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## Sex, drugs and gluttony: How the brain controls motivated behaviors

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### ABSTRACT

Bart Hoebel has forged a view of an integrated neural network that mediates both natural rewards and drug use. He pioneered the use of microdialysis, and also effectively used electrical stimulation, lesions, microinjections, and immunohistochemistry. He found that feeding, stimulant drug administration, and electrical stimulation of the lateral hypothalamus (LH) all increased dopamine (DA) release in the nucleus accumbens (NAc). However, whereas DA in the NAc enhanced motivation, DA in the LH inhibited motivated behaviors. The Hull lab has pursued some of those ideas. We have suggested that serotonin (5-HT) in the perifornical LH inhibits sexual behavior by inhibiting orexin/hypocretin neurons (OX/HCRT), which would otherwise excite neurons in the mesocorticolimbic DA tract. We have shown that DA release in the medial preoptic area (MPOA) is very important for male sexual behavior, and that testosterone, glutamate, nitric oxide (NO) and previous sexual experience promote MPOA DA release and mating. Future research should follow Bart Hoebel's emphasis on neural systems and interactions among brain areas and neurotransmitters.

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### 1. Bart Hoebel's research

Bart Hoebel is a giant among neuroscientists. He pioneered new techniques and produced seminal insights into the workings of the brain. His use of microdialysis and high performance liquid chromatography (HPLC) to collect and analyze neurotransmitters in various brain areas provided important concepts about the interactions between the hypothalamus and the mesocorticolimbic dopamine (DA) system. Much of my own work has been along the paths that he established.

His earliest article, published in *Science*, reported that food consumption inhibited, not only feeding, but also lateral hypothalamic self-stimulation, and that the ventromedial hypothalamus mediated both effects [1]. A second *Science* article extended his study of motivated behaviors to include copulation. It reported that electrical stimulation of the posterior hypothalamus promoted copulation and also mating-induced reward [2]. Still studying copulation, he became interested in the role of serotonin (5-HT) in its regulation. Acute injection of p-chloroamphetamine (PCA) inhibited female rat lordosis as a result of 5-HT release. However, chronic PCA facilitated lordosis, as a result of 5-HT depletion [3]. Therefore, 5-HT had an inhibitory effect on female sexual behavior.

Bart Hoebel later became proficient with microdialysis, and dopamine (DA), serotonin (5-HT), and acetylcholine (ACh) came to the forefront. Food intake, cocaine, and lateral hypothalamic self-

stimulation all increased DA in the mesocorticolimbic DA tract [4–6]. Furthermore, there were unexpected interactions among brain areas. For example, there was an inverse relation between the effects of DA in the lateral hypothalamus (LH) vs. the NAc [7]. DA in the LH was unpleasant and inhibited motivated behaviors, but DA in the NAc was rewarding and promoted motivated behaviors.

### 2. Hull lab research

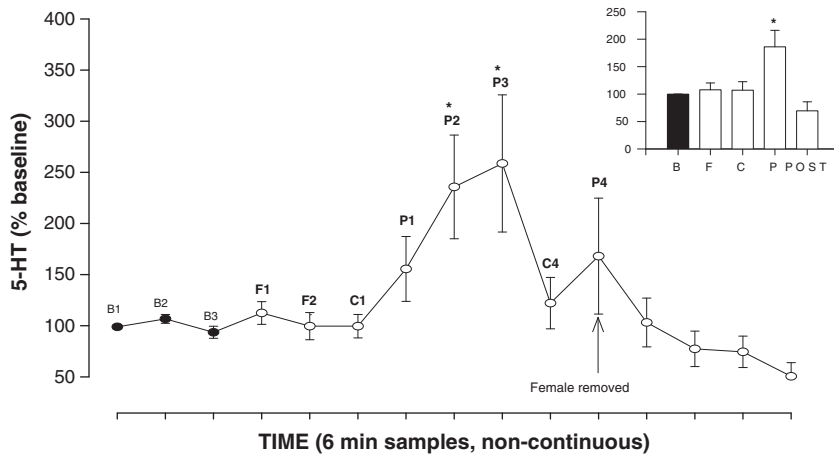
My lab has followed up on some of these ideas. We have used microdialysis, microinjection, and immunohistochemistry, together with behavioral testing, to probe the circuitry mediating male rat sexual behavior.

#### 2.1. 5-HT effects in the anterior LH

My former student Dan Lorrain used microdialysis to show that 5-HT is released in the anterior LH at the time of ejaculation [8] (see Fig. 1), just as Bart Hoebel had reported 5-HT release there with feeding [9]. Furthermore, microinjection of a selective 5-HT reuptake inhibitor (SSRI) antidepressant into the LH inhibited copulation, similar to post-ejaculatory quiescence and similar to the inhibitory sexual side effects of SSRIs used to treat depression. Thus, the Hoebel lab showed that systemic increases in 5-HT impaired female sexual behavior [10], and the Hull lab located at least one brain area, the anterior LH, where local 5-HT increases inhibited male sexual behavior [8]. In a later article, we reported that reverse-dialysis of 5-HT into the anterior (perifornical) LH decreased DA release in the NAc [11]. Therefore, 5-HT release in the LH

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**Fig. 1.** Temporal changes in extracellular serotonin (5-HT) collected from the lateral hypothalamus of male rats before and during copulation. Each data point is the mean ( $\pm$ SEM) for 6-min dialysate samples collected during baseline (B), in the presence of an estrous female (F), during copulation (C), during the post-ejaculatory interval (P), and after the female was removed (expressed as % of mean baseline levels). 5-HT levels increased during the second (P2) and third (P3) post-ejaculatory intervals, compared to the final baseline. 5-HT during P3 was also higher than in the fourth copulatory interval. Samples collected during the second and third copulation series were not analyzed, because most males ejaculated before a full 6-min sample could be collected. The summary graph (inset) shows the mean ( $\pm$ SEM) for data for the 15 sample periods collapsed into five groups, based on behavioral condition. Samples collected during post-ejaculatory intervals showed higher 5-HT levels than all other conditions  $^*p < 0.05$  versus B, F, C, and postcopulation (POST). Figure from Ref. [8] with permission.

at the time of ejaculation may contribute to post-ejaculatory quiescence, at least in part, by inhibiting the mesocorticolimbic DA pathway.

2.2. OX/HCRT in the anterior (perifornical) hypothalamus

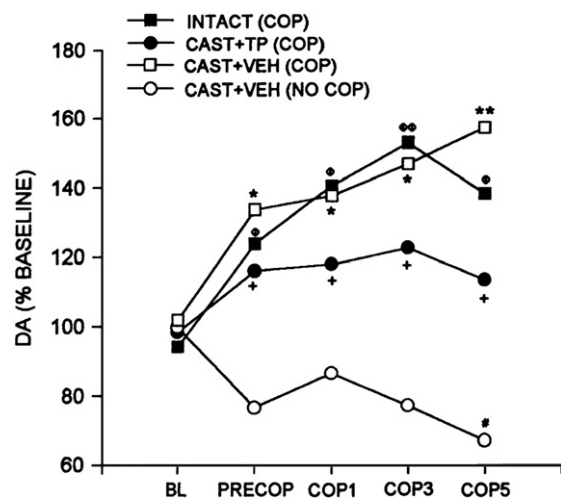
We have more recently provided a sequel to the lateral hypothalamic 5-HT story. A group of neurons in the LH produces the peptide orexin (OX, also known as hypocretin, HCRT). Furthermore, 5-HT was previously reported to inhibit those neurons [12]. OX/HCRT is primarily known for its stimulation of feeding behavior [13,14] and control of sleep-wake cycles [15,16]. OX/HCRT-containing neurons had previously been reported to project to the ventral tegmental area (VTA) [17], the source of the mesocorticolimbic DA tract. Furthermore, intra-VTA administration of OX/HCRT was reported to increase DA release in the NAc [18]. My former student John Muschamp hypothesized that the lateral hypothalamic neurons that were inhibited by post-ejaculatory 5-HT might be those OX/HCRT-containing cells. We showed that mating increased c-Fos-immunoreactivity in OX/HCRT-containing cells [19]. In addition, castration decreased the number of OX/HCRT-immunoreactive neurons, which were mostly restored by systemic injections of estradiol. OX/HCRT is behaviorally relevant, as systemic administration of an OX/HCRT antagonist impaired copulation [19]. In addition, microinjection of OX/HCRT into the VTA produced dose-dependent effects on dopaminergic cell firing. The two lower doses increased cell firing and population responses, although the highest dose apparently resulted in depolarization block of VTA dopaminergic neurons, which was reversed by stimulating DA autoreceptors with the DA agonist apomorphine. Finally, triple-label immunohistochemistry revealed that mating increased c-Fos immunoreactivity in dopaminergic neurons in the VTA that were apposed to OX/HCRT fibers. Therefore, OX/HCRT neurons appear to act in a steroid-dependent manner to activate the mesocorticolimbic DA pathway, thereby promoting sexual behavior and other natural and drug-induced rewards.

2.3. DA release in the medial preoptic area (MPOA)

In addition to the LH and mesocorticolimbic DA system, my lab has investigated the role of the MPOA, at the anterior end of the hypothalamus, in the control of male sexual behavior. MPOA lesions disrupt male sexual behavior in all vertebrate species that have been studied (reviewed in Ref. [20]). Electrical or chemical stimulation of

the MPOA enhances copulation and *ex copula* genital reflexes. Local A14 periventricular DA neurons innervate the MPOA, as do DA neurons from several other sites [21].

There is a close correlation between male rat sexual behavior and extracellular DA levels in the MPOA. DA is released in the MPOA of male rats in response to an estrous female and during copulation [22] (see Fig. 2). The recent presence of testosterone was necessary for both DA release and copulation. Intact males, testosterone-treated castrates, and oil-treated castrates that copulated showed a pre-copulatory DA increase, which was maintained or increased further during mating [22,23]. Oil-treated castrates that did not copulate did not show the increase. There was both behavioral and anatomical



**Fig. 2.** Testosterone-mediated enhancement of sexual activity may occur in part through increased DA release in the MPOA. Gonadally intact male rats showed an increase in extracellular DA during precopulatory exposure to an inaccessible estrous female, and all intact males then copulated when the female was placed in their cage. Males castrated 2 weeks before showed no DA release in response to the female, and none copulated. Two thirds of 1-week castrates copulated and showed the DA increase, whereas the remaining third did not copulate and did not show a DA increase.  $^*P < .05$ , compared to baseline for testosterone-treated castrates;  $^{**}P < .01$ , compared to final baseline for intact males or for one-week vehicle-treated castrates that copulated;  $^+P < .05$ , compared to final baseline for vehicle-treated castrates that failed to copulate. Reprinted from Ref. [22] with permission.

specificity for the DA response. Furthermore, the fact that DA increased before mating began suggests that the increase was not caused by copulation, but was probably associated with sexual motivation. Two-, five-, and ten-day regimens of testosterone treatment of castrates resulted in increasing copulatory ability that correlated closely with the restoration of DA release [24]. Testosterone treatment for two days did not restore mating or the DA response. Most of the five-day testosterone-treated castrates were able to copulate and showed a DA response, with half of them able to ejaculate. All of the castrates treated with testosterone for 10 days copulated to ejaculation, and all showed the DA response. There were again numerous correlations between copulatory measures and DA levels. Therefore, both the loss of copulation following castration and its restoration by testosterone are closely associated with the MPOA DA response to an estrous female.

Testosterone's metabolites were differentially effective in restoring DA release in long-term castrates [25]. Estradiol restored normal basal levels of DA, but not the increase in response to a female. Estradiol-treated castrates intromitted, but none showed an ejaculatory behavior pattern. Neither dihydrotestosterone nor oil vehicle maintained copulation or basal or female-stimulated DA release. However, when dihydrotestosterone was administered with estradiol, the combination restored both copulation and basal and female-stimulated DA release [25].

Although extracellular levels of MPOA DA are lower in castrates than in gonadally intact males, intracellular levels are actually higher than in intact males [26]. Indeed, there was a negative correlation between tissue (stored) DA levels and the ability to copulate [27]. Non-copulating animals (dihydrotestosterone- and oil-treated castrates) had higher levels of tissue DA than the groups that did copulate (estradiol-, estradiol + dihydrotestosterone-, and testosterone-treated castrates). Therefore, synthesis and storage of DA in the MPOA is at least as great in castrates as in intact males; the deficiency in castrates is not in their ability to synthesize and store DA, but in their ability to release their abundant stores.

#### 2.4. The role of NO in MPOA DA release

Earlier studies had reported that DA release in the striatum was facilitated by NO [28,29]. Therefore, we tested whether NO would have similar effects in the MPOA. Indeed, the precursor of NO, L-arginine, increased basal MPOA DA release, and the NO synthase (NOS) antagonist L-NMMA decreased release [30]. A different NOS inhibitor, L-NAME, inhibited copulation-induced DA release [31], an effect that was mediated by cGMP [32]. Furthermore, neuronal NOS (nNOS) immunoreactivity was decreased after castration and was restored by testosterone administration [33]. Therefore, one means by which testosterone facilitates copulation is by increasing nNOS in the MPOA, which in turn increases both basal and female-stimulated DA release in intact males and testosterone-treated castrates.

#### 2.5. The effects of sexual experience

Our lab has also investigated the effects of sexual experience. Experienced males copulate with greater "efficiency." They have shorter latencies to mount, intromit, and ejaculate and are able to ejaculate with fewer mounts and intromissions (reviewed in Ref. [20]). Merely exposing a male rat repeatedly to an estrous female is sufficient to enhance his copulatory ability and to increase c-Fos immunoreactivity in the MPOA elicited by one ejaculation [34]. NO may mediate some of the cellular effects of experience. The NOS inhibitor L-NAME, microinjected into the MPOA, prevented copulation in sexually naïve males and decreased the numbers of intromissions and ejaculations in sexually experienced males [35]. When administered into the MPOA before each of seven exposures to an estrous female, it blocked the facilitative effects of those exposures.

Furthermore, nNOS immunoreactivity in the MPOA is increased by previous sexual experience [36]. Therefore, increases in NO production in the MPOA, and its consequent increase in DA release, may mediate some of the beneficial effects of sexual experience.

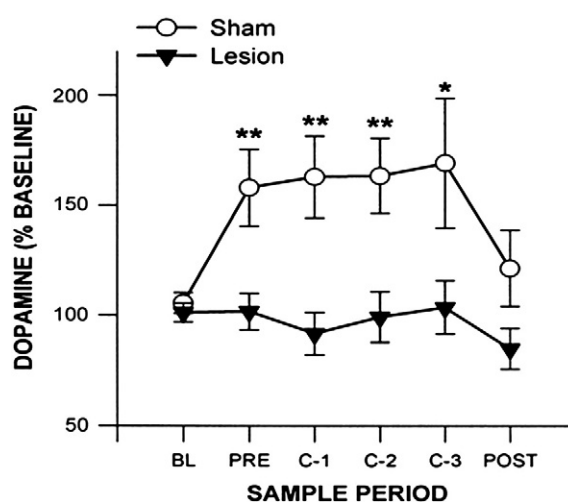
#### 2.6. Input from the medial amygdala to the MPOA

A major stimulus for the MPOA DA response to a female is an input from the medial amygdala (MeA). Juan Dominguez made large excitotoxic lesions of the amygdala, which abolished copulation in male rats [37]. However, microinjections of the DA agonist apomorphine into the MPOA completely restored copulation in those males. Smaller radiofrequency lesions of the MeA impaired, but did not abolish copulation. Basal MPOA DA levels were not affected, but the DA increase in response to the female was blocked [37] (see Fig. 3). Therefore, as with estradiol restoration of copulation in castrates [25], basal MPOA DA levels were sufficient for inefficient mating, but an additional female-stimulated increase was required for optimal copulation. In anesthetized animals, chemical stimulation of the MeA, using glutamate plus a glutamate reuptake inhibitor, increased extracellular DA levels in the MPOA, mimicking the effect of copulation [38] (see Fig. 4). Therefore, one way in which the MeA promotes copulation is by increasing DA release in the MPOA.

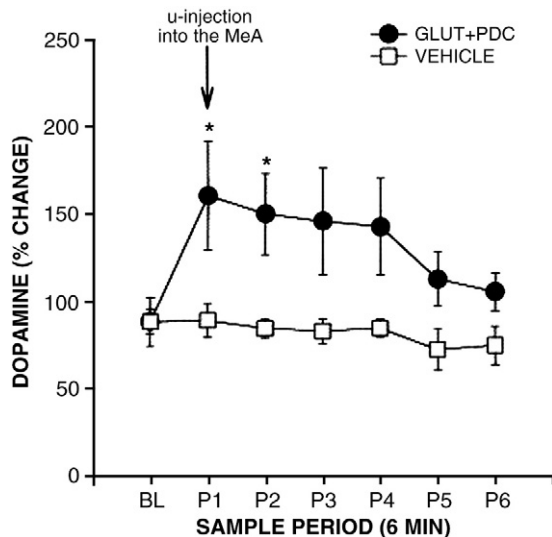
#### 2.7. Glutamate in the MPOA

One mediator of DA release in the MPOA is glutamate [39]. It is released in the MPOA during copulation, and increases by about 300% at the time of ejaculation [40]. Reverse dialysis of glutamate reuptake inhibitors increased extracellular glutamate, as expected, and also facilitated copulation. However, reverse-dialysis of serotonin (5-HT) into the MPOA impaired both copulation and ejaculation-induced glutamate release [41]. Therefore, a second site where 5-HT may inhibit mating is the MPOA, where it can decrease glutamate release.

A possible explanation for glutamate's facilitative effect on DA involves NO. The nNOS inhibitor L-NAME, when reverse-dialyzed into the MPOA, decreased baseline DA and blocked the glutamate-evoked DA release. The inactive isomer D-NAME had no effect. Glutamate binds to NMDA receptors to promote calcium influx, which activates calmodulin, which in turn activates nNOS. NO may inhibit DA uptake



**Fig. 3.** Lesions of the medial amygdala inhibit the release of DA in the MPOA resulting from exposure to an estrous female and copulation. Levels represent % changes from baseline (BL) in response to precopulatory exposure to an estrous female (PRE), during copulation (C1–C3) and after copulation (POST). Extracellular DA significantly increased during the precopulatory and copulatory stages of testing for animals with sham lesions but not for animals with MeA lesions. Values are expressed as mean  $\pm$  SEM. \* $P < .05$ ; \*\* $P < .01$ . Reprinted from Ref. [37] with permission.



**Fig. 4.** Levels of DA in dialysate from the MPOA of animals receiving MeA stimulation or vehicle microinjection. Levels represent % change from baseline (BL) in response to MeA-stimulation or vehicle microinjection; samples collected after microinjections into the MeA are post-injection samples 1–6 (P1–P6). Levels of extracellular DA significantly increased after MeA microinjections for animals receiving MeA stimulation but not for animals receiving vehicle. Values are expressed as mean  $\pm$  SEM. (\* $P < .05$ ). Reprinted from Ref. [38] with permission.

in neighboring terminals, prolonging its effects, and may also promote vesicular leakage, increasing DA release directly (reviewed in Ref. [42]). Therefore, glutamate, through its stimulation of nNOS, increases DA release in the MPOA, which in turn facilitates copulation. MPOA glutamate may also help to elicit ejaculation.

### 3. Summary

In summary, Bart Hoebel has created a “big picture” of brain areas that influence motivation for both natural rewards and drugs of abuse. Using electrical stimulation, lesions, microinjections, microdialysis, and immunohistochemistry, as well as careful and systematic behavioral observation, he mapped the brain areas and neurotransmitters that control feeding, mating, aggression, drug intake, and reward. The Hull lab has followed up on some of those ideas, including the interaction between the LH and the mesocorticolimbic DA system. We have suggested that 5-HT in the perifornical LH may inhibit sexual behavior by inhibiting OX/HCRT neurons, which would otherwise excite DA neurons in the VTA. We have studied primarily male sexual behavior, showing that testosterone and sexual experience increase nNOS in the MPOA, and that the resultant increase in NO production would increase both basal and female-stimulated DA release. Furthermore, glutamate is also released in the MPOA during mating, especially at the time of ejaculation, and glutamate, acting via NMDA receptors and calcium inflow, may increase NO, and thereby DA release. We owe much of our own success, not only to Bart Hoebel's pioneering use of microdialysis and other techniques, but also to his emphasis on neural systems and interactions of brain areas and neurotransmitters.

Finally, we owe much to Bart Hoebel for championing a warm, supportive, adventuresome, collegial, and fun atmosphere in both science and one's personal life. It is a great pleasure to know, interact with, and learn from him.

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