lead to the inhibition of sexual behavior via the antagonism of dopaminergic transmission. As a first test of this hypothesis we assessed the acute effects of a systemic injection of oPRL (4 mg/Kg) on a standard mating test started 60 minutes later, a time when it reaches the highest blood levels [40]. This preparation and dosage was chosen because it had previously shown the above commented "neuroleptic-like" effect [36]; it is also well within the range used by several

laboratories for analyzing behavioral and neuroendocrine phenomena [e.g. 40-42]. As shown in Figure 5, oPRL treatment lengthened the mount and intromissions latencies, traditional measures sexual motivation, having no other detectable behavioral effects. To our knowledge, such short-terms effects of high PRL on sexual behavior have not been assessed previously. Whereas it is generally agreed that long-lasting hyperprolactinemia induced by pituitary grafts inhibits mating activity in the male rat, the reported effects of subchronic PRL increases are contradictory. Thus, the mount and intromission latencies have been found either to decrease [43] or to increase [41] 5 to 8 days after receiving pituitary transplants, and to increase after 9 days of treatment with two daily injections of oPRL [41]. The behavioral effects in the latter study were not assessed until 3 days after the start of treatment, however. The present data, albeit preliminary, fairly suggest that an acute release of PRL can decrease sexual motivation. They call for further studies using more physiological preparations and routes of administration as well as measuring the blood levels of the hormone during the development of sexual satiety.

The opioid systems could play also a relevant role in the mechanisms of sexual satiety. Opiatergic drugs have long been known to inhibit most aspects of sexual behavior [44]. An enhanced activity of endogenous opioids during mating is suggested by the associated increase in pain thresholds [14, 45-46]. This phenomenon can be prevented by treatment with the opiate antagonist naloxone [45]. As pointed above, opioid levels have been found decreased in the brainstem of animals reaching sexual exhaustion [14]. Moreover, opiate treatments are known to modulate dopaminergic transmission in several brain areas [47], and some of these compounds have "neuroleptic-like" properties [48]. The opioids are now thought to play a complex role in the regulation of sexual behavior, having both inhibitory and stimulatory effects, which depend in part on their different sites of action [49, 50]. Whereas they probably participate in the mechanisms of sexual satiety, further studies are required to elucidate their function.

Overall, the data available point to complex neurochemical interactions underlying the inhibition of sexual drive that ensues unrestricted mating. Probably for this reason, none of the "prosexual drugs" purportedly acting through relatively specific neurotransmitter systems that have been given alone to sexually exhausted male rats, such as yohimbine, 8OH DPAT [32], and apomorphine (our studies) was able to fully restore a normal copulatory pattern, even though they all induced some degree of mating. For a complete recovery of sexual activity in the sated animal, probably it would be needed a combination of drugs modulating several neuromediators. The rationale for developing such treatments can be provided by further dynamic assesments of the neurochemical correlates of sexual exhaustion and satiety.

Acknowledgements

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Discussion - THE NEUROCHEMISTRY OF SEXUAL SATIETY. AN EXPERIMENTAL MODEL OF INHIBITED DESIRE

J.G. Pfaus

Have you looked at these animals using any kind of appetitive task on days one and two after their free copulation? In other words, do these animals still fight to gain access to females or show conditional place preference for females or anything like this?

M. Mas

No, we are at the beginning of these studies. I think that there is ground here for interesting experiments about second order reinforcement and other incentive learning models.

J.G. Pfaus

Another question is, do we know what prolactin does to bar pressing for a second order reinforcer or any kind of appetitive task?

M. Mas

I don't think that there are any data available.

B.D. Sachs

In regard to sexual exhaustion, I just want to comment that some years ago we showed that reflexive erection recovers within 12 hours of exhaustion, so the penis and the spinal cord are presumably ready by then, but the brain is not yet ready to deliver the signal.

J. Stewart

I wonder if you could comment on how you think prolactin is acting. You suggested that it is acting as a neuroleptic?

M. Mas

I could not tell you what is the exact mechanism, but the fact is that we have these data showing a profile fairly similar to that of neuroleptics. These effects: lowering ascorbic acid and motor activity and increasing extracellular dopamine and DOPAC are coincident with those of such drugs. On the other hand, if you raise the dose of prolactin you don't get the catatonic state induced by a high dose of a neuroleptic.

J. Herbert

It was not clear how long before your making the test you gave the prolactin because one of the important points about prolactin is its access to the brain. It does get into the brain but it takes a long time to do so.

M. Mas

The injection was given one hour before the test. The pharmacokinetics of prolactin has been thoroughly assessed in neuroendocrine studies. Maximal blood and CSF levels are attained around one hour after the injection.

J. Herbert

I think there is a puzzle here. If you are relating your persistent sexual exhaustion to a dopamine mechanism why is this not affecting other sorts of behaviour. I could not understand that point. If this basic procedure is depending upon dopamine inactivation someway, one would expect this to spill over to other sorts of behaviour.

M. Mas

That is a good question. We have not formally assessed any other behaviour, but I can tell you how the animal looks. It is apparently normal and it will explore a female and respond to other social stimuli.

J. Bancroft

This persisting high level of dopamine metabolized, what does that mean in pharmacological terms? Does it mean that dopamine is being released continuously during that time and metabolized?

M. Mas

Yes, and this is a typical effect of a receptor blocker. Since dopamine cannot act, the neurons producing it increase their firing and release.

J. Bancroft

So why does the prolactin go up? If there is a lot of dopamine being released, which cannot act, does that mean that it cannot suppress prolactin as well? One tends to think of prolactin rises as due to a reduction in dopaminergic activity.

M. Mas

I could not tell which goes first. The acute release of prolactin does not necessarily involve dopamine inhibition. Other releasing agents, e.g. VIP could operate.

M. Murphy

The loss of erectile function and the loss of sexual appetite in humans that occurs with hyperprolactinemia is rapidly reversed with bromocriptine supporting your hypothesis. I wonder if you would like to comment on that.

M. Mas

Yes, we considered using bromocriptine, but we gave apomorphine instead because its pharmacology in the rat is far better documented.

G. Wagner

I recall from the literature some 15 years ago that they were sampling from plasma in women during sexual stimulation and found an increase in prolactin at the time which seemed related to breast touching. Are there similar studies during sexual intercourse in men?

J.R. Heiman

Our group did a study in which men viewed an erotic video, following which there was an increase in LH, while cortisol and PRL dropped over the session. There was no change in testosterone. We thought the prolactin decrease was related to the stress

of the procedure.

J. Bancroft

It is important to discuss the issue of what happens after ejaculation. I think the state of refractoriness after ejaculation is a very interesting one, and although I suspect that there are very important differences between rodents and humans, certainly in the human this is a powerful physiological state that we do not understand very much about. So I think it is important to try to understand whether it has relevance to other situations. You were making the comparison with loss of sexual desire; I think it is a bit of a jump but an interesting jump. A few years ago when people were recording hippocampal afterdischarges following ejaculation and orgasm, the implication was that these afterdischarges were associated in some way with inhibitory mechanism. I do not know where that type of research has got to and I wonder if with these new molecular techniques anybody has looked at something comparable to that in the hippocampus.

M. Baum

There are androgen receptors in the hippocampus and this raises the question of what, if any, appetitive role maybe be played by those receptors.

B.D. Sachs

If I may pick up another other point concerning the refractory period, I would like to recall on some prepubertal boys from the Kinsey study on males, data that are certainly questionable, because they were collected by pedophiles. There is no question that prepuberal boys have nocturnal penile tumescence and to the extent that they do, it would seem to cast doubt on the androgen dependence of that response, at least prior to puberty. We know that hypogonadal men have nocturnal penile tumescence although far weaker than in normal men. With regard to the refractory period, in the case of the prepubertal boys there is no ejaculation, but their post-orgasmic refractory period is far shorter than in postpubertal men, so there are boys reported as having five, six, eight, ten orgasms within a half hour span. This raises the possibility that the refractory period is in some sense androgen-dependent, and I think it might further raise the question of whether multiple orgasm in women becomes enabled by the lower

exposure to androgen and therefore there would be shorter refractory periods, at least prior to the terminal orgasm.

J. Bancroft

It is of course possible that the refractory period is not so much androgen dependent, but linked in some way with seminal emission because it is after seminal emission occurs that the refractory period becomes most apparent. Another point, in terms of androgen, is the increasing interest in the possibility that androgen has effects on the system which are both inhibitory and excitatory.

J.T. Clark

I am not sure about the absolute dependence of the PEI on seminal emission, because you can induce seminal emission with drugs and then have the animals behave without prolonged PEIs. Further, you can prevent seminal emission with guanethidine and it does not affect PEI at all.

B.D. Sachs

Ejaculation has also been stimulated by brain stimulation and by peripheral nerve stimulation without changing subsequent copulatory behaviour, again implying that the emission itself is not responsible for the refractory period. I guess Julian Davidson talked about a spinal or a spinal-brain system that might be the orgasm centre and that might be responsible for both ejaculation and orgasm, but I do not think that emission or ejaculation could be said to be the foundation of the refractory period. Certainly, prior to the ability for emission, prepubertal boys can have orgasms, and I suspect that as the testosterone titre increases the post-ejaculatory period increases, even before ejaculation is possible.

J.T. Clark

And it would be speculative to say that as one ages one's cumulative exposure to androgen increases and the post ejaculatory interval also increases.